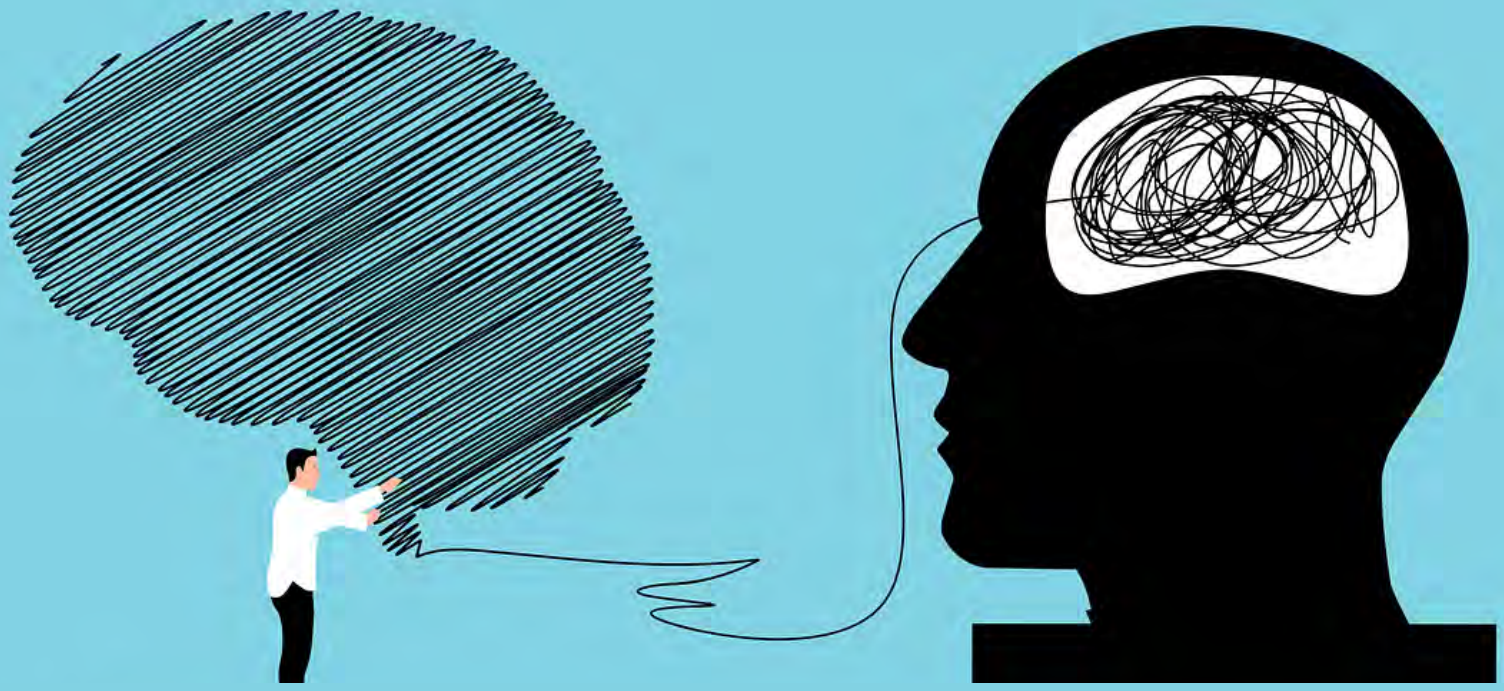
NESDA

The Netherlands Study of Depression and Anxiety: 15 years of multi-site, longitudinal data collection



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SPECIAL ISSUE

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Editorial

Fifteen years of the Netherlands study of depression and anxiety: An introduction to the special issue

This special issue of the Journal of Affective Disorders is dedicated to the Netherlands Study of Depression and Anxiety, or NESDA. This study has become a hallmark study in the field of affective disorders. Whereas in the cancer and cardiovascular field it is quite common to have large-scale cohort studies, this is much less of a tradition in the psychiatry field. When we started the NESDA project in 2005, there was quite some scepticism on how feasible it is to conduct longitudinal large-scale studies with a psychiatric patient group. Were psychiatric patients not difficult to motivate for such a study, and would they not drop out in large amounts during follow-up? In fact, nothing of this truly turned out to be a major issue. As planned, within 2.5 years the NESDA baseline cohort of around 3000 persons had been recruited, and non-response did not appear to be heavily influenced by psychiatric status (Penninx et al., 2008). In addition, the loss to follow-up due to refusal was less than 20% after 4 years, which is really comparable to what has been found in cohorts that followed somatic patients.

Fifteen years ago, we could not have imagined that the utilization of the NESDA research infrastructure would have been so large. Over 600 scientific papers have been written based on NESDA's data: Some of these papers are sole NESDA papers, but other papers utilize the NESDA data as part of larger consortia such as in the field of genetics or neuro-imaging. The multidisciplinary nature of these papers is large, and their focus ranges from psychosocial aspects of depression and anxiety disorders to its clinical course to their pathophysiology. The NESDA research infrastructure has obtained funding for almost 20 years now. This has not always been easy. Although we started out with a Dutch Scientific Research Organization grant and co-financing by our Universities and involved Mental Health Care Organizations, in the past decades lots of international organizations (e.g. the European Commission and the US National Institutes of Health) have contributed to NESDA's research infrastructure. We are very grateful for all financial contributions to our research infrastructure. Due to these, we are still able to extend our data collections and maintain a very well-organized data management system. We are proud to hear from many external researchers that they find the NESDA database easy to work with through its clear structure and documentation materials.

The goal of this special issue is to help provide some basic overviews of key findings of NESDA and to provide some novel new insights in specific recent additions to the NESDA study. The special issue starts with an overview paper by Penninx et al. (2021) that describes the longitudinal design, the types of assessments conducted over the 9 years of follow-up and the expected new initiatives in the coming years. It reports on some basic characteristics of the NESDA cohort, the response rates over the waves and the subsequently added sibling cohort.

Subsequently, we published five review papers on NESDA findings around central themes within NESDA. The first review paper by Ter Meulen et al. (2021) summarizes findings of studies of comorbidity between depression and anxiety disorders. NESDA clearly showed that comorbidity is more rule than exception, and this comorbidity is linked to a poorer subsequent course and diverse negative consequences in terms of lifestyle and somatic health outcomes. The second review paper concerns the prevalence, course and determinants of suicide ideation and attempts in persons with depressive and/or anxiety disorders (Wiebenga et al., 2021). Especially suicide ideation was prevalent and both suicide outcomes were highly recurrent. Clear risk indicators were comorbidity of depression and anxiety, higher clinical severity, sleep dysfunctions, higher aggression and hopelessness, and childhood trauma. The third review paper by Kuzminskaite et al. (2021) zooms in on the 37 studies that were conducted within the NESDA research infrastructure to examine the impact of childhood trauma. The paper emphasizes the integral large impact of childhood trauma that exceeds mental health and causes maladaptive personality characteristics and cognitions, mild stress systems dysregulations, advanced biological aging, poorer lifestyle, somatic health decline and brain alterations. The fourth review paper by Struijs et al. (2021) reviewed 62 NESDA studies which identified both transdiagnostic psychological factors (e.g., neuroticism, low implicit self-esteem, repetitive negative thinking) that may help explain the comorbidity between affective disorders and overlap in symptoms, and indications for disorder-specific psychological factors (e.g., cognitive reactivity) which support the relevance of distinct disorder categories and disorder-specific mechanisms. These results point to the relevance of both transdiagnostic and disorder-specific targets for therapeutic interventions. Finally, the fifth review paper (van Tol et al., 2021) focuses on the neurobiological findings of the NESDA study through the neuroimaging substudy that was added at several waves. It illustrates some common morphological and neurocognitive abnormalities across individuals with depression and anxiety disorders. Risk factors including childhood maltreatment and specific risk genes had an emotion processing modulating effect, apparently stronger than effects of diagnostic categories. Furthermore, brain imaging data, especially during emotion processing seemed valuable for predicting the long-term course of affective disorders, outperforming prediction based on clinical information alone.

In addition to NESDA thematic review papers, this Special Issue also includes some empirical papers on themes that either reflect central themes of NESDA (e.g. long-term course and its predictors, or health care utilization) or new data collections with novel findings. Solis et al. (2021) reports on the latest longitudinal data from NESDA: the 9-year follow-up wave. Using data from five waves and applying a categorical, discrete approach, about 40% of depressed and anxious cases showed a chronic or intermittently recurrent course. However, when applying a dimensional approach that also takes subthreshold symptoms

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into account a higher persistence of affective symptoms became evident. The enduring, fluctuating presence of subthreshold affective symptoms likely predisposes patients to frequent relapse. Wardernaar et al. (2021) using machine learning subsequently analysed predictors of differential 9-year course patterns and concluded that determinants of depression and anxiety course are mostly shared and consist of sociodemographics (e.g. old age, young age of onset, low income) and clinical characteristics (e.g. participation disability, somatic disease). Domain-specific exceptions are healthcare use for depression and somatic arousal and distress for anxiety-severity course. In the subsequent paper of Wijekoon et al. (2021), longitudinal 6-year mental health care utilization patterns were examined and compared to clinical status during that same time. Among persons with mental health symptoms there were three groups of health care users: overusers, constant underusers and a group with a changing mismatch-to-match pattern. The latter was the largest group, comprising of about 60% of the sample which generally indicated a delayed care pattern. Experiencing suicidal ideation at least at one wave throughout the study was the most important predictor for receiving delayed mental healthcare instead of not receiving (underuse) of mental health care.

Vinkers et al., (2021) integrated biological stress system data from the NESDA study and illustrated that depressive and anxiety disorders were significantly associated with changes in three biological stress systems including HPA-axis hyperactivity, increased inflammatory activity, and a higher autonomic nervous system tone. Some differentiation was observed depending on symptom profiles (atypical, energy-related depression severity was linked to immune system markers, whereas melancholic depression severity was linked to HPA-axis hyperactivity), but generally findings were stronger for cumulative indices within and across these three stress systems illustrating that an integrated approach is needed to understand stress system functionality in affective disorders. In a NESDA substudy, Di Francesco et al. (2021) used data from a 2-week ambulatory monitoring study that used ecological momentary assessment and actigraphy to measure sleep patterns in 359 depression/anxiety patients and controls. It showed that, especially among depression/anxiety patients, better self-reported sleep quality predicted higher positive affect and lower negative affect ratings the same day, while lower negative affect ratings predicted better self-reported sleep quality. These results illustrate the predictive validity of ambulatory assessments of sleep and affect during regular daily-life and indicate that the value of mobile technologies to monitor and potentially intervene in patients to improve their affect should be further explored. Finally, the paper by van Sprang et al. (2021) used data from siblings of NESDA respondents. In 939 subjects, we analysed the risk of psychopathology in adult siblings of probands with affective disorders and found that half of the siblings has a lifetime history of affective disorder, which is 2–3 times higher compared to the general population. Non-affected siblings, reported higher psychosocial vulnerability than healthy controls. However, the only modest proband-sibling resemblance across psychopathology-related features found suggests that individual mechanisms differentiate clinical trajectories across the lifespan. Identification of these mechanisms is crucial to improve resilience in subjects with familial risk.

In all, we believe this special issue will give a broad overview of findings from the NESDA project covering 15 years of research. This is a great stimulus for another 15 years of NESDA research.

CRediT authorship contribution statement

Brenda WJH Penninx: Conceptualization, Writing – original draft. **Philip Spinhoven:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

None.

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Invited Commentary to Special Issue J Aff Disorders re NESDA studies

Longitudinal cohort studies in psychiatry

Genetic and environmental interactions throughout a person's life shape the aetiology and course of her mental disorder. When individual genetic, neurobiological and personal influences, as well as sociocultural and environmental elements and their interactions across many years, are taken into account, cohort studies allow researchers to more accurately define risks, course, treatment, and preventive approaches to mental disorders. The line between population-based and clinical cohorts is blurry. While the former is superior at studying early illness mechanisms and predictors, the latter has the ability to look at disease mechanisms and courses, as well as their predictors, throughout time in defined samples.

Prospective (longitudinal) cohort studies are extremely useful for analysing causal relationships, while real causality is determined through additional experimental trials. Cohort studies, on the other hand, are costly to undertake, are prone to attrition, and require a long period of follow-up to obtain usable data. Its usefulness is determined by the researchers' ability to maintain contact with the cohort members. Nonetheless, the results are vastly better than those obtained from cross-sectional research. Prospective cohort studies are considered to yield the most reliable results in observational epidemiology and biological psychiatry.

An influential historical clinical cohort study in psychiatry followed 406 patients with affective disorders (unipolar depression, bipolar illness, and unipolar and bipolar schizoaffective disorder) over 4 decades (Angst and Preisig, 1995). The prime reference in affective disorder research is the NESDA with its now 13-year follow-up, focusing on depression and anxiety disorders. It has yielded tremendous and exciting new perspectives, reshaping our view on the course, biology and classification of these syndrome clusters (Penninx and Spinhoven 2022; www.nesda.nl/nesda-english). A parallel approach is taken by the German FOR2107 (MACS; Kircher et al, 2019; for2107.de/?lang=en) with n = 3000 participants with depression, bipolar disorder, anxiety disorders, and schizophrenia enrolled, currently in its fifth year of follow-up. Importantly, there is data on structural and functional MR brain imaging from all subjects at all-time points.

The NESDA and the FOR2107/MACS are example longitudinal cohort studies that both characterize (epi-)genetic variability, data on individual experiences such as trauma, living space, income, education level, and the consequences of social exclusion or discrimination. Both examine the interplay between genetic variability and altering environmental conditions, as well as their effects on intermediate phenotypes (e.g. brain structure, cytokines, etc.). One common goal is to ich phenotypically complement symptom based diagnostic entities. Together with a standardized survey of behaviour under various experimental conditions and its neurobiological correlates, e.g. through imaging examinations or psychophysiological measurements, a comprehensive picture of the individual person in their life contexts relevant to the development of mental problems can be created.

Replication of findings across cohorts is one of the next moves forward in the future. The key challenges here are data harmonization and protection. One of the main goals is to be able to forecast individual course trajectories and provide precision interventions. Machine learning algorithms provide a powerful conceptual and analytic framework that can integrate a variety of data types and sources. An integrative approach characterizes neurobiological components as pathophysiological functional modules nested within the complex social dynamics that shape the phenomenology of mental disorders.

Role of the Funding Source

The German Research Foundation provided funding for the FOR2107/MACS cohort.

CRediT authorship contribution statement

Tilo Kircher: Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

There is no conflict of interest.

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Research paper

Cohort profile of the longitudinal Netherlands Study of Depression and Anxiety (NESDA) on etiology, course and consequences of depressive and anxiety disorders

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ABSTRACT

Introduction: The Netherlands Study of Depression and Anxiety (NESDA, www.nesda.nl) is a longitudinal, multi-site, naturalistic, case-control cohort study set up to examine the etiology, course and consequences of depressive and anxiety disorders. This paper presents a cohort profile of NESDA.

Methods and Results: The NESDA sample recruited initially 2329 persons with a remitted or current DSM-IV based depressive (major depressive disorder, dysthymia) and/or anxiety disorder (panic disorder, social phobia, agoraphobia, generalized anxiety disorder), 367 of their siblings and 652 healthy controls, yielding a total of 3348 participants. Half-day face-to-face assessments of participants started in 2004 and since then have been repeated six times over a period of 9 years. A 13-year follow-up assessment is ongoing, at what time we also recruit offspring of participants. Retention rates are generally high, ranging from 87.1% (after 2 years) to 69.4% (after 9 years). Psychiatric diagnostic interviews have been administered at all face-to-face assessments, as was monitoring of clinical characteristics, psychosocial functioning and somatic health. Assessed etiological factors include e.g. early and current environmental risk factors, psychological vulnerability and resilience factors as well as (neuro)biology through hypothesis-driven biomarker assessments, genome-wide and large-scale '-omics' assessments, and neuroimaging assessments.

Limitations: The naturalistic design allows research into course and consequences of affective disorders but is limited in treatment response interpretation.

Conclusions: NESDA provides a strong research infrastructure for research into depressive and/or anxiety disorders. Its data have been used for many scientific papers describing either NESDA-based analyses or joint collaborative consortia-projects, and are in principle available to researchers outside the NESDA consortium.

How did the NESDA study come about?

Depressive and anxiety disorders are both listed in the disease burden top ten of the World Health Organization,(Vos et al., 2017) thereby having huge impact on health care utilization, societal costs, and public health. In addition, it is clear that there is a relative under-investment for mental health research when compared to other research fields.(Hazo et al., 2019) These two key facts were the prime reasons for the Dutch Scientific Organization (ZonMW) to grant funding for a 10-year program focusing on depressive and anxiety disorders. This research grant has provided the basis to design the Netherlands Study of Depression and Anxiety (NESDA, www.nesda.nl) in 2004. After the initial funding by ZonMW, additional funding has been obtained from involved universities and mental health care organizations as well as from supporting grants by national and international funding agencies. The combined resources have paid for NESDA's currently available research infrastructure.

As we described in our design paper in 2008,(Penninx et al., 2008)

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NESDA's main goals are to achieve more complete understanding of the etiology of depressive and anxiety disorders and obtaining a completer picture of the naturalistic course and societal and somatic consequences of depressive and anxiety disorders over the long term. As depressive and anxiety disorders are complex disorders with risk factors and consequences of multiple life domains involved, a research program into these disorders should by definition be interdisciplinary in set-up. That is why from the start, multiple research groups (e.g. psychiatry, psychology, epidemiology, (neuro)biology, genetics, sociology, general practice) from three different universities (VU Medical Center, Leiden University Medical Center and University Medical Center Groningen) have been involved. Local, active partners involved also various Mental Health Care Organizations who contributed through co-financing, recruitment and provision of researchers. This academic-clinical collaboration – embedded within a signed NESDA consortium agreement - ensured a thoroughly interdisciplinary approach fitting the scope of NESDA.

What are the main research areas that NESDA covers?

As described in our original baseline cohort profile,(Penninx et al., 2008) the overall objectives of NESDA are:

1) To improve understanding of the naturalistic long-term prognosis of depressive and anxiety disorders in terms of course (e.g. chronicity, recurrence, development of comorbidity, and suicidality) and public health consequences (disability, morbidity, mortality, health care utilization, and costs).
2) To improve understanding of clinical, psychosocial, (neuro)biological and genetic risk factors of depressive and anxiety disorders and their long-term course and consequences.
3) To examine patient's expectations, evaluation and provision of (mental) health care and their association with the long-term course and consequences of depressive and anxiety disorders.

In order to address these objectives, NESDA was designed as a naturalistic, longitudinal cohort study including participants from different health care settings (community, primary care and specialized mental health care) and in different stages of the developmental history of disorders (no history, high familial risk, subthreshold disorders, first and recurrent episodes). So, both healthy controls (those without any evidence of mental disorders) as well as persons with remitted or current depressive and/or anxiety disorders were included. It is good to realize that the diverse recruitment strategy led to the inclusion of both persons who received mental health care for current or earlier episodes as well as persons who did not. Given the debate about the validity of the categorical distinction and the undisputed close relationship between depressive and anxiety disorders in terms of shared symptoms and etiology,(Gaspersz et al., 2018; Penninx, 2015) NESDA studied depressive and anxiety disorders in concert, focusing on comorbidity patterns and employing both a dimensional and a categorical approach to the diagnoses of depressive and anxiety disorders.

It is important to emphasize that NESDA should be regarded as an overarching research infrastructure intended to foster specific research projects addressing focused research questions and hypotheses. The basic research funding received (by ZonMW, Universities and involved mental health care organizations, see www.nesda.nl) pays for personnel (trained research fieldwork staff and data managers) that work on the central data collection. Basic research funding does not pay directly for researcher time. Researchers who work on NESDA data are either academic or clinical staff at the involved universities and mental health care organizations, hired PhD-students or postdocs paid through additionally obtained funding, or external researchers affiliated with other institutions.

Since the original study set-up in 2004, many ancillary research projects have been embedded (see for examples Table 1) that have led to enrichment of the research infrastructure both in terms of additional researcher time and in terms of enrichment of the data. These ancillary studies e.g. gathered additional genome-wide genetics, transcriptomic, epigenomic, proteomic and metabolomic data (to better address objective 2). But ancillary studies have also lead to e.g. additional information on smartphone-based ecological momentary assessment and wearable-based actigraphy and to additional recruitment of siblings and offspring data. This illustrates that the NESDA research infrastructure has shown its value in stimulating other research collaborators and investors to help enrich it. NESDA data have been used for over 700 scientific papers by the NESDA consortium as well as (inter)national collaborating researchers (all output is listed on www.nesda.nl).

Table 1
Examples of ancillary projects that were embedded in the Netherlands Study of Depression and Anxiety and enriched its research infrastructure.

Ancillary study	Additional data the study brought in	Founder
Genome-wide genetic study of major depressive disorder	Genome-wide DNA data in all NESDA respondents with North-European ancestry	GAIN program of NIH
Genome-wide transcriptomics study of major depressive disorder	Genome-wide transcriptomic data in 2262 samples with North-European ancestry (1848 baseline, 414 2-year follow-up)	Godot program of NIH
Epigenetics in Major Depressive Disorder	Genome-wide sequenced epigenetics data in 1132 respondents at baseline	National Institute of Mental Health
Subclinical cardiovascular disease (CVD) status in affective disorder	Arterial stiffness and carotid-intima media thickness measures in subset of 649 respondents at 2-year follow-up	Netherlands Heart Foundation
Metabolomics profile in major depressive disorder	Metabolomics data (Brainshake platform) in all baseline and 6-year blood samples	Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL)
Addiction behavior and pathways in affective disorder	Alcohol biomarker analyses in all respondents, neuroimaging data collection in 68 respondents at 4-year follow-up	Scientific Dutch Organization
Various biological enrichments	Assessments of e.g. inflammatory markers at various waves, and baseline tryptophan pathway indicators and proteomic markers	Jansen Research, Boehringer Ingelheim and Myriad Genetics-RBM
NESDA EMA and actigraphy study	Smartphone-based ecological momentary assessment and actigraphy-tracking of mood and behavior during 2 weeks	Dutch Universities involved
NESDA sibling project	Additional recruitment and data collection in 367 siblings of NESDA patients at 9-year follow-up	Dutch Universities involved
Mood And Resilience in Offspring (MARIO) project	Additional recruitment and data collection in ~400 (expected) 10-25 year old offspring of NESDA participants at 13-year follow-up	Scientific Dutch Organization
NESDA COVID-19 online study	Various online data collections of mood and behavior during the COVID-19 pandemic (April 2020-ongoing)	Scientific Dutch Organization and EU-H2020 program

What is the NESDA design and assessment set-up?

NESDA's design is that of a naturalistic, longitudinal, multisite, case-control cohort study. After a baseline face-to-face assessment, subsequent follow-up data collection waves took place after 1, 2, 4, 6, and 9 years. See Fig. 1 for the timeline of NESDA assessments. The 1-year follow-up only contained self-report questionnaires, all other assessments consisted of a face-to-face assessment. These face-to-face assessments lasted on average three to four hours and took place at one of the research sites in the three regions around Amsterdam, Leiden and Groningen in The Netherlands. Data collection of these assessments consisted of face-to-face interviews, a medical examination, self-report questionnaires, cognitive/emotional computer tasks and – at most waves - biobanking with stored blood, and at specific waves additional saliva, hair or stool sampling. In a subgroup, structural and functional neuroimaging was conducted at various data collection waves. More detailed description of data collection is given below. Currently, the 13-year follow-up assessment is ongoing and is expected to be finalized in 2022. In 2020, we started online questionnaire assessments around the COVID-19 pandemic, in order to examine the impact of the pandemic and its quarantine measures on mental health.(Pan et al., 2020) These assessments will be repeated bi-weekly through bi-monthly (depending on societal restriction severity) till the end of the pandemic.

We did all possible efforts to keep participants motivated to continue participation in the study. For instance, if participants could not travel to the research site, they were offered transportation by taxi. If persons were living far away from the site (e.g. because they moved) or if they did not want to come to the site they were offered in-home assessment, for which a van was equipped with all assessment tools necessary to conduct the assessment as were it a clinic site. Ultimately, if participants also did not want to participate in in-home assessments, we offered phone or online assessments. Although the latter sometimes yielded incomplete information (e.g. of experimental computer task data), we attempted to collect as much data as possible (e.g. tried to arrange a blood draw) in order to reduce potential selective dropout.

Assessments were administered with computer-assisted personalized interviewing procedures with data entry checks on outliers and routing. All interviews were taped to monitor data-quality and interviewer performance. When the assessment was completed, participants were compensated with a small incentive (gift certificate of 15 euro and payment of travel costs) for their time and cooperation. Assessments were conducted by specially trained research staff (often consisting of nurses or psychologists) who were intensively supervised. After a 1-week training, they were certified to conduct assessments after approval of audiotapes of at least two complete interviews. Question wording and probing behaviour of interviewers was constantly monitored by checking a random selection of about 10% of all taped interviews. In addition, a continuous monitoring system of interviewer variances and interviewer specific item-non response was maintained through computer analyses.

As NESDA's goal is to describe the *naturalistic* course and consequences of depressive and anxiety disorders, we do not actively intervene in the eventual treatment process. Consequently, participants did not get specific feedback about their mental health symptoms or disorders, as measured during any of the assessments. We only actively acted in case of high current suicidality (as e.g. evident from the CIDI psychiatric interview). In these cases, research staff did inform both the participants and their health care providers, for which we had obtained informed consent. In addition, we provided some general feedback on blood pressure, glucose and HDL cholesterol and triglyceride measures. This was primarily done as a gesture to participants; if findings needed clinical attention, we advised participants to contact their general practitioner (GP). GPs also received a copy of the blood marker results by mail and were thus informed of the participants' (continued) participation to NESDA.

Reflection on design

It is important to note that NESDA's observational, naturalistic design does provide some limitations in data utilization and interpretation. Three main limitations are listed here. First, interpretation of treatment information that we collected on our respondents is limited. That is, respondents in our study who used antidepressant medication or were in treatment by a psychologist or psychiatrist may not be directly comparable to respondents who did not. Confouding-by-indication is likely contributing to differences among those who did and those who did not get specialized mental health care. In addition, provided treatments were not standardized by study design, so large variation in quality of health care provision across participants is likely present. Consequently, interpreting NESDA's longitudinal data in terms of treatment response is limited as there was no standardization of treatment, and discontinuation of treatment can e.g. be indicative of both successful as well as unsuccessful treatment response. Second, NESDA has a wide variety of variables and instruments assessed. This provides ample opportunities to explore unique associations within our database. The large statistical power due to our large sample size may indicate significance of associations that do not always reflect clinical relevance or large effect sizes. Also the opportunity to replicate findings is not

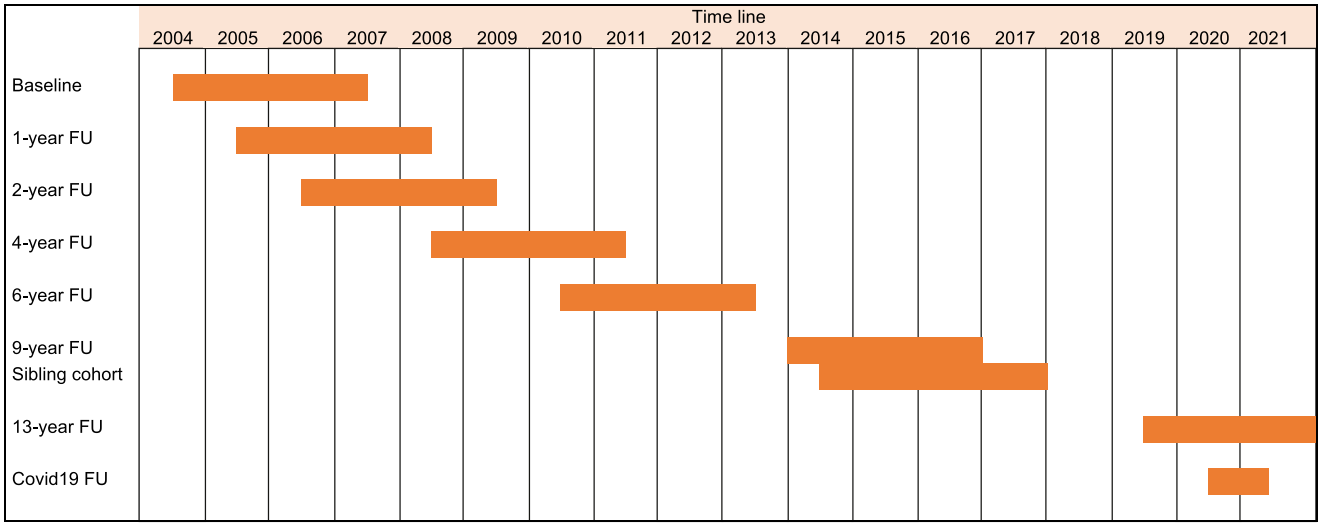

Fig. 1. Timeline with NESDA assessment schedule.

always possible as there is not a completely similar cohort elsewhere. Third, observational cohort studies – even those with longitudinal analyses – are not able to provide definitive causal inference. Causal inference often will require experimental approaches as well. However, observational cohort study results could elucidate further which associations are worth exploring in subsequent intervention designs.

Who are the NESDA participants?

The original NESDA sample was recruited between September 2004 and December 2006. NESDA's research protocol was approved by the ethical review board of each participating research center in Amsterdam, Leiden, and Groningen (METC number 2003-183). All participants provided written informed consent after having received detailed verbal and printed study information. Participants were adults (18-65 years) with or without DSM-IV based depressive and/or anxiety disorders (current or remitted; Composite International Diagnostic Interview, CIDI(Robins et al., 1988)). Participants were recruited from community, primary health care, and specialized mental health care, as described in more detail before.(Penninx et al., 2008) Patients with other clinically overt primary diagnoses (e.g., post-traumatic stress disorder, bipolar disorder, psychotic disorder, obsessive-compulsive disorder) were not included, as were persons not fluent in Dutch. In total, 2981 participants (2329 individuals with and 652 individuals without a lifetime diagnosis of depressive and/or anxiety disorders) were recruited and participated in the baseline assessment. The mean age at that time was 41.9 years (SD=13.0) and 68% was female. Table 2 provides details on sample size as well as age, gender and psychiatric status at all waves. Overall, retention rates were good, e.g. 87.1% at 2-year follow-up reducing to 69.4% at 9-year follow-up. The role of mortality on dropout is minor: A total of 59 subjects (2.0%) are known to have died during the first 9 years of follow-up. We earlier described that independent determinants of attrition at the 2-year follow-up assessment were sociodemographics (younger age, less educated, non-North-European descent, living in Amsterdam) as well as psychiatric variables (major depressive disorder and higher symptom severity).(Lamers et al., 2012) Rather similar findings were observed when we compared long-term attrition. Compared with participants who participated in at least 4 of the 5 follow-up waves (75.8%, n=2260), those who missed two or more follow-up waves (24.2%, n=721) had significantly less years of education (11.3 years versus 12.4 years, p<.001) and were more likely to have a (current) anxiety and/or depressive disorder at baseline (71.0% versus 52.6%, p<.001). Age (41.8 years versus 42.1 years, p=.66) and sex (66.4% versus 66.3%, p=.95) did not differ between participants with ≥4 waves of data versus those with <4 waves.

During the 9-year follow-up, we newly recruited 367 siblings from 256 NESDA participants with a lifetime anxiety and/or depressive disorder, totaling the number of participants to 3348. Siblings were selected when they had 100% the same biological parents as the NESDA participants and underwent a face-to-face interview that gathered much of the same information on psychopathology, psychosocial functioning and health outcomes as the standard NESDA assessments. This additional sample allows for examination of the family context within the development of depression and anxiety disorders. For this, we can e.g. compare patient-sibling discordances and concordances in aspects of mental health and psychosocial functioning. (de Kluiver et al., 2020; Kullberg et al., 2020) At the currently ongoing 13-year follow-up, we invite both the initial NESDA participants and their siblings for an additional data collection wave.

A recent extension to the NESDA projects concerns data collection in offspring. In parallel to the 13-year follow-up wave, we are recruiting 10-25 year offspring of NESDA participants for the Mood and Resilience in Offspring project (MARIO, www.mario-project.nl). This project provides opportunities to examine vulnerability and risk factors in this high-risk population and to address intergenerational research questions in the near future. In 2021-2022, we are planning to recruit also older offspring (25-50 years) thereby generating further possibilities to especially examine resilience in a high-risk population, it is also informative to compare those who are not developing mental health disorders despite their high-risk situation in order to better understand what potential protective mechanisms are.

What has been measured in the NESDA project?

Table 3 provides an extensive overview of the measurements included at the data collection waves conducted so far. This overview illustrates a few key features of the study. First, NESDA's scope is highly multidisciplinary. Central outcomes measured encompass both mental and physical health conditions as well as various indicators of social functioning. Such measures are collected at all assessment waves, so that e.g. course patterns can be determined. Determinants encompass a wide range of biological, lifestyle, psychological and social/environmental markers. Depending on changeability of determinants, some determinants are repeated, others are only assessed once or a few times, so that novel assessments could be incorporated allowing research on new research topics.

Table 2
Sample characteristics at the various waves of the Netherlands Study of Depression and Anxiety (NESDA).

	Wave and type of information							
	T0 Wave 1	FU1 Wave 2	FU2 Wave 3	FU4 Wave 4	FU6 Wave 5	FU9 Wave 6	FU9 Sibs	FU13 Wave 7
Average follow-up duration since baseline	Baseline	1 year	2 years	4 years	6 years	9 years	baseline	13 years
Mode of assessment	Int, ME & Written Q	Written Q	Int, ME & Written Q	Int & Written Q	Int, ME & Written Q	Int, ME & Written Q	Int, ME & Written Q	Int, ME & Written Q
Sample size	2981	2445	2596	2402	2256	2069	367	TBD
Response rate (ref=baseline)	Na	82.0%	87.1%	80.8%	75.7%	69.4%	na	TBD
Cumulative number of deaths	Na	2	6	21	30	59	na	TBD
Mean age (in years) Age range	41.9 (18-65)	43.8 (18-67)	44.0 (19-68)	46.0 (21-70)	47.8 (23-72)	50.8 (26-75)	51.0 (20-78)	TBD
% Female	66.4%	67.9%	66.1%	66.4%	66.3%	66.1%	55.3%	TBD
Persons with current* depressive and/or anxiety disorders	57.1%	na	37.4%	31.9%	28.5%	27.5%	23.7%	TBD
Persons with remitted** depressive and/or anxiety disorders	21.1%	na	41.7%	48.1%	51.7%	53.4%	26.2%	TBD
Persons without any lifetime depressive and/or anxiety disorders	21.9%	na	20.9%	20.0%	19.8%	19.1%	50.1%	TBD

* current is based on 6-month recency; ** remitted is based on lifetime, but not current, diagnosis; TBD=to be determined as this follow-up is still ongoing; Int=Interview, ME=Medical Examination, Q=Questionnaire.

Table 3
Overview of concepts and instruments used in the various waves of the Netherlands Study of Depression and Anxiety (NESDA).

Concept	Instrument	Wave and type of information							
		T0 W1	FU1 W2	FU2 W3	FU4 W4	FU6 W5	FU9 W6	FU9 Sibs	FU13 W7
Sociodemographics	Age, gender, education/income, ethnicity, religion, household & partner status, work status	I		I	I	I	I	I	I
Mental Health									
Psychiatric diagnoses	Composite International Diagnostic Interview (CIDI), sections Depression, Dysthymia, Bipolar, Panic Disorder, Social Phobia, Agoraphobia, Generalized Anxiety Disorder, Alcohol Use	I, GP	GP	I	I	I	I	I	I
Depression symptoms	Inventory of Depressive Symptoms	SR	SR	SR	SR	SR	SR	SR	SR
Anxiety symptoms	Beck Anxiety Inventory Fear Questionnaire Penn-State Worry Questionnaire	SR	SR	SR	SR	SR	SR	SR	SR
Suicidality	Beck Scale for Suicide Ideation	I		I	I	I	I	I	I
Manic symptoms	Mood Disorder Questionnaire	SR		SR	SR	SR	SR	SR	
Postnatal depression	Edinburgh Postnatal Depression Scale				SR				
Course of symptoms	Life-chart	I		I	I	I	I	I	I
Seasonality of symptoms	Seasonal Pattern of Affective Symptoms		SR	SR			SR	SR	
Substance use	Alcohol Use Disorders Identification Test	SR		SR	SR	SR	SR	SR	SR
Borderline / antisocial features	Personality Assessment Inventory - Borderline Features Scale					SR		SR	
OCD symptoms	Young Adult Self-Report-obsessive-compulsive symptoms score Obsessive Compulsive Inventory-R			SR					SR
ADHD symptoms	Conners' Adult ADHD Rating Scale				SR				
Posttraumatic stress	PTSS-scale of complaints				SR				
Psychotic symptoms	Community Assessment of Psychic Experiences								SR
Mental health symptoms	Distress from 4-Dimensional Symptom Q Somatization symptoms	SR SR		SR SR	SR SR				
Functioning, general health and health care									
Disability	WHO-Disability Assessment Schedule II	SR	SR	SR	SR	SR	SR	SR	SR
Disability days, work productivity	WHO-Disability Assessment Schedule II	I		I	I	I	I	I	I
Somatic conditions	Somatic disorder Q	I		I	I	I	I	I	I
Pain	Chronic Graded Pain Scale, migraine Q	SR		SR	SR	SR	SR	SR	SR
Cognition	Digit span WAIS-II Executive functioning (N-back)			T		TT			T
Health service utilization	Trimbos/iMTA Q for Costs-Psychiatry (TIC-P)	I GP	SR GP	I	I	I	I	I	I
Medication use	Medication container inspection	I GP	SR GP	I	I	I	I	I	I
Adequacy of care	Perceived need for care Q Patient evaluation of care (QUOTE Q)	I		I	I	I			
Mortality	Data and cause of death	P	P	P	P	P	P	P	P
Psychology and personality									
Anxiety cognitions	Anxiety Sensitivity Index	SR		SR			SR	SR	SR
Depression cognitions	Leiden Index of Depression Sensitivity Revised Q	SR		SR	SR	SR	SR	SR	
Locus of control	Pearlin & Schooler mastery scale	SR		SR	SR	SR	SR	SR	SR
Personality	Neuroticism-Extraversion-Openness Five Factor Inventory Type D personality scale	SR		SR	SR	SR		SR	SR
Anger trait and attacks	Spielberger Trait Anger Subscale; the Anger Attacks Questionnaire				SR				
Behavioral inhibition/approach	Behavioral Inhibition System-Behavioral Activation System scales				SR				
Approach/avoidance	Approach-Avoidance Task				T	T			
Repetitive negative thinking	Perseverative Thinking Questionnaire	SR				SR	SR		
Attentional bias	Exogeneous Cueing Task			T	T				
Implicit emotion association	Implicit Association Test (depression, anxiety, self-esteem, social rank)	T		T		T	T	T	T
Sensation seeking	Sensation Seeking Scale				SR				
Psychological flexibility	Acceptance and Action Q			SR	SR				
Happiness	Ratings of happiness					SR	SR	SR	SR
Optimism	Life Orientation Test Revised				SR				SR
Positive health	Post-Traumatic Growth Inv, Meaning in Life Q								SR
Life style									
Smoking, drug use	Past + current smoking, Fagerstrom Q, drug use	SR		SR	SR	SR	SR	SR	SR
Sleep	Insomnia Rating Scale	I		SR	SR	SR	SR	SR	SR
Physical, sport & free time activity	International Physical Activity Q	SR		SR	SR	SR	SR	SR	SR
Morning-eveningness	Munich Chronotype Q			SR			SR	SR	
Emotional eating, food intake	Dutch Eating Behavior Q, Food Frequency Q						SR		
Environmental/social factors									
Family history & composition	Family tree	I					I	I	
Important life events	Brugha List of Threatening Events Q	I	SR	SR	SR	SR	SR	SR	SR
Childhood Trauma	NEMESIS Interview, Childhood Trauma Q	I			SR			SR	
Daily hassles	Daily Hassles Q	SR							
Work content/environment	Job Content Q	SR							SR
Relationship with parents	Parental Bonding Inventory						SR	SR	
Loneliness	de Jong-Gierveld loneliness Q	SR		SR					SR

(*continued on next page*)

Table 3 (*continued*)

Concept	Instrument	Wave and type of information							
		T0 W1	FU1 W2	FU2 W3	FU4 W4	FU6 W5	FU9 W6	FU9 Sibs	FU13 W7
Social support	Close Person Inventory	SR		SR					
(Close) relationships	Experiences in Close Relations Dyadic Adjustment Scale Inventory of Interpersonal Problems						SR	SR	
Sexual functioning	Arizona Sexual Experience, Sexual distress								SR
Neighborhood characteristics	Zip-code based neighborhood characteristics					L			
(Neuro)biological assessments									
Blood biomarkers	Fasting blood sample collection & storage	ME		ME		ME	ME	ME	ME
Blood DNA	Genome-wide (epi)genetic information	ME		ME		ME	ME	ME	ME
Blood RNA	Genome-wide transcriptomic information before and after LPS-challenge	ME		ME					
Saliva biomarkers	6 saliva samples during one day, one the next morning after dexamethasone ingestion	ME							
Autonomic nervous system function	2-hour registration of heart rate (variability) and pre-ejection period	ME		ME		ME	ME		ME
Hair biomarkers (e.g. cortisol)	Hair collection					ME	ME	ME	
Microbiome	Stool collection & biobanking								ME
Physical fitness	Body mass index, hand grip strength, peak flow	ME		ME	ME	ME	ME	ME	ME
Cardiovascular condition	Blood pressure, ankle arm index Carotid atherosclerosis, arterial stiffness (subsample)	ME		ME ME		ME	ME	ME	ME
Brain imaging	Structural, functional (with emotion, cognitive paradigms), DTI, resting-state (subsample)	MRI		MRI			MRI	MRI	MRI
Ambulatory mood and behavior (2-week registration in daily life)	Actigraphy with actiwatch and ecological momentary assessment with smartphone						EA	EA	

SR = self-report; I = interview, GP = data collection through GP records; B = data collection via fasting blood sample; T = computer task, ME = medical examination; Q=Questionnaire; L= linkage based data collection (with Central Bureau of Statistics data); P= data obtained through proxy/informant; MRI = structural + functional Magnetic Resonance Imaging; EA = Ecological momentary and Actigraphy assessment during 2 weeks; LPS=lipopolysaccharides.

Second, the information is collected using various methods. Face-to-face interviews are complemented with self-report questionnaires, medical examinations, experimental computer tasks, neuroimaging assessments and extensive biobanking including blood, saliva, hair and stool samples. In addition, linkage with e.g. GP registries as well as the Central Bureau of Statistics have contributed to additional data collections. In later waves, data collection included ecological monitoring assessment using active and passive tracking through mobile phones and actigraphy.(Difrancesco et al., 2019; Schoevers et al., 2020)

What has the NESDA project found so far?

At the time this cohort profile was written, over 700 articles have been published in the scientific literature. An overview of these publications can be found on the NESDA website (www.nesda.nl). The number of publications and width of the topics under study preclude a comprehensive overview of all findings here. However, a few areas of key output are listed below.

Pathophysiology of depressive and anxiety disorders. Both the presence of depressive and anxiety disorders have been linked to hyperactivity of the HPA-axis,(Gerritsen et al., 2019; Vreeburg et al., 2010, 2009) low-grade inflammation(Lamers et al., 2019; Vogelzangs et al., 2013, 2012) and a dysregulation of the autonomic nervous system.(Hu et al., 2018; Licht et al., 2010, 2008) Proteomics and metabolomics studies further indicated systemic differences in e.g. lipid and immune markers between depressed patients, but not between anxiety patients and controls.(Bot et al., 2019, 2015) NESDA contributes to large-scale collaborative data sharing projects, e.g. in the context of genome-wide genetics studies within the Psychiatric Genetics Consortium(Sullivan et al., 2009; Wray et al., 2018) and in the context of neuroimaging studies within the ENIGMA Consortium.(Schmaal et al., 2017, 2016)

Course of depressive and anxiety disorders. Analyses of the 6-year course patterns of persons with depressive disorders yielded a picture that showed that chronicity (2 years of consecutive symptoms) is more the rule than the exception, especially when applying a broad perspective on mental health course.(Verduijn et al., 2017) Quite many depressed persons switch from depression into anxiety disorders (and back). Consequently, a focus on the course of symptoms of the index disorder at baseline only, does provide a too optimistic picture of the true course pattern. In this special issue of the Journal of Affective Disorders, we describe the 9-year course of depressive and anxiety disorders, and again confirm that for many participants these disorders have a chronic impact on their lives.(Solis et al., 2021) NESDA analyses have also examined whether we can predict the course trajectories of depressive and anxiety disorders within individuals using collected baseline characteristics. Using machine learning analyses, it appeared that individual prediction of course patterns is only partly possible, in which baseline clinical characteristics – but not biological or psychosocial characteristics - have the largest role.(Bokma et al., 2020; Dinga et al., 2018)

Heterogeneity of affective disorders. Heterogeneity of depressive and anxiety disorders is huge, which contributes to inconsistent research findings and small treatment effects.(Nandi et al., 2009) Understanding the diversity of these conditions may help us identify preventable and/or treatable factors that are only associated with specific subtypes or dimensions of these common disorders. A necessity for examining such heterogeneity is the availability of large cohorts of persons with disorders that have been richly phenotyped so that we can examine e.g. symptom networks or dimensions, or specific pathophysiological mechanisms *within* a patient (sample). This could significantly support the identification of subgroups or subdimensions within the larger pool of depression or anxiety patients that should be targeted for future personalized treatment strategies.

In NESDA we have examined the heterogeneity within the large group of depressed patients. As an example, using NESDA data, we described in various papers that immunometabolic dysregulations map more consistently to atypical behavioral depressive symptoms reflecting altered energy intake/expenditure balance (hyperphagia, weight gain, hypersomnia, fatigue and leaden paralysis).(Lamers et al., 2020, 2018; Milaneschi et al., 2017) This combined pathophysiology and symptom profile, which we termed immunometabolic depression, may negatively moderate the antidepressant effect of standard therapeutic approaches. (Milaneschi et al., 2020) However, it may be more responsive to other, novel (e.g. anti-inflammatory or lifestyle) therapeutic approaches and

therefore deserves future (treatment) studies that examine its clinical importance.

The heterogeneity of anxiety disorders has so far received less attention. In many NESDA papers, we examined the impact of type of anxiety disorder (e.g. panic disorder, social phobia or generalized anxiety disorder) but generally have found that type of anxiety disorder seems to be less important in associations with sociodemographics, biomarkers or course determination.(Ter Meulen et al., 2021) However, this research is complicated by the fact that many persons with anxiety disorders have multiple disorders.(Hovenkamp-Hermelink et al., 2016) The severity, number and disability of anxiety disorders appears to be more relevant than the specific type of anxiety disorder in associations with e.g. risk determinants and course.(Batelaan et al., 2014; Klein Hofmeijer-Sevink et al., 2012; Spinhoven et al., 2016)

Synthesis of other findings in NESDA. This special issue of the Journal of Affective Disorders includes a few papers in which we give a synthesis of key findings around certain central NESDA themes. For instance, Ter Meulen et al. (Ter Meulen et al., 2021) synthesized the high prevalence and the strong impact that comorbidity of depressive and anxiety disorders had in NESDA. Wiebenga et al. (Wiebenga et al., 2021) described results of the various NESDA papers that examined suicidality ideation and attempt prevalence, correlates and course patterns. NESDA's findings on the impact of childhood trauma on the functioning of the brain, mind, and body, which together contribute to a higher vulnerability for affective disorders, are summarized by Kuzminskaite et al.(Kuzminskaite et al., 2021) Also, NESDA's findings (van Tol et al., 2021) regarding the neuroimaging correlates of depressive and anxiety disorders are part of this special issue of the Journal of Affective Disorders.

Can I work with NESDA data?

With some delay, NESDA data are made available to scientific researchers outside the NESDA consortium. Some data, such as the genome-wide DNA and RNA data, are available online through the DBgap site of NIH (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000486.v1.p1). Most other data are not freely accessible, but access can be obtained by submitting a publication proposal. Providing that the proposed publication does not overlap with already published NESDA findings or with ongoing research activities, permission to use the data requested is given for a period of 1 year, and automatically withdrawn if the manuscript has not been submitted for publication within that period. A data sharing agreement needs to be signed in line with current General Data Protection Regulation (GDPR) guidelines. There could be a small fee involved in getting access to the data, in order to support covering our central data management efforts involved. More information and a publication proposal form can be obtained via the website (www.nesda.nl) or the principal investigator (nesda@ggzingeest.nl). NESDA adopts a publication bias prevention policy, which implies that all research questions and hypotheses specified in the publication proposal should be included in the manuscript, regardless of the significance of the findings.

Conflict of interest

BP has received (unrestricted) research funding from Boehringer Ingelheim and Jansen Research. Other co-authors have nothing to declare.

CRediT authorship contribution statement

Brenda W.J.H. Penninx: Conceptualization, Funding acquisition, Project administration, Writing - original draft. **Merijn Eikelenboom:** Conceptualization, Project administration, Writing - review & editing. **Erik J. Giltay:** Conceptualization, Writing - review & editing. **Albert M. van Hemert:** Conceptualization, Funding acquisition, Writing - review & editing. **Harriëtte Riese:** Conceptualization, Writing - review & editing. **Robert A. Schoevers:** Conceptualization, Funding acquisition, Writing - review & editing. **Aartjan T.F. Beekman:** Conceptualization, Funding acquisition, Writing - review & editing.

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Review article

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

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ABSTRACT

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

1. Introduction

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

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

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

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

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

2. Methods

2.1. Search strategy

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

2.2. Study sample and depressive and/or anxiety diagnosis

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

2.3. Outcome measures

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

3. Results

3.1. Study selection

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

3.2. Prevalence and temporal sequence

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

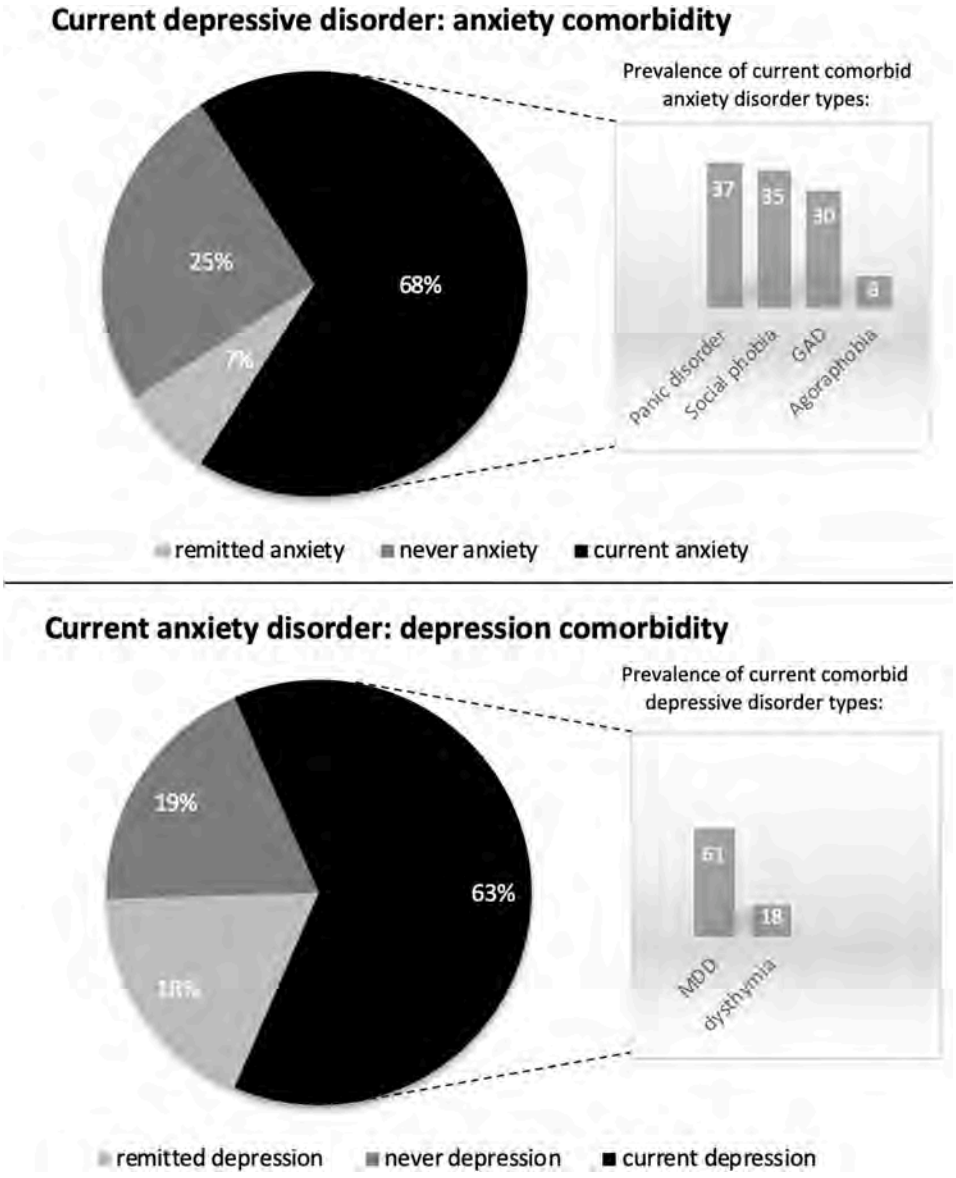

Fig. 1. Comorbidity patterns among those with current (12-month) depressive (upper pie chart; n=1275) and current anxiety (bottom pie chart; n=1363) disorders in NESDA at baseline. The column charts at the right show the type and percentage of anxiety comorbidity in depressive disorders (upper column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

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

3.3. Course

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

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

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

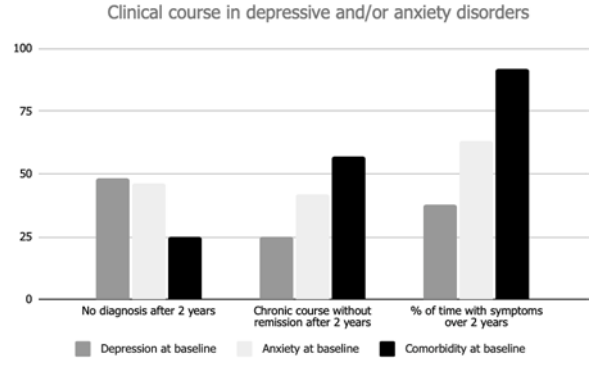

Fig. 2. Clinical course indicators over 2 years in n=1209 subjects with current (1-month recency) single depressive (dark grey; n=267), single anxiety (light grey; n=487) or comorbid disorders (black; n=455) at baseline (data based on (Penninx et al., 2011)).

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

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

3.4. Longitudinal patterns

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

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

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

3.5. Sociodemographic and vulnerability indicators

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

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

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

3.6. Neurobiological indicators

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

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

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

3.7. Functional, somatic and other mental health indicators

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

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

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

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

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

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

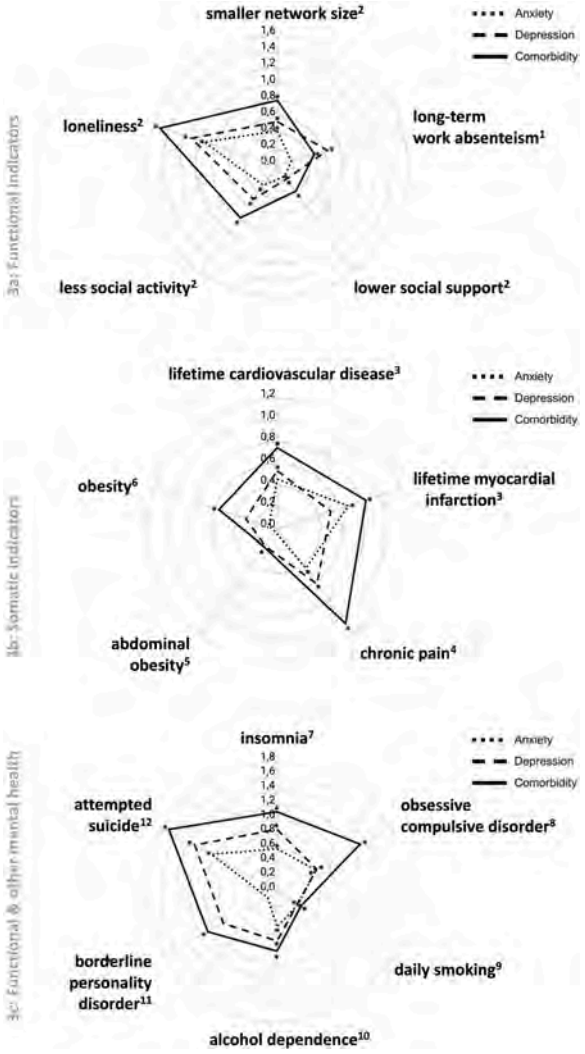

Fig. 3. Spider graphs displaying effect sizes (ES) of several cross-sectional outcome indicators of single anxiety disorders (dotted line), single depressive disorders (striped line) or comorbid depressive and anxiety disorders (continuous line), versus controls as reference group. Corresponding ES and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

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

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

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

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

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

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

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

4. Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

Data availability

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

Author statement

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

Declaration of Competing Interest

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

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Supplementary materials

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

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Prevalence, course, and determinants of suicide ideation and attempts in patients with a depressive and/or anxiety disorder: A review of NESDA findings

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ABSTRACT

Background: Depressive and anxiety disorders are often associated with suicide ideation (SI) and attempt (SA). However, analyses of prevalence, course, and more specific risk mechanisms are needed to improve knowledge and detection of high risk individuals with depressive and anxiety disorders. Previous studies often lacked statistical power, assessment of detailed determinants and follow-up measurements.
Methods: The Netherlands Study of Depression and Anxiety (NESDA), a large cohort study, overcomes some earlier limitations. Scale for Suicide Ideation and Compositive Interview Diagnostic Instrument data were analyzed to report on prevalence of SI and SA. Additionally, important sociodemographic, clinical, psychological, environmental, and neurobiological determinants and course of SI and SA identified in depressive and/or anxiety disorder respondents in 16 NESDA articles were summarized.
Results: Within respondents with 12-month diagnosis (n=1,783), SI and 12-month SA prevalence ranged from 17.1-20.1% and 0.8-3.0% respectively across 5 waves during 9-year follow-up and SI was highly recurrent. Both SI and SA were especially associated with comorbid depression and anxiety, higher clinical severity, sleep dysfunctions, higher aggression and hopelessness, and childhood trauma. In the (neuro)biological domain, SI was linked with immune dysregulation and SA with abnormal brain activity during emotion processing and genetic risk.
Limitations: Most articles were cross-sectional in nature, preventing causal inferences and no conclusions could be drawn about the overall magnitude of results.
Conclusion: SI and SA are multifactorial phenomena and especially prevalent amongst comorbid depressive and anxiety respondents. Considering many overlapping SI and SA determinants, more neurobiological determinants and use of innovative methodological techniques are desirable.

1. Introduction

Suicide is a major worldwide public health concern with almost 800.000 deaths each year (Turecki & Brent, 2016; WHO, 2016). In most cases, suicide is paired with mental disorders. Of all individuals that die by suicide, approximately 60% were found to be diagnosed with a depressive disorder in a study by Cavanagh et al. (2003). Suicide risk is also increased in individuals with an anxiety disorder (Bentley et al., 2016) and a comorbid depressive and anxiety disorder is paired with a higher suicide risk than either disorder alone (Bolton et al., 2010).

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However, results on the prevalence of suicide ideation (SI) and attempts (SA) in depressed and anxious individuals have been found to be inconsistent (Dong et al., 2019). Amongst patients with a major depressive disorder, estimates of lifetime SA varied from 5 to 15% (Baldessarini et al., 2019; Chen & Dilsaver, 1996). Also, the prevalence of SI has consistently been found to be higher than that of SA's, but the extent of this difference can also vary widely. To the best of our knowledge, there have been no epidemiological studies thus far examining the prevalence of SI and SA in patients with a depressive and/or anxiety disorder across time.

Despite variation in prevalence rates, it can be said that the majority of individuals with a depressive and/or anxiety disorder do not think about, let alone attempt or commit suicide (Baldessarini et al., 2019). Although this is fortunate, relying solely on these disorders to determine suicide risk can lead to many false-positives and a lack of predictive power. Therefore, more specific determinants of important suicidal processes (*e.g.* SI and SA) that transcend mentioned mental disorders need to be identified (May & Klonsky, 2016; O'Connor & Nock, 2014). Improving detection of high risk individuals and identifying treatable targets within this population may aid clinicians and inform suicide models. Thus far, a multitude of studies have investigated suicide risk factors and it has become clear that, besides depression and anxiety, a wide range of other variables play a role in the emergence of suicidal processes (Franklin, 2017; Turecki et al., 2019). Previous research indicates that suicidal processes involve an interaction between predispositional and developmental factors and stressors (O'Connor & Nock, 2014; Turecki et al., 2019; Van Heeringen & Mann, 2014) and this line of thought has been incorporated in various contemporary models of suicide (e.g. Jollant et al., 2011; Klonsky & May, 2015; O'Connor & Kirtley, 2018). Predispositional factors may include biological underpinnings and traumatic childhood events. Examples of stressors are clinical factors like mental disorders or environmental factors like life events such as loss of jobs or a partner. Developmental factors such as personality traits and cognitive deficits might mediate the relationship between predispositional factors and stressors (Lengvenyte et al., 2019; Schmaal et al., 2020; Turecki et al., 2019; Van Heeringen & Mann, 2014).

However, it has been found that specific determinants of suicidal processes can vary per population, meaning that suicide has a remarkably heterogeneous etiology (Turecki & Brent, 2016). This further emphasizes the need to study a major subgroup such as individuals with depressive and/or anxiety disorders in isolation. Interestingly, few studies have focused their attention on this subgroup (Baldessarini et al., 2019; Hawton et al., 2013; Uebelacker et al., 2013). Often such studies have also been limited by small sample sizes, mainly focusing on sociodemographic and clinical variables, decreased generalizability by using inpatient groups, and a lack of analyses differentiating respondents that act on suicidal thoughts via a SA from respondents with suicidal thoughts that do not (Aaltonen et al., 2019; Abreu et al., 2018; Batterham, et al., 2013; Hawton et al., 2013; May & Klonsky, 2016; Oquendo et al., 2006). The Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2008) is a large, ongoing longitudinal cohort study that has the ability to overcome several of these limitations. NESDA includes an array of variables from sociodemographic, clinical, psychological, environmental, and biological domains that provides a basis for comprehensive, holistic examinations of determinants of SI and SA. NESDA also allows for investigations of determinants of future SI or SA and the course of SI in depressed and/or anxious patients, which are especially scarce (Abreu et al., 2018; Hawton et al., 2013; O'Connor & Nock, 2014; Oquendo et al., 2006).

Therefore, the present review summarized NESDA data and results in order to: (1) describe the prevalence and course of SI and SA over time and (2) present an integrated overview of the most important cross-sectional and longitudinal sociodemographic, clinical, psychological, environmental, and neurobiological determinants of SI and SA within individuals with a depressive and/or anxiety disorder.

2. Methods

2.1. Eligibility criteria

Research articles included in this review needed to: 1) make use of NESDA data, 2) include analyses of SI or SA in respondents with a depressive and/or anxiety disorder, and 3) focus on the relationship between sociodemographic, clinical, psychological, environmental, and/or neurobiological factors and the outcomes SI and/or SA or examined the course of SI or SA. Articles were excluded if: 1) the main aim of the article was to evaluate psychometric properties of suicide risk assessment instruments and 2) the article was not submitted to a scientific journal by August 3, 2020.

2.2. Information sources

Comprehensive searches were performed in various databases in order to obtain a complete overview of the associations found between the five variable domains and suicide ideation and attempt, and the course of suicide ideation and attempt within NESDA. The primary source of relevant NESDA articles was the NESDA website (www.nesda.nl), since it has a collection of all research articles published in a peer-reviewed journal using NESDA data and submitted research proposals. To verify that no relevant articles were missed, the following databases were additionally consulted: PubMed, Embase, PsycInfo, Web of Science, and Scopus. Furthermore, authors with an active, unpublished research proposal were requested to provide information about the status of their article.

2.3. Search strategy and study selection

Database searches were conducted by two investigators (J.W. and S.M.). Within the NESDA publications database, the search term "suicid*" was used to scan titles. For other databases, the following definitive search strategy was implemented and was minimally adapted depending on the database: ("suicid*"[Title/Abstract] AND ("NESDA"[Text Word] OR "Netherlands Study of Depression and Anxiety"[Text Word])) OR ("Penninx"[All Fields] AND "suicid*"[All Fields]). Publication dates could run from inception to August 3, 2020. The articles found were evaluated by the two investigators, who were blinded during the process, using Rayyan (Ouzzani et al., 2016). First, articles found were compiled in Rayyan and screened using titles and abstracts. Second, full-text articles were examined. Lastly, investigators resolved any discrepancies with the help of a third investigator (J.D.). The procedure of selecting studies can be found in a PRISMA (Moher et al., 2009) flow diagram (Fig. S1).

2.4. Measurement of suicidality and psychiatric diagnoses

SI and SA were measured in NESDA using various instruments. On waves 1 and 3 to 6, SI in the past week was measured using the five screening items of the Scale for Suicidal Ideation (SSI; Beck et al., 1979). A positive score on one of the items meant that SI was present. On wave 1 and 3 the history of SA was assessed with the following yes/no question that was taken from the WHO/Euro multicenter study on parasuicide (Platt et al., 1992): "Have you ever made a serious suicide attempt to end your life, for instance by harming or poisoning yourself or by getting into an accident?". This question was followed by questions about the number of lifetime attempts and the last time an attempt was made. On wave 4 to 6, history and number of SA's were only assessed since the last interview. Questions were similar to the ones of earlier waves. For all analyses in the present article, a SA in the past year was used at each wave. A past year SA was obtained by determining whether the year of the last SA occurred within a year of the interview date of the respondent.

The presence of mental disorders as defined by the DSM-IV

classification system (American Psychiatric Association, 2001) were assessed using the Compositive Interview Diagnostic Instrument (CIDI) version 2.1 at waves 1 and 3 to 6. The psychometric properties of the CIDI were found to be good (Wittchen, 1994).

Approval for the study was granted by the Research Ethics Committee of the VU University Medical Centre (2003/183). Respondents were all asked to sign informed consent after receiving information about the study verbally and in writing. A detailed overview of the NESDA study can be found in Penninx et al. (2008).

2.5. Statistical analyses

The prevalence of current SI and a 12-month SA within respondents with a current depressive and/or anxiety disorder (1-year diagnosis) was calculated at each of the 5 waves. The total sample consisted of 2981 respondents (ages 18 to 65 years old) at baseline. Of the full sample, only respondents with a current depressive and/or anxiety disorder (1-year diagnosis) were included in analyses at each wave (*i.e.* wave 1 and 3-6). We also analyzed the number of times respondents, with a 1-year depressive and/or anxiety disorder at baseline and at least two follow-up measurements (n=823), had SI and a past year SA across all waves. The latter was done to get an indication of the variability of SI and SA within individuals with a depressive and/or anxiety disorder across time. Lastly, sample characteristics, including sociodemographic variables mean age and gender and the clinical variables mean severity of depression and anxiety, were calculated. IBM SPSS version 25.0 for Mac was used to calculate percentages and means and create graphs.

2.6. Synthesis of results

The prevalence of SI and SA within NESDA respondents with a depressive and/or anxiety disorder and NESDA articles analyzing the course of SI and SA will first be discussed. Next, an overview of the most important cross-sectional and longitudinal determinants identified for SI and SA within respondents with a depressive and/or anxiety disorder will be made per study domain (*i.e.* sociodemographic, clinical, psychological vulnerabilities, environmental risk, and neurobiological).

3. Results

3.1. Study selection

By searching the NESDA website, 12 articles (published between 2010 and 2020) were found that met inclusion criteria. Four more articles were included that were found via other databases (De Wit et al., 2020; Lamers et al., 2016; Peyrot et al., 2013; Van Eeden et al., 2019) and that were missed in the title search within the NESDA database (*see* Figure S1). These articles were either recently published online and not yet added to the NESDA database or the abstract and not the title contained the search terms. See Tables S2a and S2b for an overview of the included studies and their sample characteristics, outcome measures, included determinants, statistical analyses, and main findings. Three studies focused on the course of SI, twelve articles focused on cross-sectional determinants of SI and/or SA, and three studies focused on longitudinal determinants of SI or SA. Of these articles, one examined both cross-sectional as well as longitudinal determinants of SI and SA (De Wit et al., 2020) and one examined the course as well as longitudinal determinants of SI (Kivelä et al., 2019).

3.2. 9-year prevalence and course of suicidal ideation and suicide attempt

The prevalence of current suicidal ideation and a past year suicide attempt across waves in respondents with an anxiety, depressive, comorbid anxiety and depressive disorder and an anxiety and/or depressive disorder (1-year diagnosis) using NESDA data are presented in Figure 1. Within all individuals with an anxiety and/or depressive disorder, SI ranged from 17.1-20.1% and past year SA ranged from 0.8-3.0% across the 9-year follow-up period, showing that SI is far more prevalent than SA. Respondents with a comorbid anxiety and depressive disorder consistently had the highest percentage of SI and SA at each wave (SI: 24.7-31.3%; SA: 2.1-4.4%) and respondents with an anxiety disorder the lowest (SI: 6.1-11.3%; SA: 0.0-0.3%). Respondents with a depressive disorder fell in between the other two groups at each wave (SI: 15.2-18.1%; SA: 0.5-3.8%). The prevalence of SI was relatively stable and constant across waves, whilst the number of past year SA's, although negligible in individuals with an anxiety disorder, steadily decreased in the group with a depressive or comorbid depressive and anxiety disorder and the total sample. Further analyses revealed that SI and a past year SA were recurrent within a number of cases across waves. Of respondents with a 12-month depressive and/or anxiety disorder at baseline and at least two follow-up measurements (n=823), 20.8% experienced SI at one assessment point, 22.4% experienced SI at more than one, and 1.9% experienced SI at all assessment points across 9 years. Also, 4.4% experienced SA in the past year at one assessment point, 1.4% experienced SA in the past year at more than one, and, at the most, a past year SA was experienced at three assessment points by 0.7%

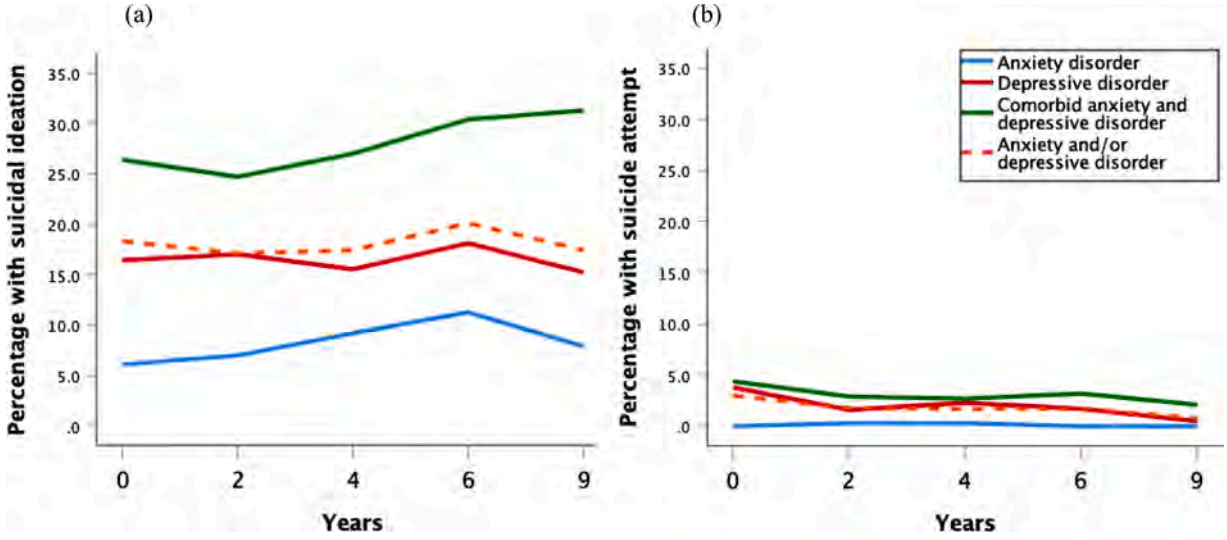

Fig. 1. Percentage of (a) current suicidal ideation and (b) past year suicide attempt among persons with a current (1-year recency) depressive, anxiety, comorbid depressive and anxiety disorder and depressive and/or anxiety disorder at the various waves during 9-year follow-up.

of respondents. These numbers indicate that especially SI is highly recurrent with almost a quarter of the respondents with a depressive and/or anxiety disorder experiencing current SI at multiple assessment points across a long period of time.

As presented in Table S1, the number of participants with an anxiety and/or depressive disorder decreased from 1783 participants at baseline to 634 participants at 9-year follow-up. As the total number of participants with an anxiety and/or depressive disorder decreased, so did the clinical severity of patients. The latter is based on a consistent decrease in the number of participants with a comorbid anxiety and depressive disorder over the years and a decline of the severity of depression and anxiety after two years as was measured with the Inventory of Depressive Symptomatology - self rate version (IDS-SR; Rush et al., 1996) and Beck Anxiety Inventory (Beck et al., 1988) respectively. Although the latter finding compliments the steady decrease in SA's, it does not coincide with the relative stability of SI over the years.

Three NESDA articles were published on the course of SI across time and all found that SI is highly recurrent in various groups of respondents (Lamers et al., 2016; Kivelä et al., 2019; van Eeden et al., 2019), which is in line with previously mentioned results. A 9-year follow-up study by Van Eeden et al. (2019) found that there was little within-person variability with regards to SI as a symptom in patients with a 1-month major depressive disorder at baseline. The severity of SI, as measured using item 18 (*i.e* 'thoughts of death or suicide') of the IDS-SR, was quite stable and presented little fluctuations over time. Patients that had SI at the baseline measurement generally tended to continue to have suicidal ideation across future measurements and those without SI at baseline were unlikely to develop it later. The 9-year follow-up study by Kivelä et al. (2019) found that of the NESDA respondents with SI at baseline, as measured by the SSI, 33% reported SI after 2 years, 31% after 4 years, 26% after 6 years, and 23% after 9 years. Within participants with SI at baseline, 16% continued to have SI at all assessment points. Kivelä et al. (2019) furthermore found that, although SI was relatively recurrent, the severity of SI did decrease over time in participants with SI at baseline. Those with more hopelessness had a significantly greater decrease of suicidal ideation over time and those with more borderline personality traits had less decline of suicidal ideation over time. In a 6-year follow-up study by Lamers et al. (2016), it was found that, amongst respondents with a major depressive disorder, specifically individuals with a severe melancholic subtype had more persistent SI compared to those with a severe atypical or moderate subtype. No articles using NESDA data were published investigating the course of SA.

3.3. Cross-sectional determinants of suicidal ideation and suicide attempt

3.3.1. Sociodemographic determinants

SI. Results of cross-sectional sociodemographic, clinical, psychological, and environmental determinants of SI and SA can be found in Table 1. Although sociodemographic variables such as age, employment status, and income could not differentiate SI from non-suicidal respondents (Eikelenboom et al., 2012; Wiebenga et al., 2020), small significant associations were found between male gender (Eikelenboom et al., 2012) and more years of education (Wiebenga et al., 2020) and higher SI.

SA. There is an indication that higher age may play a role in increasing the likelihood of SA compared to a non-suicidal group (Eikelenboom et al., 2012), although the same result was not found for currently suicidal respondents with a past SA compared to non-suicidal individuals (Wiebenga et al., 2020). Fewer years of education was associated with SA when compared to non-suicidal individuals in three articles (Eikelenboom et al., 2012; Peyrot et al., 2013; Wiebenga et al., 2020), but only significantly in two (Eikelenboom et al., 2012; Peyrot et al., 2013). Gender, employment status, and income did not distinguish SA from

Table 1
Cross-sectional sociodemographic, clinical, personality, and psychosocial determinants of suicidal ideation and suicide attempt.

Variable Domain	SI vs. NS[a]	SA vs. NS[a]	SA vs. SI[a]	Discussion of results
Sociodemographic				
Age in years	= (1,2)	= (2) ↑ (1)	= (2)	SA vs. NS: small significant association was found between higher age and SA in 1
Gender, female	= (2) ↓ (1)	= (2)	= (2)	SI vs. NS: Female gender decreases likelihood of SI in both 1 and 2, but only significant in 1
Years of education	= (1) ↑ (2)	= (2) ↓ (1,6)	↓ (2)	SI vs. NS: small positive association in 1 and 2, but only significant in 2 SA vs. NS: negative association with SA in 1, 6, and 2, but only significant in 1 and 6
Employment	= (2)	= (2)	= (2)	
Income	= (2)	= (2)	= (2)	
Non-Western descent (versus Western)	= (2)	= (2)	↑ (2)	
Clinical				
Depressive disorder (versus anxiety disorder)	↑ (1,2)	= (2) ↑ (1)	= (2)	SA vs. NS: increased likelihood of SA in 1 and 2, but only significantly in 1
Comorbid depressive and anxiety disorder (versus anxiety disorder)	↑ (1,2)	↑ (1,2)	= (2)	
Lifetime alcohol use disorder	= (2)	↑ (2)	= (2)	
Severity of depression	↑ (1,2)	↑ (1,2)	= (2)	
Severity of anxiety	↓ (1)	= (1)		
Age of onset	↓ (1)	↓ (1,2)	= (2)	
Duration of symptoms	= (1,2)	= (1,2)	= (2)	
Use of psychotherapy or antidepressants	= (2)	= (2)	= (2)	
Insomnia	↑ (4)	= (4)		
Sleep duration	↑ (4)	↓ (4)		
Psychological vulnerability				
Extraversion and other Five-Factor Model traits	↓ (2) = (2)	= (2)	= (2)	SI vs NS: lower extraversion associated with SI
Hopelessness	↑ (3) = (2)	↑ (3) = (2)	↑ (3) = (2)	Increased likelihood of past SI and SA in all comparisons in remitted depressed patients
Aggression	= (3) ↑ (2)	↑ (3,2)	= (2) ↑ (3)	SI vs. NS: increases likelihood of SI in current depressive and/or anxiety disorder SA vs. NS: increases likelihood of SA in current depressive and/or anxiety disorder and remitted depressed patients SA vs. SI: increases likelihood of SA in remitted depressed patients
Other cognitive reactivity profiles	= (3,2)	= (3,2)	= (3,2)	
Locus of control	= (2)	↑ (2)	= (2)	
Implicit depression association	↑ (5)	↑ (5)		
Implicit anxiety association	↑ (5)	↑ (5)		
Environmental risk				
Childhood trauma	↑ (2)	↑ (6,2)	↑ (2)	

(*continued on next page*)

Table 1 (*continued*)

Lifetime or recent stressful life events	= (2)	= (6,2) ↑ (6)	= (2)	SA vs. NS: positive association with lifetime stressful life events in 6. Not with recent stressful life events in 6 and 2.
Social support	= (2)	↓ (2)	= (2)	
Loneliness	= (2)	= (2)	= (2)	
Married or partner, yes	= (2)	= (2)	= (2)	

Abbreviations: NS = non-suicidal; SI = suicidal ideation; SA = suicide attempt.
Symbols: '↑' – significant positive association; '↓' – significant negative association; '=' – no significant association.
References: 1 = Eikelenboom et al., 2012; 2 = Wiebenga et al., 2020; 3 = Antypa et al., 2010; 4 = Dolsen et al., 2020; 5 = Glashouwer et al., 2010; 6 = Peyrot et al., 2013.
[a] Reference/comparison group.

non-suicidal respondents (Wiebenga et al., 2020).

SI vs. SA. When comparing SI and SA directly, individuals with SA were more likely to have a non-Western descent and less years of education (Wiebenga et al., 2020).

3.3.2. Clinical determinants

SI. The most consistent determinants for SI were a depressive disorder and comorbid depressive and anxiety disorder (both compared to an anxiety disorder) and higher severity of depression (Eikelenboom et al., 2012; Wiebenga et al., 2020). When compared to non-suicidal respondents, respondents with SI were also more likely to have a lower age of onset (Eikelenboom et al., 2012), lower severity of anxiety (Eikelenboom et al., 2012) and dysfunctional sleep in the form of insomnia and a longer sleep duration (> 10h) (compared to a normal sleep duration (7-9h)) (Dolsen et al., 2020). The duration of symptoms was most consistently not found as a determinant of SI (Eikelenboom et al., 2012; Wiebenga et al., 2020) and no associations were found between the use of psychotherapy or antidepressants and a comorbid lifetime alcohol use disorder and SI (Eikelenboom et al., 2012; Wiebenga et al., 2020). Taken together, several mental disorders and severity markers as well as sleep dysfunctions - both insomnia and hypersomnia - seem to play an important role in SI.

SA. A comorbid depressive and anxiety disorder (compared to an anxiety disorder) and higher severity of depression have been indicated as constant across two papers for respondents with SA compared to no suicidality (Eikelenboom et al., 2012; Wiebenga et al., 2020). The likelihood of SA was also higher in respondents diagnosed with a depressive disorder (Eikelenboom et al., 2012; Wiebenga et al., 2020), but only significantly in the article by Wiebenga et al., (2020), and a lifetime alcohol use disorder (Wiebenga et al., 2020). A short sleep duration (< 6h) (compared to a normal sleep duration (7-9h)) (Dolsen et al., 2020) was also associated with a SA. The severity of anxiety (Eikelenboom et al., 2012), use of psychotherapy or antidepressants (Wiebenga et al., 2020), insomnia (Dolsen et al., 2020), and especially the duration of symptoms (Eikelenboom et al., 2012; Wiebenga et al., 2020) did not differentiate SA from non-suicidal respondents. Further analyses of recurrent SA showed that more comorbid borderline personality traits were associated with recurrent SA, especially higher levels of 'anger' and lower levels of 'fights' (Stringer et al., 2013). Interestingly borderline traits were not associated with having had a single SA compared to no SA (Stringer et al., 2013).

SI vs. SA. Direct comparisons between SA and SI revealed that no clinical variables were able to differentiate SA from SI (Wiebenga et al., 2020).

3.3.3. Psychological vulnerabilities

SI. For the Big Five personality traits, consisting of neuroticism, extraversion, openness, agreeableness, and conscientiousness, only lower extraversion scores were associated with SI when compared to non-suicidal respondents (Wiebenga et al., 2020). Furthermore, when compared to non-suicidal respondents, no associations were found between SI and locus of control (Wiebenga et al., 2020) and the following four cognitive reactivity profiles: acceptance/coping, control/perfectionism, risk aversion, and rumination (Antypa et al., 2010; Wiebenga et al., 2020). Importantly, the only cognitive reactivity style associated with current SI was higher aggression (Wiebenga et al., 2020), although the same association was not found for respondents with a history of suicidal ideation (Antypa et al., 2010). However, higher hopelessness did increase the likelihood of past SI (Antypa et al., 2010), but not for respondents with current SI (Wiebenga et al., 2020). Lastly, having more implicit associations with anxiety and depression showed to be associated with SI (Glashouwer et al., 2010).

SA. In two articles, higher scores on aggression were found to increase the likelihood of SA in people with a remitted or current depressive and/or anxiety disorder (Antypa et al., 2010; Wiebenga et al., 2020) and higher hopelessness increased the likelihood of SA only in the remitted depressed group (Antypa et al., 2010). Other cognitive reactivity styles (Antypa et al., 2010; Wiebenga et al., 2020) and the Big Five personality traits (Wiebenga et al., 2020) were not found to play a role in SA. Furthermore, a higher locus of control (Wiebenga et al., 2020) and stronger implicit associations with anxiety and depression (Glashouwer et al., 2010) were also found in respondents with SA compared to no suicidality.

SI vs. SA. When directly comparing SA to SI, SA showed higher hopelessness scores (Antypa et al., 2010) and higher aggression scores (Antypa et al., 2010) than SI in remitted depressed patients only. Other psychological vulnerabilities were not able to distinguish SA from SI (Antypa et al., 2010; Wiebenga et al., 2020).

3.3.4. Environmental risk

SI. The only environmental risk factor associated with SI when compared to a non-suicidal group was suffering more childhood trauma

Table 2
Cross-sectional (neuro)biological determinants of suicidal ideation and suicide attempt.

Variable Domain	SI vs. NS[a]	SA vs. NS[a]	SA vs. SI[a]
Neuroimaging - functional MRI			
Bilateral fusiform gyri	= (1)	↓ (1)	↓ (1)
Bilateral amygdala	= (1)	= (1)	= (1)
Anterior cingulate cortex	= (1)	= (1)	= (1)
Dorsolateral prefrontal cortex	= (1)	= (1)	= (1)
Dorsomedial prefrontal cortex	= (1)	= (1)	= (1)
Inflammatory markers			
Interleukin-6	↑ (2)	= (2)	
C-reactive protein	= (2)	= (2)	
Tumor necrosis factor-α	= (2)	= (2)	
Plasma androgen levels			
Total testosterone	= (3)		
Androstenedione	= (3)		
5α-DHT	= (3)		
DHEAS	= (3)		

Abbreviations: NS = non-suicidal; SI = suicidal ideation; SA = suicide attempt; DHEAS = dehydroepiandrosterone sulfate; 5α-DHT = 5α−dihydrotestosterone; functional MRI = functional magnetic resonance imaging.
Symbols: '↑' – significant positive association; '↓' – significant negative association; '=' – no significant association.
References: 1 = Ai et al., 2018; 2 = Dolsen et al., 2020; 3 = De Wit et al., 2020.
[a] Reference/comparison group.

(Wiebenga et al., 2020).

SA. More experiences of childhood trauma were associated with SA when compared to non-suicidal individuals in two articles (Peyrot et al., 2013; Wiebenga et al., 2020). Lower social support (Wiebenga et al., 2020) and more stressful life events (lifetime) (Peyrot et al., 2013) were also found to play a significant role in increasing the likelihood of SA compared to non-suicidal individuals. Recent stressful life events, however, did not (Peyrot et al., 2013; Wiebenga et al., 2020) and neither did loneliness or the presence/absence of a partner (Wiebenga et al., 2020).

SI vs. SA. Although more childhood trauma was a determinant for both SI and SA when compared to non-suicidal respondents (Peyrot et al., 2013; Wiebenga et al., 2020), it was also the only environmental determinant that could distinguish SA from SI when directly compared to one another (Wiebenga et al., 2020). Participants with SA did show even more childhood trauma compared to solely SI.

3.3.5. *(Neuro)biological determinants*

SI. Results of (neuro)biological determinants for SI and SA from articles using NESDA data can be found in Table 2. In a NESDA subsample (n=301), we conducted structural and functional imaging assessments. We further assessed biological markers in fasting samples in all respondents (*i.e.* inflammatory marker levels, androgen status, and genetic information).

Using functional MRI, two tasks (*i.e.* 'Tower of London' and 'Facial Affect Recognition') were related to imaging outcomes; on both tasks no differences in brain activity for respondents with SI compared to non-suicidal respondents were revealed (Ai et al., 2018). When examining blood biomarkers, higher levels of the inflammatory marker interleukin-6 (IL-6) were found to be associated with a higher risk of SI, while C-reactive protein and tumor necrosis factor-α were not associated with SI when compared to non-suicidal respondents (Dolsen et al., 2020). No further associations were revealed between plasma androgen levels (*i.e.* total testosterone, Androstenedione, 5α-DHT, and DHEAS) and SI (De Wit et al., 2020).

SA. During a functional MRI task (*i.e.* the Facial Affect Recognition task), respondents with SA showed lower activation in the bilateral fusiform gyri compared to respondents without SA when confronted with pictures of emotional (angry, happy, neutral, sad, and fearful) faces (Ai et al., 2018). No differences were found between respondents with SA and without SA for the executive planning task (Tower of London) (Ai et al., 2018). No association was further found between three inflammatory markers (*i.e.* interleukin-6, C-reactive protein and tumor necrosis factor-α) and SA (Dolsen et al., 2020), nor between plasma androgen levels (*i.e.* total testosterone, Androstenedione, 5α-DHT, and DHEAS) and SA (De Wit et al., 2020) when compared to respondents without SA.

Samples from the NESDA cohort were also included in one meta-analysis about suicidal symptoms (*i.e.* SI, planning, or SA) and subcortical brain structure within the ENIGMA consortium (http://enigma.ini.usc.edu/) as well as to two Genome-Wide Association Studies (GWAS) investigating genetic risk variants for SA through collaboration within the Psychiatric Genomics Consortium (https://www.med.unc.edu/pgc/). In the meta-analysis on brain structure, no associations between subcortical volume and suicidal symptoms in MDD patients were found (Renteria et al., 2017). Only compared to healthy controls, respondents with MDD and suicidal symptoms showed smaller intracranial volumes and a trend of smaller subcortical volumes and larger ventricular volumes (Renteria et al., 2017). In one of the GWAS, respondents with SA and MDD showed one significant Single Nucleotide Polymorphism (SNP, rs45593736 an intron of the *ARL5B* - an ADP-ribosylation factor-like gene) and a weak association with a second SNP (rs28591567 in *LOC105374524* - a non-coding RNA) compared to respondents with MDD without SA (Mullins et al., 2019). In the second GWAS, six loci of the protein coding gene *ABI3BP* (ABI Family Member 3 Binding Protein) showed a suggestive association for MDD with SA, as compared to MDD without SA (Perlis et al., 2010). Findings from the GWASs could not be confirmed in replication cohorts (Mullins et al., 2019, Perlis et al., 2010). NESDA data was also combined with data from the NTR (Netherlands Twin Register; https://tweelingenregister.vu.nl/) to investigate the haplotypes of the 5-HTTLPR (a polymorphism of the serotonin transporter gene SLC6A4) and rs25531 (a SNP also in gene *SLC6A4*), in respondents with MDD and SA compared to MDD respondents without SA (amongst other comparisons) (Peyrot et al., 2013). No effect was found for the 5-HTTLPR/rs25531-haplotypes and respondents with SA.

SI vs. SA. Only one (neuro)biological NESDA study, investigated differences between respondents with SA compared to respondents with SI directly. Ai et al. (2018) revealed lower activation in the bilateral fusiform gyri during a facial affect recognition task (for all emotional faces) in SA compared to SI.

3.4. *Longitudinal determinants of suicidal ideation and suicide attempt*

Three articles were involved in investigating determinants of future SI and SA (De Wit et al., 2020; Eikelenboom et al., 2019; Kivelä et al., 2019). A 6-year follow-up study by Eikelenboom et al. (2019) found that especially sociodemographic and several clinical variables predict future SA. Predictors found were younger age, less years of education, unemployment, insomnia, current antidepressant use, current SI, and previous SA. Psychological vulnerabilities and environmental risk did not play a role in predicting future SA. Furthermore, De Wit et al. (2020) did not find plasma androgen levels, of the neurobiological domain, to predict future SI or SA. Lastly, Kivelä et al. (2019) investigated predictors of persistent SI versus non-persistent SI and found that persistent SI was predicted by insomnia and hopelessness, but not by any sociodemographic or environmental risk factors.

4. Discussion

In the present review, a thorough overview has been presented of the prevalence, course, and determinants of SI and/or SA in patients with a depressive and/or anxiety disorder using data from the 9-year cohort study NESDA. NESDA has allowed for comprehensive cross-sectional and longitudinal examinations of a wide variety of determinants for SI and SA. With the aid of a large patient cohort, extensive multivariate analyses, and a multifaceted approach to the complex phenomena of SI and SA in 16 papers, the integration of results in the current review has indicated that our comprehension of their prognosis and etiology has been further extended and solidified.

4.1. *9-year prevalence and course of suicidal ideation and suicide attempt*

Within NESDA respondents with a 1-year depressive and/or anxiety disorder, the percentage of respondents with current SI was relatively consistent at each measurement and much higher than the number of respondents with a past year attempt. Unlike SI, the percentage of respondents with a past year SA decreased across a time span of 9 years. The latter coincided with a decrease in the clinical severity of respondents as indicated by a decrease in the number of respondents with a comorbid depressive and anxiety disorder and severity of depression and anxiety over the years. NESDA papers by Eikelenboom et al. (2018) and Lamers et al. (2016) also mentioned that MDD patients lost to follow-up had a higher clinical severity and this was also found in the study by Kivelä et al (2019) where participants with incomplete data

were more likely to have a history of SA. Thus, the percentage of SA at follow-up measurements might be underestimated. Furthermore, not only were prevalence rates of SI stable within diagnostic groups over time, we also found that almost a quarter of the respondents with a recent diagnosis had a recurrent pattern of suicidal thoughts. SA was recurrent within a far smaller number of respondents.

Although the NESDA paper by Kivelä et al. (2019) also showed SI to be recurrent over time, within a number of respondents with SI at baseline, the severity of SI decreased. Van Eeden et al. (2019) further found that SI was a stable symptom over time in NESDA respondents with current MDD at baseline and, according to Lamers et al. (2016), this was especially the case in depressed patients with a melancholic subtype. Recurrence of SI over time was also found in other longitudinal studies, however, the number of assessment points have often been limited and investigations often involved a general population sample (Borges et al., 2008; Ten Have et al., 2009). Overall, although SI is experienced like a fleeting state for some, it seems likely that a significant number of respondents experience SI in a trait-like manner. This distinction underlies the importance of adapting research designs and may also have implications for prevention efforts (Klonsky, May, & Saffer, 2016).

As expected, respondents with a comorbid anxiety and depressive disorder had a higher percentage of SI and SA over time than respondents with an anxiety or depressive disorder (Bolton et al., 2010; Sareen et al., 2005; Uebelacker et al., 2013). Considering the 1-year prevalence of SA's of 8% in patients with MDD in a meta-analysis by Dong et al. (2019), the 1-year SA prevalence within NESDA, ranging from 0.8-3.0%, seems rather low in comparison. However, after excluding studies with a small sample size, the 1-year prevalence found by Dong et al. (2019) decreased to 2.6%, which is more comparable to results in the present study. As far as we know, the finding that the 1-year SA prevalence amongst anxiety disorders was consistently close to 0.0% gave new insights into this patient group.

4.2. Determinants of suicidal ideation and suicide attempt

Multiple determinants have been found for SI and SA's in patients with a depressive and/or anxiety disorder from various variable domains, emphasizing the complex nature of these phenomena. The findings complement the biopsychosocial model of suicide risk as presented by Turecki et al. (2019), which indicates that suicide risk is determined by a multitude of factors from the sociodemographic, clinical, psychological, environmental, and neurobiological domains. They attest to the idea that the etiology of suicide risk is heterogeneous and that the relative association between variables from these domains and suicide risk varies depending on the individuals at hand. In this review we have presented the most important determinants for SI and SA specifically in patients with depressive and/or anxiety disorders.

4.2.1. Sociodemographic determinants

Multiple socio-economic determinants were found to increase suicidality. Years of education was found to be one of the most commonly found sociodemographic determinants for suicidality, since it was associated with SI cross-sectionally and with SA both cross-sectionally as well as longitudinally. Also, it was one of the few determinants that was able to distinguish SA from SI when compared directly to one another. Noteworthy is that more years of education increased the likelihood of SI, but in all other comparisons decreased the likelihood of SA. Lower education has been found to be a determinant of attempt in various studies (May & Klonsky, 2016; Nock et al., 2008), but there is little understanding about how education confers suicide risk (Phillips & Hempstead, 2017). Another socio-economic factor found to play a role in predicting a future attempt was being unemployed, which is a result supported by previous studies that also indicated that unemployment was associated with suicidal acts in mood disorder patients (Baldessarini et al., 2019; Sarchiapone et al., 2007).

Although being female was found to be associated with an increased likelihood of SI and attempt in the general population at a cross-national level (Nock et al., 2008), male gender was found to independently increase the likelihood of suicidal ideation in NESDA respondents with a depressive and/or anxiety disorder. Male gender was also found to be a significant suicide risk factor in multiple meta-analyses investigating depressed respondents, but specifically for SA and death by suicide (Dong et al., 2019; Hawton et al.; 2013).

Lastly, non-Western descent was also one of only few variables to distinguish SA from SI directly. This result ties in with other studies that showed an increased SA risk in Dutch women of non-Western descent (Burger et al., 2009; Van Bergen et al., 2010, 2018). However, considering the lack of research in this area, it is a finding that requires further investigation.

4.2.2. Clinical determinants

Results found in the present study consistently support the importance of depressive and comorbid depressive and anxiety disorders as determinants of SI and SA. This has frequently been found in other studies (e.g. Bolton et al., 2010; Sareen et al., 2005; Uebelacker et al., 2013). Also, a comorbid lifetime alcohol disorder increased the likelihood of SA and comorbid borderline personality traits increased the likelihood of recurrent SA's and is in line with previous studies (Aaltonen et al., 2016; Sokero et al., 2003).

Higher depression severity and an earlier age of onset of a depressive or anxiety disorder were shown to consistently increase odds of SI and SA. This result was not surprising, considering that Oquendo et al. (2004) state that depression severity is one of the three most important predictors of suicidal behavior in patients with a mood disorder.

Other robust clinical variables were found besides indicators of diagnoses and clinical severity, such as sleep disturbances. Higher levels of insomnia increased the likelihood of SI, persistence of SI, and a future SA, a longer duration of sleep increased the odds of SI, and a shorter sleep duration was associated with a past SA. Recently a meta-analysis confirmed that insomnia is indeed significantly associated with SI and, to a lesser degree, with SA's (Harris et al., 2020).

Previous SI and SA's were found to significantly predict a future SA in depressed patients. This is not surprising, considering that a SA has been found to be one of the most robust predictors of another SA or death by suicide in multiple studies (Beautrais, 2011; Sokero et al., 2005; Uebelacker et al., 2013). Also, a SA has hardly been found to occur without first experiencing SI (Sokero et al., 2003; Spijker et al., 2010).

Lastly, it should be mentioned that SI and SA have many overlapping determinants, which might also explain why the clinical variables in NESDA could not distinguish SA from SI. A meta-analysis (May & Klonsky, 2016) and cross-national longitudinal study by Nock et al. (2009) found similar results.

4.2.3. Psychological vulnerabilities

Various personality traits were associated with SI and SA. Lower extraversion was associated with SI and no other associations were found between Five-Factor Model (FFM) personality traits and SI and SA. Aggression was associated with SI and SA and was one of two personality traits to distinguish SA from SI when compared directly to one another. Also, hopelessness was found to increase the likelihood of SI (past as well as persistent, but not current SI) and SA and could distinguish SA from SI, but mainly in remitted patients. Systematic reviews also consider higher hopelessness, lower levels of extraversion, and higher aggression to be important suicide risk factors (Brezo et al., 2006; Ribeiro et al., 2018). Other studies also found no further evidence for other FFM traits in mood disorder respondents in extensive multivariate analyses (Aaltonen et al., 2016; Spijker et al., 2010).

Lastly, evidence was found in NESDA that implicit depressive and anxiety associations might be associated with SI and SA. This is an important finding, considering the need for more objective measures of suicide risk. Self-report questionnaires and clinical interviews are prone

to problems such as social desirability, mood-congruent biases, errors in reporting SA's (Eikelenboom et al., 2014), and withholding information about suicidality (McHugh et al., 2019) and are not yet good enough at predicting which individuals are at greatest suicide risk (Lindh et al., 2020). However, the implicit self-beliefs did not provide additional variance over and above explicit self-depressive (anxious) beliefs. Developments in the suicidology field have led to a more suicide specific IAT testing implicit associations with death and suicide related words, which has shown to predict suicide risk beyond other putative suicide risk factors (Barnes et al., 2016).

4.2.4. Environmental risk

Childhood trauma was most commonly found to be associated with suicidality of all environmental risk factors studied. Associations were found between childhood trauma and SI and SA in multiple papers, and was one of few variables that could distinguish SA from SI. Other studies indicate that childhood trauma is a key suicide risk factor in patients with mood disorders (Aaltonen et al., 2016; Baldessarini et al., 2019; Lee & Jung, 2006; Jollant et al., 2011; Sarchiapone et al., 2007). Also, a meta-analysis by May & Klonsky (2016) found that a history of sexual abuse was one of the few putative suicide risk factors able to distinguish SA from SI.

Other environmental risk factors that determined SA were more lifetime stressful life events and less social support. According to the interpersonal-psychological theory of suicidal behavior (Joiner et al., 2009), a thwarted sense of belongingness, which could result from social isolation, is a key component contributing to suicidal desire. Furthermore, although the association between stressful life events and SA's was not robust, there is evidence from other studies that this determinant could be an important stressor involved in the suicidal process (Lee & Jung, 2006).

4.2.5. (Neuro)biological determinants

Of the limited (neuro)biological variables investigated in NESDA studies so far, a few were linked to SI and/or SA. Abnormalities were found for the fusiform gyrus (Ai et al., 2018) during an affect recognition task for SA compared to non-suicidal respondents and respondents with SI, while no results were revealed in a meta-analysis about structural MRI to which NESDA data was added (Renteria et al., 2017). The findings by Ai et al. (2018) are in line with the conclusions of a recent imaging review by Schmaal et al., (2019). They conclude that especially brain regions for reward and affect are related to suicidality. A recent meta-analysis by Huang et al. (2020), additionally revealed that only functional abnormalities play a role in individuals with suicidality, but not brain structure, which further confirms the findings in NESDA. Hence, more research into functional brain abnormalities (mainly in regions associated with emotion processing) is urgently needed.

Inflammation has been indicated as a contributing stress system that can influence suicide. Reviews have so far indicated that, although results have been heterogeneous for most inflammatory cytokines, the association between higher levels of IL-6 and SI and SA has commonly been found (Ganança et al., 2016; Black and Miller, 2015). A study of the NESDA cohort (Dolsen et al. 2020) also found higher levels of IL-6 in individuals with SI, but not in SA when compared to non-suicidal patients. The latter finding may be explained by the large number of possible confounders for which Dolsen et al. (2020) adjusted, which is often not done as extensively in other studies (Ganança et al., 2016), and results may vary depending on psychiatric diagnosis (Black & Miller, 2015). So far, we still know too little about inflammatory markers that specifically link to either SI or SA and further studies, especially longitudinally, are required.

Androgen levels, which have recently been indicated as risk factors for SA and death by suicide, as high androgen levels are linked to aggression and violent behavior (Lenz et al., 2019; Stefansson et al., 2016), were not identified as important determinants in NESDA (De Wit et al., 2020). This is surprising, considering the association between higher aggression and SI and SA that has been confirmed in NESDA (Peyrot et al, 2013; Wiebenga et al., 2020). So far, only a small number of studies have investigated androgen levels in individuals with suicidality and depression. Former studies that revealed a relation between androgen levels and suicide attempt were conducted in respondents with bipolar disorder (Sher et al, 2012, 2014) or schizophrenia (Markianos et al., 2009; Tripodianakis et al. 2007). The differences in NESDA findings compared to former studies might therefore be a reflection of general differences in persons with mental conditions instead of associations that are specific to suicidality per se.

Genetic variations were further found to link to SA in respondents with depression. In recent literature, several polymorphisms (*i.e.* a variance in a DNA sequence) have been found in association with suicide (Cheung et al., 2020), and the two GWASs included in the current review (Perlis et al., 2010; Mullins et al., 2019) contribute to these findings. The variety of genetic differences found in respondents with suicidality left us, so far, unable to pinpoint specific genetic risk markers linked to suicide risk (Mullins et al., 2020; Peyrot et al., 2013; Cheung et al., 2020; Mirkovik et al., 2016). Therefore, we need more replication studies and larger GWAS samples, to better understand the influence genetic variations have on suicidality. The findings regarding (neuro)biological determinants conclude that suicide underlies a complex interplay of (neuro)biological factors including functional brain abnormalities, inflammation, and polygenetic architecture.

4.3. Implications for future research

Although various important determinants of SI and SA have been identified in patients with a depressive and/or anxiety disorder, SI and SA have many determinants in common. Since only a few variables are able to distinguish attempt from ideation, more studies are needed that are able to disentangle determinants that are specific to SI and SA (May, Klonsky, & Klein, 2012; Qiu, Klonsky, & Klein, 2017).

This review has made it clear that NESDA data provide opportunities for further investigations of (neuro)biological determinants. Previous research has pointed out that other stress system dysregulations, besides dysregulations of inflammatory responses, in the HPA-axis and the autonomous nervous system may play a role in suicidality (Chang et al. 2016; O'Connor et al., 2016; Melhem et al., 2016; Wilson et al., 2016). To date, findings in this area remain inconsistent and understudied. Also, there are possibilities for further fMRI studies. We are in need of a more accurate picture about the brain regions involved in suicide. Since most former studies found a relation between functional abnormalities in regions responsible for the processing of emotions, future studies should focus on these. Furthermore, most of the neuroimaging studies investigated SA and not SI, therefore more studies should also include SI. In addition, we are in need of more GWASs in large samples, to be able to identify more genetic markers contributing to this polygenetic trait.

Also, innovative techniques to the study of determinants of SI and SA should be prioritized, such as network analysis that provides new insights into the way various determinants interact with SI and SA and each other and which determinants might be most important (De Beurs, 2017). Franklin et al. (2017) further recommends the application of modern statistical techniques such as machine learning, which is especially important with a multifactorial problem such as suicidal behavior. Furthermore, suicide is known to fluctuate rapidly over time and few studies are able to capture state changes during the onset of SI and SA. Ecological momentary assessment studies have the ability to overcome such problems by monitoring individuals in real-time (Kleiman & Nock, 2018).

Lastly, multiple papers identified an association between markers of socio-economic status, such as education and unemployment, and SI and SA, but research in this area remains scarce. Therefore, further studies into the mechanisms involved in this relationship and implementation of preventative interventions with regards to these factors should be performed. Especially during the current COVID-19 pandemic, when

unemployment figures and financial stress are rising, and keeping education accessible has become challenging (Gunnel et al., 2020).

4.4. Limitations

Despite the strengths provided by NESDA, the current review contains several limitations that should be noted. Unlike smaller-focused meta-analyses, the present review cannot draw firm conclusions about the general magnitude of the findings, since variables utilized in this review were investigated in a limited number of NESDA papers. Papers included in the review also varied methodologically. For example, some papers focus only on depressed patients, whilst others use both depressed and/or anxious patients and some papers focused solely on current diagnoses, whilst others include both current and remitted individuals. Also, the extent to which authors adjusted for other variables varied and most papers were cross-sectional, limiting conclusions that can be drawn about the independent contribution of variables found in some instances and causality respectively. Furthermore, respondents that were lost to follow-up were usually more clinically severe, which may have led to underestimation of prevalence rates.

5. Conclusion

Although a multitude of suicide risk factors have been discovered in the past, research has often been limited by sample size, a lack of comprehensive multivariate analyses and follow-up measurements, and generalizability. Few have examined the prevalence, course, and determinants of SI and SA specifically in a large longitudinal cohort of patients with a depressive and/or anxiety disorder in such a multifaceted way. It has become clear that, in the current sample, SI and SA are most prominent in individuals with a comorbid depressive and anxiety disorder and least prominent in patients with an anxiety disorder and suicidal ideation is highly recurrent over time. Also, NESDA results confirm the complex and multifactorial nature of suicide ideation and attempt. SI and SA are both especially linked with more and less years of education respectively, a depressive and comorbid depressive and anxiety disorder (when compared with anxiety disorders), higher clinical severity, sleep dysfunctions, higher hopelessness and aggression, and childhood trauma. SI was also associated with male gender, higher introversion, and immune dysregulation and SA with unemployment, alcohol use disorder, lower social support, abnormal brain activity during emotion processing, and genetic risk. Therefore, suicide risk assessment of people with a depressive and/or anxiety disorder should take into account multiple variable domains to improve early detection and treatment of at-risk individuals.

Contributors

B. Penninx and M. Eikelenboom are principal investigator and project manager respectively of the Netherlands Study of Depression and Anxiety and gave information about the dataset. All authors contributed to the conception and design of the study. J. Wiebenga, J. Dickhoff, and S. Mérelle contributed to the writing of the article and inclusion of articles in the review. J. Wiebenga performed the statistical analyses. B. Penninx and M. Eikelenboom gave advise on what statistical analyses needed to be performed. All authors provided feedback on drafts of the manuscript and interpreted the results and all authors have approved the final manuscript.

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Data Availability Statement

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

Declaration of Conflicting Interests

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.01.053.

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Review article

Childhood Trauma in Adult Depressive and Anxiety Disorders: An Integrated Review on Psychological and Biological Mechanisms in the NESDA Cohort

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ABSTRACT

Background: Childhood trauma (CT) has adverse consequences on mental health across the lifespan. The understanding of how CT increases vulnerability for psychiatric disorders is growing. However, lack of an integrative approach to psychological and biological mechanisms of CT hampers further advancement. This review integrates CT findings across explanatory levels from a longitudinal adult cohort – the Netherlands Study of Depression and Anxiety (NESDA).

Methods: We reviewed all studies ($k = 37$) from the NESDA cohort ($n = 2981$) published from 2009 to 2020 containing CT findings related to psychopathology and potential psychological and biological mechanisms of CT.

Results: CT was associated with a higher risk of anxiety and depressive disorders with the strongest associations in the comorbid group. CT predicted the onset of these disorders, recurrence, and poorer outcomes (more comorbidity and chronicity). CT was associated with maladaptive personality characteristics and cognitions (e.g., higher neuroticism and negative self-associations), mild stress systems dysregulations (heightened levels of cortisol and inflammation), advanced biological aging (increased epigenetic aging and telomere attrition), poorer lifestyle (higher smoking rate and body mass index), somatic health decline (e.g., increased metabolic syndrome dysregulations), and brain alterations (e.g., reduced mPFC volume and increased amygdala reactivity).

Limitations: Literature review of one cohort using mixed analytical approaches.

Conclusion: **:** CT impacts the functioning of the brain, mind, and body, which together may contribute to a higher vulnerability for affective disorders. It is essential to employ an integrative approach combining different sources of data to understand the mechanisms of CT better.

1. Introduction

Childhood trauma (CT) is one of the most robust and significant risk factors for depressive and anxiety disorders. CT is commonly defined as "all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation, resulting in actual or potential harm to the child's health, survival, development or dignity in the context of a relationship of responsibility,

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trust or power" [(World Health Organization (WHO) 1999), p.15]. CT is operationalized as emotional (or psychological) abuse, physical abuse, sexual abuse, and neglect (emotional or physical) before the age of 18 years (Butchart et al., 2006). There is uncertainty about the frequency and severity of CT worldwide, as it is mostly hidden and unreported due to fear, stigma, and societal acceptance of this type of violence (Pinheiro, 2006). Discrepancies between CT rates reported by child-protection agencies and community studies (self-report) suggest that most incidences of CT are underreported (Gilbert et al., 2009, Sedlak and Ellis, 2014). So far, sexual and physical abuse in childhood has been most frequently investigated, while emotional abuse and neglect the least (Gilbert et al., 2009, Moody et al., 2018). Unfortunately, CT is common in the clinical and general population. For instance, a recent systematic review on the international lifetime prevalence of self-reported CT combining clinical and general population revealed the rates of emotional abuse of approximately 21.7% in Europe and 23.9% in North America (Moody et al., 2018).

CT has severe and long-lasting effects on both mental and somatic health across the lifespan. About one-third of all adult-onset psychiatric disorders are related to CT (Sedlak and Ellis, 2014), with lifelong effects on morbidity and mortality (Gilbert et al., 2009, Chen et al., 2016). Moreover, CT increases the risk of negative life events, suicidality, sleep problems, and cognitive problems (Angelakis et al., 2019, Norman et al., 2012, van Harmelen et al., 2010). CT not only affects mental health but also increases the risk of obesity, diabetes, lung disease, and cardiovascular disorders (Widom et al., 2012, Danese and Tan, 2014). For instance, exposure to CT has not only been associated with three to four times increased risk for depression and anxiety but also with two to three times increased risk of adult cancer, respiratory and cardiovascular disease (Hughes et al., 2017). This is relevant as somatic health generally receives limited attention within psychiatry, notwithstanding higher mortality rates and a greatly reduced lifespan. There is increasing evidence that CT-related affective disorders represent a clinically distinct subtype of psychopathology (Teicher and Samson, 2013), characterized by earlier emergence, more severe and recurrent symptoms, as well as worse treatment outcomes be it psychotherapy, pharmacotherapy, or combined treatment (Teicher and Samson, 2013, Hovens et al., 2012, Miniati et al., 2010, Nanni et al., 2012, Nelson et al., 2017). Despite the severity and high prevalence of CT across affective disorders, it is largely unknown why and how CT is associated with persistently poor outcomes for both anxiety and depression, and no targeted treatments exist that reverse the detrimental effects of CT. CT is, therefore, a major public health problem, and arguably the most potent predictor of poor mental health across the lifespan.

Biological research findings suggest that severe stress in early life elevates cortisol levels that over-activate glucocorticoid receptor (GR). The consequence of this glucocorticoid overproduction during early life is the abnormal development of the stress systems (Lupien et al., 2009, Roberts and Lopez-Duran, 2019, van Bodegom et al., 2017). Although this response may be adaptive in the short-term, it comes at the cost of long-term maladaptation: a reduced capacity to adequately and dynamically respond to stress across the lifespan (McLaughlin et al., 2010, Daskalakis et al., 2013). Precise mechanisms of CT, leading to poorer outcomes across the lifespan are heterogeneous, spanning from psychological, environmental to the biological. Unraveling the mechanisms through which CT impacts mental health outcomes so far has been difficult, due to the methodological heterogeneity among the studies and the focus on one type of the mechanism. Hence, this review aims to summarize and integrate CT findings from a large longitudinal adult sample - The Netherlands Study of Depression and Anxiety (NESDA), in relation to psychopathology and discuss different psychological and biological mechanisms that may underlie the long-lasting impact of CT.

2. The Netherlands Study of Depression and Anxiety (NESDA)

The Netherlands Study of Depression and Anxiety (NESDA; $n = 2981$) is an ongoing longitudinal cohort study examining the course and consequences of depressive and anxiety disorders (Penninx et al., 2008). NESDA sample includes Dutch-fluent adults between 18 and 65 years old with a current or remitted depressive and/or anxiety disorder (78% Composite International Diagnostic Interview, CIDI) (Robins et al., 1988) and healthy controls (22%). Participants were recruited between September 2004 and February 2007 from three different settings: community (19%), primary health-care (54%), and specialized mental health-care (27%). Individuals with a primary clinical diagnosis of other psychiatric disorders, such as post-traumatic stress disorder, bipolar disorder, psychotic disorder, or obsessive-compulsive disorder, were excluded. All participants were assessed on various sociodemographic, lifestyle, (mental) health, and biological factors during a 4-hour clinic visit. A subgroup of NESDA participants ($n = 301$) with or without (healthy controls) depressive and/or anxiety disorder underwent magnetic resonance imaging (MRI) assessment at the baseline. These individuals aged between 18 and 55 years and had no history of major internal or neurological disorders. NESDA protocol was approved by the ethical review board of each participating research center in Amsterdam, Leiden, and Groningen. All participants provided written informed consent. More detailed information on NESDA can be found in Penninx et al. (Penninx et al., 2008).

Within NESDA, CT was examined in 37 articles (identified from the list of all publications to date on the NESDA website: www.nesda.nl) focused on psychopathology as well as potential psychological and biological mechanisms underlying CT. Exposure to CT in NESDA was assessed twice: at the baseline using the structured Childhood Trauma Interview (CTI) (de Graaf et al., 2004), and at a 4-year follow-up using the self-reported Childhood Trauma Questionnaire-Short Form (CTQ-SF) (Bernstein et al., 2003). Both the CTI and the CTQ-SF retrospectively assess different types of CT: emotional neglect, emotional abuse, physical abuse, sexual abuse, and/or physical neglect (additionally assessed by the CTQ-SF) before the age of 16, thus, while growing up. The strong correlation between the CTI and the CTQ-SF with a 4-year time difference (total score, $r = 0.77$; subscales, $r = 0.57$-0.61) indicated high consistency of retrospective reports (Kuzminskaite et al., 2020, Spinhoven et al., 2014). Due to the fact that it was assessed at the baseline and had the largest completeness (99.6%), the majority of research within NESDA focuses on the CTI. In the CTI, each CT type is answered as "no" or "yes" with a further frequency indication as (0) - "never", (1) - "once or sometimes", and (2) - "regularly, often, or very often" (range 0-2). In the case of CT, participants are asked about the perpetrator: biological father, biological mother, stepfather or friend of the mother, stepmother or friend of the father, siblings, other family member, or somebody else. Intercorrelations between different CT types ranged from modest to large, with the highest correlation between emotional neglect and emotional abuse ($r = .61, p < .001$) (see Fig. 1 for correlations and density plots). Hence, the sum of the number of CT types and frequency of exposure to CT (childhood trauma index, range 0-8) is often used as a gradient and has been particularly associated with the prevalence, chronicity, and development of psychopathology in a dose-response manner (Hovens et al., 2012, Hovens et al., 2010, Wiersma et al., 2009, Hovens et al., 2015).

3. Epidemiological Findings of CT Within NESDA

3.1. CT Prevalence and Impact on Affective Disorders

Concerning the prevalence rates of CT within NESDA ($n = 2970$; exposure of at least once as assessed by the CTI), emotional neglect and emotional abuse were the most common types (38.9% and 24.8%, respectively), followed by sexual (18.5%) and physical abuse (13.8%) with approximately half of participants (48.6%) having experienced at least one type of CT. Out of participants with CT, the majority scored in the mild childhood trauma index range (score 1-3; 55.5%), with 44.5% scoring in the more severe range (score $\geq$ 4). If emotional neglect or

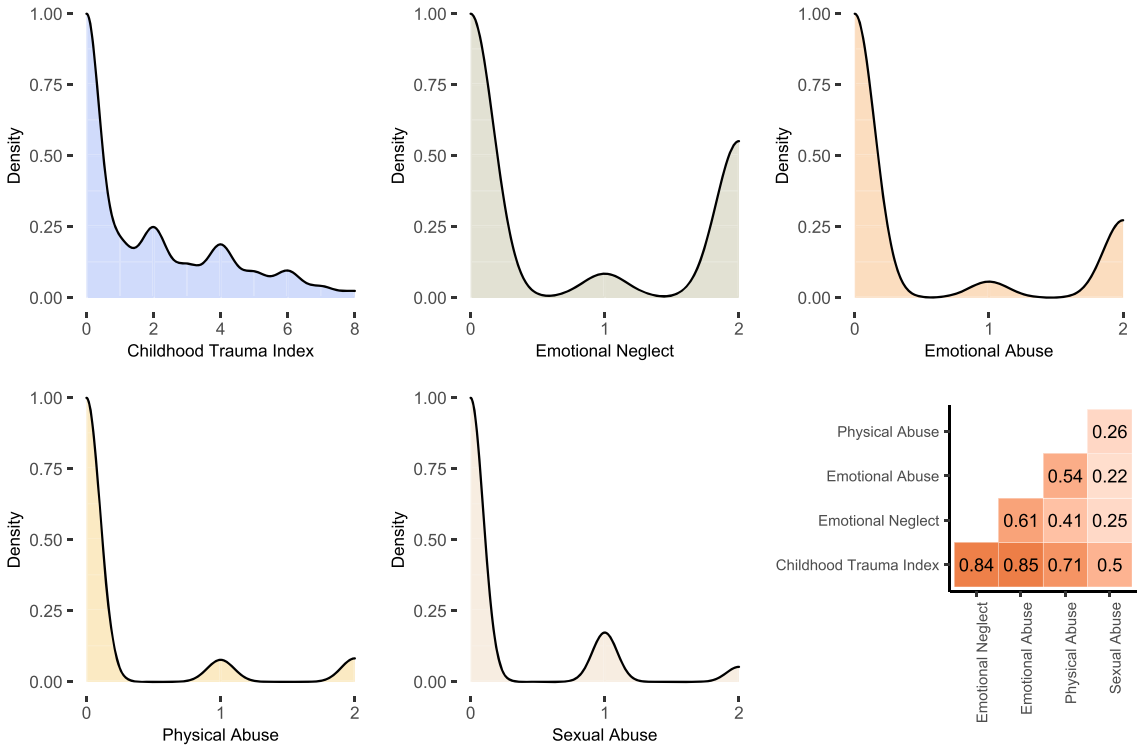

Fig. 1. Scaled density plots for childhood trauma index and each trauma type with corresponding intercorrelations (Pearson's *r*).
Note: all correlation p-values < .001

emotional abuse were present, more than 80% reported the frequency of "regularly, often, or very often". This was lower for physical (52%) and sexual abuse (23.3%). Emotional neglect, emotional abuse, and physical abuse were most often identified as perpetrated by family members (61-84%), while sexual abuse by someone else (71%). For additional details, also see Hovens et al. (Hovens et al., 2010).

Many previous studies that reported a relationship between CT and depressive or anxiety disorders in adulthood have focused on lifetime psychopathology (Kessler et al., 1997) and the more obvious forms of maltreatment, such as physical and sexual abuse. Within NESDA, the emphasis was on multiple types of CT (i.e., emotional neglect, emotional, physical, and sexual abuse), and the specificity of associations with psychopathology (depressive versus anxiety disorders) (Hovens et al., 2010). In a sample of 1931 participants, we demonstrated that exposure to any type of CT was associated with a higher risk of current anxiety and depressive disorders in increasing strength from current anxiety to current depressive to current comorbid disorder (OR = 2.3, 4.8, and 9.4, respectively, for CT score 4-8 versus 0). All types of CT were also consistently and strongly associated with the presence of current anxiety and depressive disorders in adulthood. These findings concurred with a previous meta-analysis (Norman et al., 2012) and showed robust evidence of the impact of emotional neglect, emotional and physical abuse on the presence of depressive and anxiety disorders in adulthood according to a robust dose-response gradient. For all CT types, strongest associations were found in the comorbid group. Since comorbidity is associated with an increased number and severity of symptoms, our results suggest that CT contributes to the severity of psychopathology. Childhood life events (i.e., divorce of parents, early parental loss, and placement in care) were not consistently associated with psychopathology (Hovens et al., 2010).

Some studies have additionally analyzed associations between different types of CT and various depressive and anxiety disorders, suggesting that different trauma types may be linked to somewhat different psychopathology manifestations (van Veen et al., 2013, Spinhoven et al., 2010). Although all CT types were significantly associated with almost all depressive and anxiety disorders (i.e., dysthymia, major depressive disorder (MDD), generalized anxiety disorder, social phobia, panic disorder, agoraphobia), when controlled for comorbidity of disorders and different trauma types, emotional neglect appeared to be particularly associated with dysthymia, MDD, and social phobia, while sexual abuse with dysthymia only (Spinhoven et al., 2010). Adjusting for CT types and psychopathology status, emotional neglect was also found to be independently associated with the general distress and anhedonic depression symptom profiles, while sexual abuse with the general distress and anxious arousal (van Veen et al., 2013). These findings suggest that maltreatment, especially, emotional neglect, seem to be stronger associated with manifestations of depression.

Moreover, CT often occurs within families, and recently also siblings of respondents with lifetime depression and/or anxiety were invited to participate in the NESDA study. In a subsample consisting of 256 families ($n = 636$), siblings showed the most similarity in their reports of emotional abuse and/or emotional neglect followed by physical abuse, whereas sexual abuse was mostly reported by one person within a family (Kullberg et al., 2020). In line with these observations, the mean family level of emotional maltreatment and physical abuse, but not sexual abuse, were associated with more depressive symptoms. Hence, particularly in the case of more visible forms of CT, findings implicate that in addition to individual maltreatment experiences, the context of siblings' experiences is another crucial risk factor for adult depressive symptomatology.

3.2. CT and the Course of Affective Disorders

Exposure to CT as a predictor of the 2-year course of depressive and anxiety disorders was studied in a follow-up sample of 1209 NESDA participants with a baseline diagnosis of depressive and/or anxiety disorder (Fig. 2) (Hovens et al., 2012). The results confirmed that a reported history of CT was associated with a poor outcome, characterized

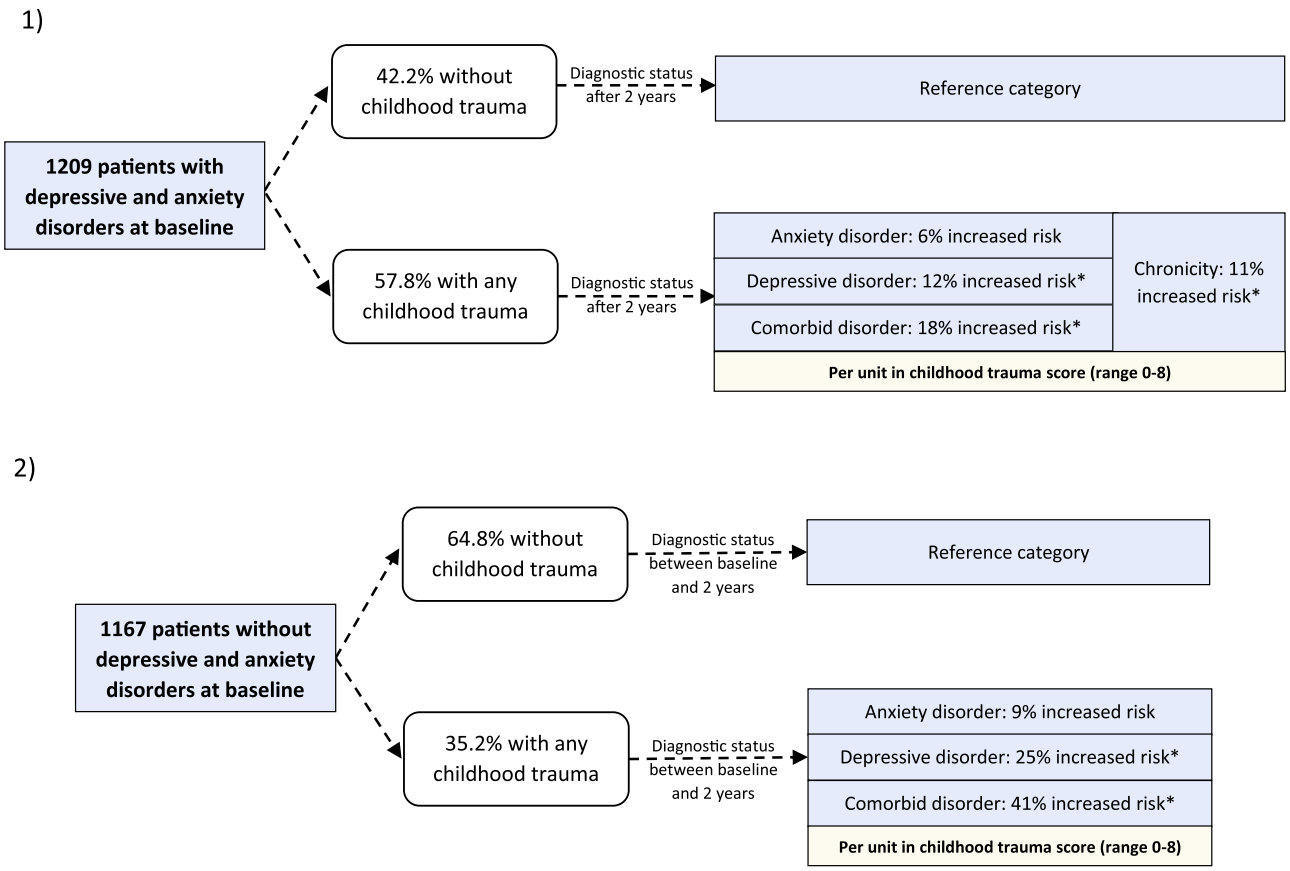

Fig. 2. The impact of childhood trauma on the 2-year course of depressive and/or anxiety disorders within the NESDA cohort with (1) and without (2) psychopathology at the baseline (see also: Hovens et al. (2012). Impact of childhood life events and trauma on the course of depressive and anxiety disorders. *Acta Psychiatr Scand, 126*(3), 198-207; Hovens et al. (2015). Impact of childhood life events and childhood trauma on the onset and recurrence of depressive and anxiety disorders. *J Clin Psychiatry, 76*(7), 931-938).
*$p < .001$

by more comorbidity and chronicity (Wiersma et al., 2009, De Venter et al., 2017). This prospective study was different from the handful of previous studies in terms of considerably larger sample size and the inclusion of a range of CT types. We found that childhood emotional neglect, emotional abuse, and physical abuse were all (consistently and strongly) associated with the persistence of both depressive and comorbid depressive and anxiety disorders. Emotional neglect and emotional abuse were also associated with a higher occurrence of a chronic course. No significant associations were found between childhood sexual abuse and the course of anxiety and depressive disorders, which was surprising and counter-intuitive. This could partially be attributed to a somewhat lower statistical power for sexual abuse when compared to emotional neglect and abuse. The CT score was predictive of both depressive or comorbid disorder and a chronic course after a 2-year follow-up. The impact of CT on diagnostic status and course at a 2-year follow-up was not as strong for anxiety disorders.

Additionally, we explored the differential impact of different types of CT on the onset or recurrence of anxiety, depressive, and comorbid disorders in a sub-sample of 1167 NESDA participants without current baseline depressive and/or anxiety disorder followed over a 2-year time period (Fig. 2) (Hovens et al., 2015). Prospective evidence of CT predicting onset and recurrence of adult affective disorders is scarce and limited to children samples followed until (young) adulthood (Widom et al., 2007, Moffitt et al., 2007, Clark et al., 2010). We found that a history of CT significantly predicted the first onset and recurrence of depressive and comorbid disorders, but only slightly increased the risk for anxiety disorders. Among the CT types, emotional neglect was the main independent predictor of first onset and recurrence of any depressive or comorbid disorder at 2-year follow-up, suggesting that the relationship between CT and psychopathology is predominantly driven by emotional neglect. In line with NESDA previous cross-sectional studies (Hovens et al., 2010, Spinhoven et al., 2010), childhood life events were not associated with the 2-year onset and recurrence of depressive and/or anxiety disorders. Our findings on the course of depression in adults with reported CT were confirmed in a meta-analysis (Nanni et al., 2012), suggesting that maltreated individuals were twice more likely to develop both recurrent and persistent depressive episodes than those without a history of maltreatment. Altogether, NESDA findings indicate that individuals with the history of CT are at particular risk for depressive disorders and comorbid depression-anxiety, which further results in the personal and societal burden. For instance, findings within NESDA showed that individuals with severe childhood trauma had significantly reduced work functioning in terms of absenteeism and presenteeism, which was partially explained by current depressive and comorbid depressive and anxiety disorders (De Venter et al., 2020).

3.3. Psychological Mechanisms Linking CT and Psychopathology

3.3.1. Maladaptive Personality Characteristics and Cognitions

Exposure to CT may alter basic cognitive assumptions about the self and others, that over time may become ingrained in an individual's personality. The Five-Factor Model (FFM), in which individual personality differences are grouped to the five major dimensions of neuroticism, extraversion, openness, agreeableness, and conscientiousness, presently constitutes one of the dominant models comprehensively examining personality functioning (Kotov et al., 2010). The

development of the less adaptive personality characteristics has been proposed as a potential underlying mechanism explaining the link between CT and subsequent psychopathology (Kim et al., 2009). In line, within NESDA, the severity of CT corresponded with more maladaptive personality characteristics and cognitive reactivity styles, including higher levels of neuroticism, openness, hopelessness, rumination, and external locus of control and lower levels of extraversion, agreeableness, and conscientiousness (Table 1) (Hovens et al., 2016). Specifically, emotional neglect and abuse were associated with all personality characteristics in a detrimental direction, whereas physical and sexual abuse predicted only neuroticism, openness, rumination, hopelessness, and external locus of control (Hovens et al., 2016). Adopting a person-centered approach to personality, we have also identified five latent (mal)adaptive personality types, which primarily differed in the degree of neuroticism, extraversion, and, to a lower extent, conscientiousness and agreeableness with openness to experience not being related to a personality type (Spinhoven et al., 2016). In line with the findings by Hovens et al. (Hovens et al., 2016), individuals reporting more severe CT showed the most maladaptive personality types (Spinhoven et al., 2016). Additionally, individuals with high levels of neuroticism were found to be particularly vulnerable to the impact of cumulative stress (including CT) on depression outcomes (Vinkers et al., 2014), suggesting that personality is both a moderator and a potential mediator of psychopathology.

Within NESDA, CT has also been associated with lower levels of optimism with emotional abuse and/or emotional neglect showing the strongest association, even after adjustment for potential confounders (Broekhof et al., 2015). This is in line with a study among 20,000 Finnish workers, showing a dose-response association between childhood adversities and optimism (Korkeila et al., 2004). In addition, another NESDA study investigated the association between different types of abuse and negative self-associations and found that emotional abuse and/or emotional neglect, compared to other types of abuse, had the strongest association with both self-reported and automatic (implicit) negative self-associations to words such as "useless", "inadequate", or "insecure" (van Harmelen et al., 2010). One of the explanations for the particularly strong link between emotional maltreatment and negative cognitions is that in the case of emotional abuse or emotional neglect, negative self-associations are explicitly handed to the child by the parent (e.g., "you are worthless"). Moreover, automatic and explicit negative self-associations partially mediated the link between emotional abuse and/or neglect and depressive or anxious symptomatology (van Harmelen et al., 2010), and may also alter emotional regulation strategies that underlie optimistic outcome expectancies (Rose and Abramson, 1992). Overall, NESDA findings on potential psychological mechanisms of CT suggest that CT may generate maladaptive personality characteristics, including higher levels of neuroticism and negative self-associations, as well as lower levels of extraversion and optimism.

3.4. Biological Mechanisms Linking CT and Psychopathology

3.4.1. Dysregulated Biological Stress Systems

Alterations in the activity of the major stress systems, namely, the hypothalamic-pituitary-adrenal (HPA)-axis, the immune-inflammatory system, and the autonomic nervous system (ANS), are at the center of the biological psychiatry research seeking to explain the enduring impact of CT. Stressful life events can irreversibly dysregulate the functioning of stress systems by chronically stimulating the release of cortisol, the secretion of pro-inflammatory cytokines, and the alteration of sympathetic and parasympathetic nervous system activity (Danese and Baldwin, 2017, Koss and Gunnar, 2018, Young-Southward et al., 2019). These vital stress systems are also firmly connected by regulating each other's functioning, e.g., HPA-axis is involved in the regulation of inflammatory processes, which in turn stimulate the release of cortisol. Despite being inconclusive and generally suggesting small additive effects, a body of evidence indicates dysregulated stress systems as factors, at least partially explaining the enduring impact of CT (Ioannidis et al., 2020). Recent meta-analyses confirmed significant associations between CT and blunted wake-up cortisol as well as cortisol response to experimental social stress conditions (Bernard et al., 2017, Bunea et al., 2017). Nevertheless, the more static patterns of basal cortisol, cortisol awakening response (CAR), diurnal cortisol slope, or cortisol response to acute stress were not consistently associated with CT (Bernard et al., 2017, Fogelman and Canli, 2018). Meta-analytic evidence also concluded CT as being significantly linked to heightened levels of adult pro-inflammatory C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) (Baumeister et al., 2016). Evidence on the autonomic dysregulation is rather inconsistent, but generally suggesting blunted heart rate (HR) and pre-ejection period (PEP) with inconclusive findings on respiratory sinus arrhythmia (RSA) in response to experimental psychological stress conditions (Young-Southward et al., 2019, Sijtsema et al., 2015, Lovallo et al., 2012).

Within NESDA, we not only examined associations between CT and separate commonly assessed markers of major stress systems, but also employed an integrative approach including cumulative markers within each stress system and across all systems (Table 1). Although higher retrospective CT scores in the NESDA cohort were generally associated with slightly elevated salivary cortisol and blood inflammation levels, the number of significant associations was very limited (Kuzminskaite et al., 2020, Holleman et al., 2012). Regression coefficients were small, but rather comparable to the effects observed in previous meta-analyses, both in terms of the direction and the magnitude, somewhat contradicting findings on blunted wake-up cortisol (Bernard et al., 2017, Fogelman and Canli, 2018, Baumeister et al., 2016). Direct associations between CT and stress systems within the total NESDA cohort could have been hard to discern due to the genetic moderation, at least within the HPA-axis (Gerritsen et al., 2017), or by an overrepresentation of psychopathology, characterized by significantly dysregulated stress systems within NESDA (Hu et al., 2016, Vogelzangs et al., 2016, Vreeburg et al., 2009). Consequently, to increase contrast, we compared individuals with severe CT (including those with and without psychopathology) to healthy controls without CT, resulting in significantly elevated levels of the CAR, cumulative HPA-axis markers, CRP, IL-6, cumulative inflammation, and cumulative stress markers across all systems, partially explained by unhealthy lifestyle and higher rates of chronic diseases (Kuzminskaite et al., 2020). Moreover, individuals with more occurrence of CT showed lower levels of CAR or evening cortisol when more demands, less control, and less social support at work was reported (Holleman et al., 2012), suggesting that a history of CT may be important in how the HPA-axis responds to recent life stress. Taken together, our findings suggest that the direct impact of CT on stress systems is small and may be influenced by the presence of psychopathology as well as poorer lifestyle, somatic health, and recent life stress.

3.4.2. Accelerated Biological Aging, Unhealthy Lifestyle, and Somatic Health Decline

CT not only affects the brain but also extends its effects to poor health behaviors and the functioning of our entire body. A recent meta-analysis has shown significant associations between multiple exposures to CT and poor adult lifestyle behaviors such as physical inactivity, obesity, smoking, sexual risk-taking, heavy alcohol and illicit drug use (Hughes et al., 2017). In line, within NESDA, we found that individuals with severe CT had significantly higher rates of smoking and body mass index (BMI) than healthy controls without CT (Table 1) (Kuzminskaite et al., 2020). This was also true when comparing those with and without CT whilst not excluding psychopathology, suggesting lifestyle as an essential factor for understanding the impact of CT on health outcomes. Moreover, meta-analytic findings on 38 studies confirmed that individuals with retrospectively reported CT showed a 40% increased risk of adult cardiometabolic disease, consisting of cardiovascular diseases, diabetes, and metabolic syndrome (Jakubowski et al., 2018). In line with these findings, within NESDA, we found that individuals with CT,

Table 1
Studies examining CT-related personality characteristics, cognitions, stress systems' functioning, biological aging, lifestyle, and somatic health in the NESDA cohort.

Study	Focus	Sample	CT	Outcome
		Personality Characteristics and Cognitions		
van Harmelen et al. (2010)	Negative self-associations	n = 2483 of which 48.3% with CT	CTI: multiple incidences per trauma type, and any trauma	CT was associated with (implicit and explicit) enhanced negative self-associations. When compared to physical and sexual abuse, emotional abuse and/or neglect had the strongest link to negative self-associations.
Vinkers et al. (2014)	Neuroticism	n = 2274 of which ~45% with CT	CTQ-SF and CTI: total severity scores of any trauma (as a part of the cumulative stress index including CT, major life events, and daily hassles)	The impact of the cumulative stress index, including CT and other stressors, on depression, was most pronounced in vulnerable individuals with high levels of trait neuroticism.
Broekhof et al. (2015)	Optimism	n = 2104 of which ~45% with CT	CTI: a sum of trauma frequency per CT type (range 0-2)	CT was associated with lower levels of optimism with emotional abuse and/or neglect showing the strongest association.
Hovens et al. (2016)	Personality characteristics and cognitive reactivity styles	n = 1474 of which 57.4% with CT	CTI: a sum of trauma frequency per CT type (range 0-2), and a total sum of the number and frequency of any trauma (range 0-8)	CT was associated with lower levels of extraversion, agreeableness, and conscientiousness, and higher levels of neuroticism, openness, hopelessness, rumination, and external locus of control. Emotional neglect and abuse were associated with all personality characteristics in detrimental direction, whereas physical and sexual abuse predicted only neuroticism, openness, rumination, hopelessness, and external locus of control.
Spinhoven et al. (2016)	Maladaptive personality types	n = 2938 of which 44.5% with CT	CTI: multiple incidences per CT type, and a total sum of the number of trauma (range 0-4)	CT severity was progressively associated with more maladaptive personality types. Prevalence rates of CT types were higher at higher levels of maladaptive personality functioning.
		Biological Stress Systems		
Holleman et al. (2012)	Salivary cortisol	n = 1995 of which ~45% with CT	CTI: multiple incidences of any type of trauma, and a total sum of the number and frequency of any trauma (range 0-8)	CT was not associated with saliva cortisol levels. Those reporting higher scores of total CT had a lower CAR or evening cortisol levels when reporting more demands, less control or less social support at work.
Gerritsen et al. (2017)	HPA-axis genes, salivary cortisol, hippocampal and amygdala volume	n = 2327 of which 50% with CT	CTI: a total sum of the number and frequency of any trauma (range 0-8)	NR3C2 gene (which codes for MR) AA (vs. G) allele carriers with CT showed higher cortisol levels after DST.
Kuzminskaite et al. (2020)*	Salivary cortisol, blood inflammatory markers, and ANS activity	n = 2778 of which 47.9% with CT	CTI: a sum of trauma frequency per CT type (range 0-2), and a total sum of the number and frequency of any trauma (range 0-8); CTQ-SF: total severity scores	No consistent associations between CT and cortisol, inflammation, or autonomic activity in the total sample. Those with severe CT as compared to healthy controls without CT showed the strongest evidence for slightly elevated levels of cortisol, inflammation, and cumulative stress systems' markers, partially explained by an unhealthier lifestyle and poorer health.
		Biological Aging, Lifestyle, and Somatic Health		
van Reedt Dortland et al. (2012)	Metabolic risk factors	n = 2755 of which ~45% with CT	CTI: a sum of trauma frequency per CT type (range 0-2)	Sexual, emotional, and physical abuse were associated with lower levels of HDL cholesterol, higher waist circumference, and overall increased metabolic risk. Emotional neglect was associated with lower SBP. Sexual abuse was the most unfavorable correlate of metabolic risk.
Verhoeven et al. (2014)	Telomere length	n = 1095 with current MDD from n=2407 of which ~45% with CT	CTI: a total sum of the number and frequency of any trauma (range 0-8)	CT was not associated with telomere length in individuals with current MDD.
Verhoeven et al. (2015)	Telomere length	n = 2936 of which ~45% with CT	CTI: a sum of trauma frequency per CT type (range 0-2), and a total sum of the number and frequency of any trauma (range 0-8); CTQ-SF: total severity scores	CT was not associated with shorter telomere length.
Bomhof-Roordink et al. (2015)	Subclinical cardiovascular disease	n = 650 of which 47.5% with CT	CTI: a sum of trauma frequency per CT type (range 0-2), and a total sum of the number and frequency of any trauma (range 0-8)	Increased central arterial stiffness was found in individuals with CT, especially in those with highest trauma score. Severity of depression and anxiety partially mediated this association. All CT types, except sexual abuse, showed significant associations with increased central arterial stiffness.
Generaal et al. (2016)	Musculoskeletal pain	n = 1646 of which ~45% with CT	CTI: a total sum of the number and frequency of any trauma (range 0-8)	CT was associated with both the presence and the severity of chronic pain. Associations remained significant after depression, anxiety, and antidepressant adjustment.
Révész et al. (2016)	Telomere attrition	n = 1860 of which ~45% with CT	CTI: a total sum of the number and frequency of any trauma (range 0-8)	Higher baseline CT score predicted larger 6-year telomere attrition.
Han et al. (2018)	DNA methylation	n = 811 with current MDD from 1130 of which ~45% with CT	CTI: a total sum of the number of any trauma (range 0-4)	CT was positively associated with epigenetic aging in individuals with current MDD.
Kuzminskaite et al. (2020)*	Smoking and BMI	n = 2778 of which 47.9% with CT	CTI: a total sum of the number and frequency of any trauma (range 0-8)	Individuals with severe CT had significantly higher rates of smoking and BMI than healthy controls without CT.

Note. * Same study.
Abbreviations: ANS, autonomic nervous system; BMI, body mass index; CT, childhood trauma; CTI, childhood trauma interview; CTQ-SF, childhood trauma questionnaire-short form; CAR, cortisol awakening response; DST, dexamethasone test; HDL, high-density lipoprotein; MDD, major depressive disorder; MR, mineralocorticoid receptor; SBP, systolic blood pressure.

especially those with severe CT, showed more subclinical cardiovascular disease symptoms as represented by the increased central arterial stiffness (Bomhof-Roordink et al., 2015). Exposure to CT, especially sexual abuse, was also associated with more metabolic syndrome dysregulations when compared to no CT exposure (van Reedt Dortland et al., 2012). These results were most clearly present for dyslipidemia and abdominal obesity, but not for hypertension and hyperglycemia components of the metabolic syndrome. Results could not be explained by a poorer lifestyle (e.g., smoking, alcohol use, or physical inactivity) in individuals with CT. The adverse health effect of CT is not limited to cardiovascular outcomes. In addition, within NESDA, CT has also been associated with more presence and severity of chronic musculoskeletal pain (Generaal et al., 2016).

Observational research shows that exposure to adverse childhood events leads to dramatically different life-course trajectories, including a two-times higher risk for premature mortality but also the increased onset of various somatic conditions (Bellis et al., 2013). Consequently, CT seems to be more generally linked to an increased risk for age-related health conditions. This leads to the suggestion that CT can more generally accelerate the aging process. Although chronological age is invariable, people differ in biological age, which may fall behind or outpace chronological age. Biological aging is a multi-faceted and complex process that manifests across multiple levels. Therefore, there is no single indicator that captures biological aging completely; multiple indicators exist (Han et al., 2019). Examples of molecular indicators of biological age are short telomere length, decrease in mitochondrial deoxyribonucleic acid (DNA) copy number, and more advanced epigenetic, transcriptomic, or metabolomic age. Within NESDA, we measured epigenetic aging (via sequencing of all DNA methylation sites) and telomere length (via quantitative polymerase chain reaction). Both DNA methylation and telomere length showed more accelerated aging in depressed individuals versus controls (Han et al., 2018, Verhoeven et al., 2016, Verhoeven et al., 2014). As compared to controls, most advanced epigenetic aging was present in depressed individuals with CT (Han et al., 2018). Although cross-sectionally CT was not associated with telomere length (Verhoeven et al., 2014, Verhoeven et al., 2015), more considerable telomere attrition from baseline to 6-year follow-up was found to be present in individuals with more severe CT (Révész et al., 2016). Overall, these NESDA findings support the hypothesis that CT may produce long-lasting biological "scars" that have an impact on advanced or premature aging processes later in life.

3.4.3. *Altered Brain Structure and Function*

CT has been hypothesized to alter brain development via sustained activation of the HPA-axis and the immune system. During stress, the sympathetic nervous system activates immune cells to stimulate the release of the pro-inflammatory markers (Pongratz and Straub, 2014). As such, chronic activation of the HPA-axis and immune system are thought to be one of the mechanisms through which CT may impact on the structure and function of the brain (Danese and Baldwin, 2017, Danese and van Harmelen, 2017).

Structural MRI studies. Within NESDA, studies on brain structure (Table 2) have predominantly focused on key emotional brain regions (medial prefrontal cortex, mPFC), the limbic regions (hippocampus and amygdala), and conducted exploratory whole-brain analyses. The findings showed reduced dorsal mPFC volume in both patients and healthy controls with emotional abuse and/or emotional neglect (van Harmelen et al., 2010). This is in line with a review suggesting that CT-related mPFC reductions may not be directly related to vulnerable emotional functioning (Moreno-López et al., 2019). Indeed, we observed that patients with CT reported significantly more negative life events than healthy controls with CT, which may, in turn, lead to depressive and anxiety disorders (van Harmelen et al., 2010). While reduced amygdala volume was linked to CT, hippocampal and anterior cingulate cortex (ACC) volumes were not directly related to CT in the NESDA sample (van Harmelen et al., 2010, Molendijk et al., 2012, Gerritsen et al., 2015, van Velzen et al., 2016). However, there were additional indications that genetic influences may play a role in reducing amygdala, ACC, and hippocampal volumes for individuals with CT (see the section below) (Gerritsen et al., 2017, Molendijk et al., 2012, van Velzen et al., 2016). The hippocampal effects may contribute to increased vulnerability to the development of psychopathology in the NESDA sample; as Gerritsen et al. (Gerritsen et al., 2015) showed that in those individuals with CT, a diagnosis of MDD was associated with smaller hippocampal volume.

Functional MRI (fMRI) studies. Concerning studies on brain function (Table 2), individuals reporting emotional abuse and/or emotional neglect showed amygdala hyperresponsivity to emotional faces (van Harmelen et al., 2013), suggesting persistent vigilance towards the detection of emotional facial expressions. CT was associated with hypoactivity in the mPFC during a task that required higher-order cognitive processing (van Harmelen et al., 2014). Hippocampal activity during emotional memory was not affected by CT (van Harmelen et al., 2014), although hippocampal activity to negative emotional words may be modulated by genetic influences (Molendijk et al., 2012) as well as CT-related amygdala and posterior cingulate cortex (PCC) responses to emotional faces (Opmeer et al., 2014). Finally, we examined emotional brain connectivity during rest using fMRI within the limbic, salience, and default networks associated with emotion regulation and self-reflective processing and found widespread reductions in connectivity patterns of these networks related to CT (van der Werff et al., 2013). For instance, a decrease in connectivity between the right amygdala and the precuneus in individuals with CT was reported, which is essential for emotion regulation and self-reflective processing. Reduced connectivity with the precuneus within the salience network may be related to the NESDA findings of more negative self-cognitions in individuals with CT (van Harmelen et al., 2010). In individuals with CT exposure, but no psychopathology, increased negative connectivity was found between the dorsal ACC and the lingual gyrus and occipital fusiform gyrus (van der Werff et al., 2013), suggesting that in resilient individuals with CT increased ability to downregulate emotional processing and responses in verbal declarative memory may play a role, leading to improved ability to re-appraise negative situations, or recall positive autobiographical memories (Ioannidis et al., 2020, Askelund et al., 2019).

In conclusion, findings from the NESDA study indicate that in individuals with emotional maltreatment reduced mPFC and amygdala volumes are found, as well as amygdala hyperactivity, mPFC hypoactivity, and reduced connectivity in limbic, salience, and default-mode networks.

3.4.4. *Is Everyone Similarly Vulnerable to the Impact of CT?*

Although CT is a major risk factor for depression and anxiety, considerable heterogeneity exists in outcomes after exposure to CT. Several theories posit that the impact of CT may be dependent on individual characteristics. However, these characteristics are generally difficult to identify due to methodological heterogeneity and lack of replicated findings.

Within NESDA, some individuals seemed to be particularly more vulnerable to the impact of CT. First, the impact of a cumulative stress index, including CT and other stressors, on depression was most pronounced in at-risk individuals with high levels of neuroticism (Vinkers et al., 2014), suggesting that the adverse effects of CT may primarily

Table 2
Studies examining CT-related brain structure and function in the NESDA cohort.

Study	Paradigm	Sample	CT	Approach	Outcome
			MRI Studies		
van Harmelen et al. (2010)	Structural	Emotional abuse/ neglect, yes (n = 84), no (n = 97)	CTI: multiple incidences of emotional abuse and/or emotional neglect	ROI: hippocampal, amygdala, mPFC volume + whole brain	Emotional abuse/neglect was associated with a reduction in left dorsal mPFC volume, independent of gender, psychiatric status, and other types of abuse. No effects of emotional abuse/neglect on amygdala or hippocampal volume.
Molendijk et al. (2012)*	Structural	Val^{66}val (n = 103; 79% with CT); val^{66}met allele (n = 54; 43% with CT)	CTI: a total sum of the number and frequency of any trauma (range 0-8)	ROI: hippocampal volume + whole brain	Smaller hippocampal volume in val^{66}met allele carriers. No main effect or moderation effect by CT. No effects of the BDNF genotype found in other brain areas.
Gerritsen et al. (2015)	Structural	n = 262 (50% with CT)	CTI: a total sum of the number of any trauma (range 0-4)	ROI: hippocampal volume	No main effect of CT on hippocampal volume. In those with CT, a diagnosis of MDD was associated with smaller hippocampal volume, but not in those without CT.
van Velzen et al. (2016)	Structural	CT, yes (n = 146), no (n = 143)	CTI: at least one type of CT	ROI: amygdala and hippocampal volume; rostral and caudal ACC cortical thickness and surface area	CT was associated with lower amygdala volume. This was more pronounced in maltreated BDNF vall^{66}met allele carriers. Decreased cortical thickness of the ACC in CT with val/val genotype.
Gerritsen et al. (2017)	Structural	n = 225 (from n = 2327 with genome data of which 50% with CT)	CTI: a total sum of the number and frequency of any trauma (range 0-8)	ROI: amygdala and hippocampal volume	NR3C2 gene (which codes for MR) AA (vs. G) allele carriers with CT had smaller hippocampal and amygdala volumes.
			fMRI Studies		
Molendijk et al. (2012)*	Emotional memory encoding and retrieval	Val^{66}val (n = 103; 79% with CT); val^{66}met allele (n = 54; 43% with CT)	CTI: a total sum of the number and frequency of any trauma (range 0-8)	ROI: hippocampus + whole brain	Hippocampal activity to negative and neutral (vs. baseline) word encoding higher in BDNF val^{66}met allele carriers. Hippocampal encoding activity in response to negative words was higher in those with CT (vs. no CT) and interacted with genotype: CT predicted increased hippocampal activation in those with val/val allele, but not in met allele carriers.
van Harmelen et al. (2013)	Emotional face processing	Emotional abuse/ neglect, yes (n = 60), no (n = 75)	CTI: multiple incidences of emotional abuse and/or emotional neglect	ROI: dorsal, ventral mPFC, ACC, and amygdala + whole brain	Emotional abuse/neglect was associated with enhanced bilateral amygdala reactivity to emotional faces in general, and independent of psychiatric status. No support for differential mPFC functioning.
van der Werff et al. (2013) *Psychological Medicine*	Resting-state functional MRI	Emotional abuse/ neglect, yes (n = 44), no (n = 44)	CTI: multiple incidences of emotional abuse and/or emotional neglect	ROI (seed-based): bilateral amygdala (limbic network), bilateral dorsal ACC (salience network), and the PCC (DMN)	Emotional abuse/neglect was associated with decreased negative connectivity between the right amygdala and bilateral occipital cortex, decreased positive connectivity between right amygdala and OFC, insular to subcortical structures, including the hippocampus and putamen. Decreased negative connectivity between left dorsal ACC and angular cortex and precuneus. Decreased positive connectivity between the left dorsal ACC seed and a bilateral frontal cluster containing the mPFC, the paracingulate gyrus, and the frontal pole. No differences in the left dorsal mPFC seed in the DMN.
van der Werff et al. (2013) *Child abuse and Neglect*	Resting-state functional MRI	CT (n = 22), matched controls without CT (n = 11)	CTI: at least one type of CT; CTQ: total severity score of any trauma	ROI (seed-based): bilateral amygdala (limbic network), bilateral dorsal ACC (salience network) and the PCC (DMN)	CT was associated with an increase in negative connectivity between left dorsal ACC and the lingual gyrus and the occipital fusiform gyrus in the resilient group (healthy individuals with CT) when compared to the healthy controls (no psychopathology and no CT) and when compared to patients with MDD/anxiety with CT.
Opmeer et al. (2014)	Emotional face processing	Emotional abuse/ neglect, yes (n = 56), no (n = 62)	CTI: multiple incidences of emotional abuse and/or emotional neglect	ROI: amygdala + whole brain	Within carriers of the C-allele risk genotype, emotional abuse/neglect was associated with higher amygdala activation, but did not influence activation in non-risk carriers. In the PCC, lower activation was seen in those with emotional abuse/neglect and the risk genotype, whereas genotype did not influence PCC activation in those without trauma. Those carrying the risk genotype with experience of emotional abuse/neglect made a faster gender decision than those without trauma.

(*continued on next page*)

Table 2 (*continued*)

Study	Paradigm	Sample	CT	Approach	Outcome
van Harmelen et al. (2014)	Emotional memory encoding and retrieval	Emotional abuse/ neglect, yes (n = 96), no (n = 98)	CTI: multiple incidences of emotional abuse and/or emotional neglect	ROI: hippocampus, amygdala, dorsal, ventral mPFC, dorsolateral PFC, and the dorsal and pregenual ACC + whole brain	Dorsal mPFC hypoactivity during encoding and recognition of (subsequently) correctly recognized positive, negative, and neutral words in adults with emotional abuse/ neglect.

Note. * Same study.

Abbreviations: ACC, anterior cingulate cortex; BDNF, brain-derived neurotrophic factor; CT, childhood trauma; CTI, childhood trauma interview; CTQ-SF, childhood trauma questionnaire-short form; DMN, default mode network; DST, dexamethasone test; mPFC, medial prefrontal cortex; MR, mineralocorticoid receptor; MDD, major depressive disorder; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PCC, posterior cingulate cortex; ROI, regions of interest.

surface in those with personality traits linked to a vulnerability for psychopathology. Second, maltreated men carrying the CA haplotype of the mineralocorticoid receptor (MR) showed increased depressive symptoms, whereas those carrying the CG haplotype showed increased resilient mental health functioning, indicating important sex-dependent effects of MR on depression susceptibility following CT (Vinkers et al., 2015). Third, maltreated individuals who carried the AA allele of the NR3C2 gene, which codes for MR and mediates rapid cortisol effects in the limbic structures, showed reduced hippocampal and amygdala volumes as well as increased cortisol levels after the dexamethasone suppression test (Gerritsen et al., 2017). Hippocampal and amygdala volumes were also reduced in individuals reporting CT with the val^{66}met genotype of the brain-derived neurotrophic factor (BDNF), playing a critical role in the neural growth (Molendijk et al., 2012, van Velzen et al., 2016, Hariri et al., 2003), while the ACC thickness was reduced in the maltreated individuals carrying the val/val genotype (van Velzen et al., 2016). Individuals with the BDNF val^{66}met genotype also showed reduced serum BDNF levels when exposed to CT (Elzinga et al., 2011). Finally, individuals with BDNF val/val allele were characterized by increased hippocampal activity to negative emotional words (Molendijk et al., 2012), while those with C-allele of neuropeptide Y genotype (NPY) showed particularly increased behavioral responding, higher amygdala activity, and lower PCC activity in response to emotional faces (Opmeer et al., 2014).

Drawing firm conclusions about specific genes mentioned above is difficult, as they show small effects and, therefore, require considerable sample sizes. Consequently, findings on polygenic risk scores (PRS), reflecting a sum of the relevant risk alleles representing a cumulative genetic risk, could provide more conclusive evidence. In line, within NESDA, the effect of PRS on MDD was significantly increased in the presence of CT, suggesting that individuals with CT and high PRS are particularly at risk for developing depression (Peyrot et al., 2014). While some characteristics of individuals more sensitive to the impact of CT have been revealed, collaborative research, especially on genetic characteristics, is necessary to replicate findings and allow firmer conclusions.

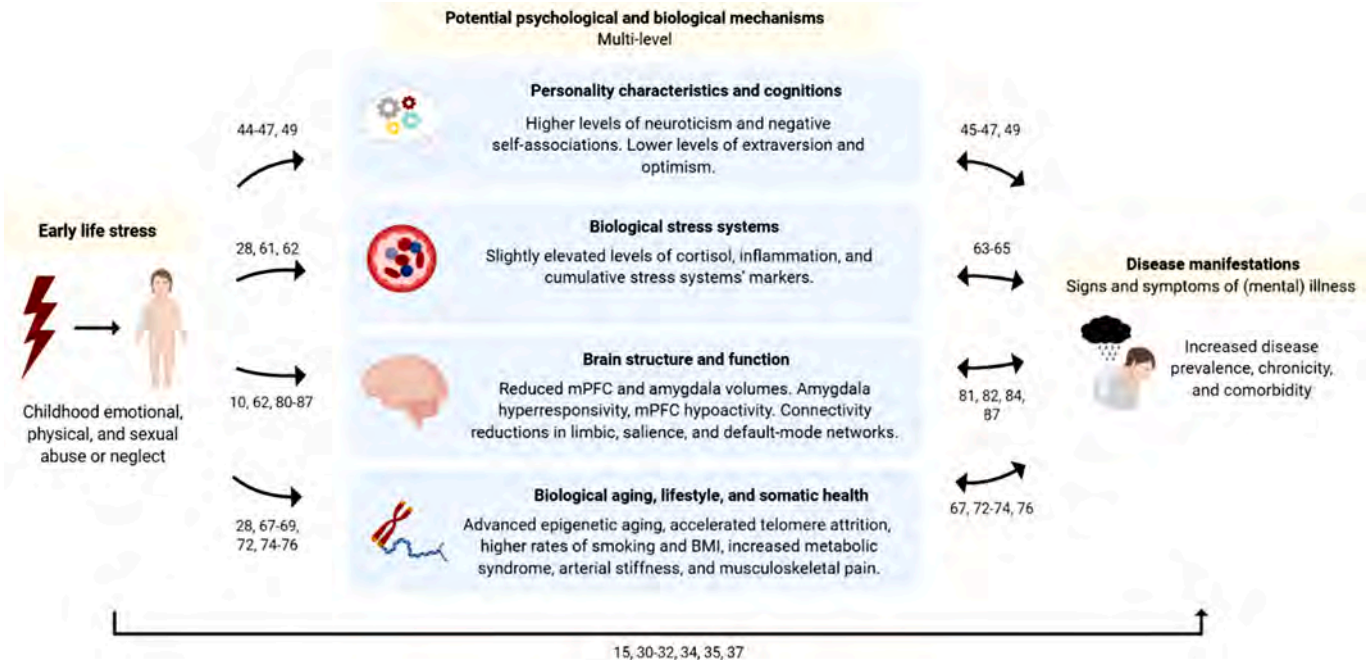

Fig. 3. CT-related psychological and biological changes involved in (mental) illness manifestations in the NESDA cohort (Created with BioRender.com).

Note: numbers indicate study reference, i.e. 10 van Harmelen et al. (2010), 15 Hovens et al. (2012), 28 Kuzminskaite et al. (2020), 30 Hovens et al. (2010), 31 Wiersma et al. (2009), 32 Hovens et al. (2015), 34 van Veen et al. (2013), 35 Spinhoven et al. (2010), 37 De Venter et al. (2017), 44 Hovens et al. (2016), 45 Spinhoven et al. (2016), 46 Vinkers et al. (2014), 47 Broekhof et al. (2015), 49 van Harmelen et al. (2010), 61 Holleman et al. (2012), 62 Gerritsen et al. (2017), 63 Hu et al. (2016), 64 Vogelzangs et al. (2016), 65 Vreeburg et al. (2009), 67 Bomhof-Roordink et al. (2015), 68 van Reedt Dortland et al. (2012), 69 Generaal et al. (2016), 72 Han et al. (2018), 73 Verhoeven et al. (2016), 74 Verhoeven et al. (2014), 75 Verhoeven et al. (2015), 76 Révész et al. (2016), 80 Molendijk et al. (2012), 81 Gerritsen et al. (2015), 82 van Velzen et al. (2016), 83 van Harmelen et al. (2013), 84 van Harmelen et al. (2014), 85 Opmeer et al. (2014), 86 van der Werff et al. (2013), 87 van der Werff et al. (2013).

Abbreviations: BMI, body mass index; CT, childhood trauma; mPFC, medial prefrontal cortex

4. Discussion

This review summarized and integrated the potential mechanisms through which CT exerts its adverse effects using findings from the large longitudinal adult NESDA cohort. NESDA results indicated that CT has a negative impact on the onset and the course of affective disorders, both for depression and/or anxiety disorders and their comorbidity. These findings are in line with a large and convincing body of literature, showing that CT negatively impacts mental health across the lifespan and is, therefore, one of the most prominent public health risks for poor mental outcomes (Angelakis et al., 2019, Norman et al., 2012, Widom et al., 2012, Danese and Tan, 2014, Hughes et al., 2017). Findings also suggested existing interindividual differences, with some individuals exposed to CT being at significant risk for psychopathology or further biological CT-related alterations.

To better understand who is at risk and, ultimately, develop personalized (preventative) interventions, it is essential to determine the mechanisms by which CT exerts its adverse outcomes. Our review suggested a wide range of possible pathways in the psychological and biological domains (Fig. 3). Specifically, within NESDA, CT was associated with more maladaptive personality characteristics and cognitions (higher levels of neuroticism and negative self-associations; lower levels of extraversion and optimism), stress systems' dysregulations (slightly elevated levels of cortisol and inflammation), advanced biological aging (accelerated epigenetic aging and telomere attrition over time), poorer lifestyle (higher rates of smoking and BMI), somatic health decline (increased metabolic syndrome dysregulations, arterial stiffness, and musculoskeletal pain), and brain alterations at the structural and functional level (reduced mPFC and amygdala volumes; amygdala hyperresponsivity and mPFC hypoactivity). CT was also linked to more negative life events and diminished work functioning, indicating additional personal and societal burden. From all CT types, emotional abuse and/or emotional neglect seemed to show the most profound effect. However, this was mostly true when all types of CT were considered together.

Our findings demonstrated the complexity of an organism, suggesting that the impact of CT on poor mental health outcomes is probably a result of a complex interaction of genes, brain processes, environment, and psychological factors (Teicher and Samson, 2013, Daskalakis et al., 2013, Ioannidis et al., 2020). Although most findings within NESDA on CT, impacting the brain, mind, and body, fit well with the key hypotheses and explanatory biological models, we have to be cautious of causal inferences of the succession of pathways (Danese, 2019, Danese and McEwen, 2012). It is currently unknown how different systems interact due to a lack of theoretic underpinnings and comprehensive longitudinal projects integrating psychological, environmental, and biological factors in the same samples in the context of CT. For instance, obesity is likely to mediate CT's impact on adult inflammation (Miller and Chen, 2010); however, other factors such as HPA-axis functioning are also likely playing a role in this relationship (Miller and Chen, 2010, Hewagalamulage et al., 2016). Considering longitudinal findings in NESDA, baseline maladaptive personality characteristics, predominantly, neuroticism mediated the relationship between CT and the course of depressive and anxiety disorders (De Venter et al., 2017, Hovens et al., 2016, Spinhoven et al., 2016). Most likely, CT results in increased neuroticism levels, leading to a higher vulnerability to psychopathology (Roy, 2002). However, it may well be that children with higher neuroticism levels are also more likely to experience and/or report CT. To disentangle the impact of CT, its potentially pre-existing factors, and succession of pathways leading to psychopathology, prospective-longitudinal studies are required. Nevertheless, most research to date relies on cross-sectional studies or longitudinal studies with factors such as neuroticism being assessed only at one-time point, forbidding the inference of change before the CT (Ioannidis et al., 2020, Moreno-López et al., 2019, Danese, 2019).

To advance our knowledge, there are currently several unmet needs in psychiatric research concerning CT and affective disorders: lack of comprehensive longitudinal projects investigating how multiple systems interact to result in affective disorders, and how these different interactions sustain and proliferate symptomatology. It is essential to elucidate the time path between CT, its underlying mechanisms, and psychopathology, as well as investigate how genes and environment are both involved in adverse CT outcomes. For instance, parenting behaviors can be well affected by the psychiatric state of the parent, resulting in more CT, especially, emotional maltreatment, and further child risk for affective disorders (Banyard et al., 2003). Therefore, the increased risk for psychopathology in individuals with CT may be partially related to genetic transmission. One valuable method would be to link findings from epidemiological child/adolescent studies to adult population studies in line with the ongoing Mood and Resilience in Offspring (MARIO; www.mario-project.nl) cohort study, investigating intergenerational transmission of mood disorders.

The current review has some limitations as it focuses on CT findings within one – albeit large and well-defined – cohort, and replications of integrative approaches related to CT are essential. At the same time, this is also a strength as the findings are comparable since the assessment of CT and other methodology were homogenous. We, therefore, encourage other large cohorts to employ a similar approach and integrate different CT findings from the same cohort. Moreover, we refrained from analyzing the associations and relations between the different CT findings as publications have used data from various waves, and sometimes only studied subsamples from the total NESDA cohort. Lastly, NESDA is an adult cohort with self-reported CT. Hence, it is unknown whether CT findings in adulthood are comparable to those in childhood and whether they would be different if CT was assessed prospectively.

This review has shown that CT impacts the functioning of the brain, mind, and body. All these aspects most likely work together and contribute to a higher vulnerability for affective disorders across the lifespan. An integration of mechanistic explanations at different psychological, biological, and environmental levels is essential to better understand the life-long adverse effects of CT in the context of affective disorders.

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Data Availability Statement

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

CRediT authorship contribution statement

Erika Kuzminskaite: Conceptualization, Visualization, Project administration, Writing - original draft, Writing - review & editing. **Brenda W.J.H. Penninx:** Conceptualization, Methodology, Supervision, Writing - original draft, Writing - review & editing. **Anne-Laura van Harmelen:** Writing - original draft, Writing - review & editing. **Bernet M. Elzinga:** Writing - original draft, Writing - review & editing.

Jacqueline G.F.M. Hovens: Writing - original draft. **Christiaan H. Vinkers:** Conceptualization, Supervision, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

All authors declare no competing interests.

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Review Article

Psychological risk factors and the course of depression and anxiety disorders: A review of 15 years NESDA research

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ABSTRACT

Background: The Netherlands Study of Depression and Anxiety (NESDA; $N_{baseline}$=2981) is an ongoing longitudinal, multi-site, naturalistic, cohort study examining the etiology, course, and consequences of depression and anxiety. In this article we synthesize and evaluate fifteen years of NESDA research on prominent psychological risk factors for the onset, persistence, recurrence, and comorbidity of affective disorders.

Methods: A narrative review of 62 NESDA articles examining the specificity and predictive value of neuroticism, behavioral inhibition, repetitive negative thinking, experiential avoidance, cognitive reactivity, locus of control, (implicit) self-esteem, (implicit) disorder-specific self-associations, and attentional bias for the course of affective disorders.

Results: All self-reported risk factors showed cross-sectional relationships with singular and comorbid affective disorders, and prospective relationships with the development and chronicity of depression and anxiety disorders. High neuroticism, low self-esteem, and negative repetitive thinking showed most prominent transdiagnostic relationships, whereas cognitive reactivity showed most pronounced depression-specific associations. Implicit self-esteem showed predictive validity for the persistence and recurrence of anxiety and depression over and above self-reported risk factors. Automatic approach-avoidance behavior and attentional bias for negative, positive, or threat words showed no relationship with affective disorders.

Conclusion: NESDA identified both (a) transdiagnostic factors (e.g., neuroticism, low implicit self-esteem, repetitive negative thinking) that may help explain the comorbidity between affective disorders and overlap in symptoms, and (b) indications for disorder-specific risk factors (e.g., cognitive responsivity) which support the relevance of distinct disorder categories and disorder-specific mechanisms. Thus, the results point to the relevance of both transdiagnostic and disorder-specific targets for therapeutic interventions.

1. Introduction

Depression and anxiety disorders represent major problems for public health (Ormel et al., 2008). The disability and health care costs of depression and anxiety disorders are especially high due to their chronic (intermittent) course (Mathers and Loncar, 2006). Despite several effective treatments, recurrence is common in both depression and anxiety disorders (Bruce et al., 2005; Hardeveld et al., 2013). Taking also diagnostically unstable recurrence into account, reported recurrence rates are as high as 66.3% (Scholten et al., 2016). This points to the importance of improving our understanding of factors involved in the origin, chronicity, and recurrence of affective disorders. This was the prime reason for the Dutch Organization for Health Sciences to grant funding in 2004 for a large scale, long-term longitudinal research program focusing on depressive and anxiety disorders: The Netherlands Study of Depression and Anxiety (NESDA, www.nesda.nl). The design of NESDA provided an excellent infrastructure to examine psychological risk factors involved in the (chronic) course of affective disorders. In this

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Table 1
Sample characteristics at the various waves of the Netherlands Study of Depression and Anxiety (NESDA).

	Wave 1	Wave 2	Wave 3	Wave 4	Wave 5	Wave 6
Average follow-up duration since baseline	Baseline	1 year	2 years	4 years	6 years	9 years
Sample size	2981	2445	2596	2402	2256	2069
Response rate	na	82.0%	87.1%	80.8%	75.7%	69.4%
Persons with current* anxiety and/or depressive disorders	57.1%	na	37.4%	31.9%	28.5%	27.5%
Persons with remitted** anxiety and/or depressive disorders	21.1%	na	41.7%	48.1%	51.7%	53.4%
Persons without any lifetime anxiety and/or depressive disorders	21.9%	na	20.9%	20.0%	19.8%	19.1%

Note. * current is based on 6-month recency
** remitted is based on lifetime, but not current, diagnosis; na = not available.

review we synthesize fifteen years of NESDA research on the relevance of prominent candidate psychological risk factors in the development and course of depression and anxiety disorders, condensed in more than sixty articles, and critically reflect on how these findings might inform treatment of affective disorders.

At the start of the study, NESDA included persons diagnosed with a current depression and/or anxiety disorder, a history of depression and/or anxiety disorder, and individuals without a current or past disorder (Penninx et al., 2008). Participants were recruited from 2004 to 2016 in different settings (general population, primary care and mental health care organizations), in multiple waves (baseline, 1, 2, 4, 6 and 9 year follow-up). At baseline 57% of participants were diagnosed with a current affective disorder (Table 1). NESDA's ultimate aim was to provide starting points for improving treatment options. Therefore, the emphasis of the psychological measures that were included in NESDA was on malleable risk factors.

Due to its large sample size and longitudinal design, NESDA provided an excellent opportunity to complement available evidence on psychological risk factors in multiple important ways. First, earlier cross-sectional findings could be replicated in a well-powered study that allowed for comparison of well-defined clinical groups, including remitted individuals, and those with comorbid disorders. Second, NESDA allowed researchers to test the disorder-specificity of particular risk factors. At the start of NESDA, most research examining psychological factors in affective disorders was restricted to particular disorder (e.g., cognitive reactivity in depression), precluding the opportunity to test whether this particular factor might more generally contribute to affective disorders (i.e. having a 'transdiagnostic' association with both anxiety and depression). Third, prospective relationships of particular psychological measures with both remittance and chronicity, as well as the development of comorbidity could reliably be examined. Fourth, the inclusion of multiple psychological measures during the same assessment wave allowed to examine to what extent the relationships between particular risk factors and the course of affective disorders represented unique or (partly) overlapping relationships. Fifth, NESDA not only relied on self-report measures but also included implicit performance-based measures of constructs that are central to cognitive models of emotional disorders but are not accessible to introspection such as attentional bias (Bar-Haim et al., 2007; McCabe et al., 2000), negative automatic self-associations (Beevers et al., 2015) and automatic approach/avoidance behavior (Rinck and Becker, 2007). Finally, the inclusion of individuals without a history of affective disorders provided a helpful reference group to examine the relevance of the included psychological measures as risk factors for the first onset of anxiety and/or depression disorders in those who developed a first episode after inclusion in the study (Glashouwer et al., 2011; Kruijt et al., 2013).

In line with dimensional models of psychopathology, NESDA included anxiety and depression symptom severity measures next to categorical measures based on a clinical interview. This further facilitated empirical scrutiny of general versus disorder specific involvement of the psychological risk factors in affective disorders. To guarantee the study's feasibility and to promote participants' long-term commitment for repeated assessments over a (very) long time span, only a very limited number of measurement instruments could be part of the study. Initial selection of measures was heavily inspired by the rapidly accumulating evidence in the late 1990s and early 2000s for the importance of dysfunctional cognitive processes in the development of affective disorders (Mathews and MacLeod, 2005), which still is highly topical (Teachman et al., 2019).

We selected measures of constructs that already showed promise as a candidate risk factor in earlier research in the context of anxiety (e.g. anxiety sensitivity; Taylor, 1999), and depression (e.g., cognitive reactivity; Segal et al., 1999), and measures of mechanisms that showed promise in both anxiety and depression disorders (e.g., repetitive negative thinking; Papageorgiou and Wells, 2008). Next to these relatively specific psychological constructs, also more generic trait characteristics/personality dimensions with an established link to psychopathology were measured (e.g., neuroticism; Ormel et al., 2004)

Each of these psychological risk factors in NESDA shall be introduced below and we review their key outcomes across all articles listed under 'psychological vulnerabilities' on the NESDA website (https://www.nesda.nl/publication-category/psychological-vulnerabilities/). Each section sets out to answer the following research question: "what are the cross-sectional and prospective relationships of psychological risk factors studied within NESDA with affective disorders and their comorbidities?" This review concludes with an integration of the overall pattern of findings and a reflection on the relevance of differentiating between general and disorder-specific risk factors, and how this connects to our understanding and treatment of affective disorders.

2. Personality

2.1. Basic personality dimensions

Personality captures relatively stable patterns of feelings, thoughts, needs, wants, and behavior over time and across context (John et al., 2008). Undesirable extremes of normal personality variation have historically been understood as psychopathology, a notion that regains influence within psychiatry (Bucher et al., 2019; Kotov et al., 2017). Personality differences comprise the broadest conceptual level of psychological risk in NESDA and were operationalized using the Big Five personality factors of neuroticism, extraversion, conscientiousness, agreeableness, and openness to new experiences (Costa and Mccrae, 1995).

Neuroticism and extraversion were the most studied risk factors of emotional disorders in NESDA, and were also often included in articles that focused on other (psychological) risk factors. The Big Five was assessed at baseline and at two- and four-year follow-up, showing a mean-level decrease in neuroticism (from M = 36.3 [SD= 9.4] to 32.7 [8.5]), and an increase in extraversion (M = 36.9 [7.4] to 38.1 [7.4]; see Struijs et al., 2020). As extraversion levels typically decrease over adulthood this suggests that the NESDA trajectory is likely to reflect recovery from baseline affective problems. Across the NESDA studies highly specific subgroups of participants were selected, and average neuroticism scores therefore differed substantially across papers (from M = 15.40 [7.40] to 46.00 [5.70]), just as for extraversion (from M =

29.90 [6.20] to 42.60 [6.20]). Studies using conscientiousness, agreeableness, and openness showed comparable mean-level differences.

Neuroticism captures a broad vulnerability index from characteristic levels of negative affect and self-consciousness, avoidance, vigilance, worry, rumination, to increased sensitivity to threat, punishment, and uncertainty (Ormel et al., 2013). Neuroticism also underlies the concept of a neurobiological Behavioral Inhibition System and avoidance motivation (BIS; Larsen et al., 2020). High extraversion taps into the tendency to experience frequent intense positive affect and to be sociable, assertive, energetic, risk-taking, and excitement seeking, versus being more reserved and solitary. Dispositional optimism, a positive attitude to life and generalized positive expectations towards the future (Carver et al., 2010), and the Behavioral Approach System (BAS) both refer to motivational systems that are also measured by extraversion (Larsen et al., 2020). High conscientiousness taps into the tendency to be self-disciplined (achievement oriented), persistent, reliable, ordered, and dutiful (norms/rules), and captures the self-regulation that plays a protective role during the development of emotional disorders and during recovery. High agreeableness captures the tendency to be kind, cooperative, trustworthy, trusting, generous and empathic. High openness to new experiences taps into the tendency to be perceptive, creative, reflective, flexible, curious, and to appreciate fantasy, aesthetics, and novelty.

2.1.1. Cross-sectional associations

The basic personality dimensions showed moderate to strong intercorrelations (r = .30 to .70), and substantial associations with anxiety and depression symptom severity and disorders (effect size r = .55 to .85, see Kok et al., 2017; Mesbah et al., 2019; Noteboom et al., 2016; Spinhoven et al., 2013, 2014). Compared to individuals without a history of affective problems, individuals diagnosed with anxiety (i.e., GAD, agoraphobia, and panic disorder), and depression (i.e., MDD, dysthymia) disorder, were characterized by higher neuroticism and lower extraversion and conscientiousness scores (Cohen's d > 0.80) and lower agreeableness (d = ~0.50). The personality differences between the diagnostic groups were much smaller in comparison (ds < 0.50). In multivariate models, disorder groups were marked by high neuroticism levels (Noteboom et al., 2016) and low extraversion as reflected in low positive affect and low sociability (Spinhoven et al., 2014).

Neuroticism showed substantial correlations with many of the more specific psychological risk factors, such external locus of control (LoC), hopelessness, rumination, worry, experiential avoidance, and fearful avoidance (r = .65 to .80); and all these specific risk factors also showed substantial correlations with cognitive reactivity (r > .50, Kruijt et al., 2013) and low extraversion (r ≤ -.45, see Boschloo et al., 2010; Drost et al., 2014; Glashouwer et al., 2011, 2012; Hovenkamp-Hermelink et al., 2019; Kok et al., 2017; Spinhoven, Elzinga, et al., 2015; Spinhoven, Drost, et al., 2016; Struijs, Lamers, Spinhoven, et al., 2018; Struijs et al., 2020). These concepts are thus all closely related.

Happiness and emotional well-being levels were highest in participants without a history of affective problems, followed by participants who recovered from an anxiety and/or depressive disorder, and lowest in participants with current affective problems (Spinhoven, Elzinga, et al., 2015). Extraversion and to a lesser extent neuroticism consistently forecasted future happiness and emotional well-being, also when the model was statistically controlling for concurrent measurements of affective disorders and symptoms, which may (temporarily) influence personality scores. Most participants with a current anxiety or depression disorder were reasonably happy, but among those with comorbid problems, almost half felt unhappy to a certain extent. Dispositional optimism was associated with a lower risk of current anxiety, depression, and their comorbidity, and fewer current and past mood disorders (Broekhof et al., 2015).

2.1.2. Longitudinal relationships

Individuals who did not improve in their anxiety and depression over two to six years follow up as indexed by clinical interview (CIDI) and symptom measures (BAI/IDS-SR) typically reported higher baseline neuroticism and lower conscientiousness and extraversion (Karsten et al., 2012; Spinhoven et al., 2012). The personality scores showed correlated changes with the occurrence, recovery, or persistence of affective disorders over time (Karsten et al., 2012; Spinhoven et al., 2013), indicative of their intimate co-development. Especially neuroticism predicted unfavorable course trajectories of anxiety and depression symptoms and disorders over up to nine years follow-up (OR = 1.24 to 1.66). Part of the prospective effect of neuroticism on anxiety and depression was mediated by more stressful life events (Jeronimus et al., 2013). Also, low extraversion and poor sociability (OR = 0.61-0.83) were risk factors for such unfavorable trajectories (see Hovenkamp-Hermelink et al., 2019; Hovens et al., 2016; Spinhoven et al., 2011, 2013; Struijs et al., 2013; Struijs, Lamers, Spinhoven, et al., 2018; Struijs et al., 2020; Wiersma et al., 2011). Neuroticism, extraversion, worry, rumination, and anxiety sensitivity predicted the course of anxiety symptoms (R^2 < 6%), although none of these factors was a unique predictor (Spinhoven, Batelaan, et al., 2016), which is often an indication of multicollinearity, also suggested by their substantial intercorrelations.

At baseline participants with a primary diagnosis of bipolar disorder had been excluded from NESDA. Mesbah and colleagues (2019) identified risk factors for the emergence of (hypo)manic episodes and symptoms (using the MDQ) in patients initially diagnosed with anxiety or depressive disorders. They identified high neuroticism (HR= 1.70) and low agreeableness (HR= 0.52) as predictors of the incidence of (hypo)manic episodes (N = 31/1888, 1.6%) or symptoms (233/1319, 18%) within the follow up period two to seven years after the baseline assessment. Once concomitant psychopathology and childhood adversity (HR = 0.77) were considered, only low agreeableness showed independent predictive validity. Thus, participants who developed (hypo) manic episodes described themselves as less cooperative, likeable, and unwilling to follow advice than those who did not develop (hypo)manic episodes.

The strong overlap of risk factors surfaced in the multivariate analyses in which more specific risk factors stopped being predictive of anxiety and depression when neuroticism was part of the model. For example, experiential avoidance predicted the onset, recurrence, and maintenance of depressive disorders over four years (Spinhoven, Drost, et al., 2016), but this relationship was fully explained by neuroticism, rumination, and worry. Also, the predictive validity of anxious and depressed self-associations for the onset of anxiety disorders over the next two years strongly attenuated once neuroticism and baseline anxiety and depression symptoms were part of the model (Glashouwer et al., 2011). There were, however, also specific risk factors that showed prognostic relationships that were independent of neuroticism such as differences in cognitive reactivity (Kruijt et al., 2013) and implicit self-esteem (van Tuijl et al., 2020).

2.1.3. Concluding remarks

Most personality risk factors were shared across anxiety and depression diagnostic categories (i.e. transdiagnostic), especially neuroticism, whereas some other personality risk factors showed relationships with specific symptoms of affective disorders, such as low extraversion or sociability. The personality risk factors showed strong correlations, also with external locus of control, hopelessness, rumination, worry, experiential avoidance, and fearful avoidance, which suggests that they cover similar phenotypic trait space and rely on shared machinery. The studies are in keeping with the broader literature that identified personality differences as the strongest available psychological predictors of future anxiety and depression problems. The NESDA results were consistent with the idea of a "healthy personality" with low neuroticism and relatively high levels of extraversion, conscientiousness, agreeableness, and openness (Bleidorn et al., 2020), as these participants were least likely to develop affective problems. Finally, the

correlated changes between personality scores and occurrence, remission, and persistence of affective disorders over time underscores their co-development.

2.2. Locus of control

Locus of control (LoC) is a personality construct that combines mastery and perceived constraints. To index LoC within NESDA, the Pearlin mastery scale was used (Pearlin and Schooler, 1978). A lower score indicates a more externally oriented LoC, the belief that outcomes in one's life are mainly due to chance or fate, whereas higher scores reflect a more internally oriented LoC, when one feels able to influence actions, other persons, and situations (mastery). LoC proved to be rather stable over up to nine years (Hovenkamp-Hermelink et al., 2019; Struijs et al., 2020), with NESDA participants becoming slightly more internally oriented over time (Hovenkamp-Hermelink et al., 2019; Hovens et al., 2016).

2.2.1. Cross-sectional associations

To provide some insight into the associations between the psychological vulnerability markers in NESDA; at baseline, more external LoC was positively associated with neuroticism (r=0.57), hopelessness (r=0.54), rumination (r=0.43), worry (r=0.54), anxiety sensitivity-physical concerns (r=0.19), anxiety sensitivity-social cognitive concerns (r=0.40), and negatively with extraversion (r=-0.41; Struijs et al., 2018). More external LoC was associated with more intense depressive symptoms (Struijs et al., 2013). This relationship was specifically carried by the cognitive symptoms of depression. Participants with an anxiety and/or depression disorder diagnosis showed lower scores on the mastery scale (i.e, external LoC) than participants without a history of affective disorders (Kok et al., 2017; Vlasveld et al., 2013), whereas remitted respondents scored between these two groups (Vlasveld et al 2013). The baseline data of individuals diagnosed with depression disorder in the past year showed that a more external LoC was also associated with more chronicity of depression (Wiersma et al., 2011). A study restricted to individuals diagnosed with panic disorder showed that LoC scores did not differ between subtypes of panic disorder (Pattyn et al., 2015).

2.2.2. Longitudinal relationships

External LoC showed independent predictive value for depressive symptoms at one-year follow up (Struijs et al., 2013); notably this predictive relationship was restricted to the cognitive symptoms of depression. In addition, participants with a more external LoC generally showed a relatively unfavorable course of affective disorders over 2-9 years (range of odds 1.25-1.45) in terms of chronicity of anxiety and depression disorder diagnoses as well as symptom severity (Hovenkamp-Hermelink et al., 2019; Struijs et al., 2018), despite adjustment for their mutual overlap, thus an external LoC proved to be a generic risk factor for affective disorders.

Two studies showed that LoC might also play a role in the impact of (self-reported) stressful life situations on (the course of) anxiety and depression symptomatology. One study showed that more external LoC mediated the relationship between childhood maltreatment and more intense symptoms of anxiety/depression as well as lower remission rates of anxiety and/or depressive disorder diagnosis at four year follow up (Hovens et al., 2016). The other study indicated that external LoC predicted higher anxiety and depression severity, but was unrelated to the incidence of positive and negative life-events (Hovenkamp-Hermelink et al., 2019). Meanwhile, more negative life-events in those with relatively high depression severity showed a prospective relationship with more external LoC, whereas more positive life-events were associated with more internal LoC. This unidirectional prospective association between life events and LoC is consistent with the view that LoC might be an important moderator/mediator of the link between experienced stress and the severity of depression symptoms. Accordingly, these NESDA findings highlight the relevance of stress related changes in LoC as one of the mechanisms that may link stress experiences to changes in vulnerability for psychopathology.

2.2.3. Concluding remarks

The NESDA findings are consistent with the view that individuals with a more externally oriented LoC are more likely to show both anxiety and depression symptoms and disorders and an unfavorable (chronic) course, which makes LoC a transdiagnostic vulnerability. In addition, the findings suggest that negative stressful experiences promote the development of a more external LoC. Combined, this points on the relevance of stress-driven changes in LoC as a mechanism that can help explain how stressful experiences may increase risk of developing (chronic) affective disorders.

2.3. Approach and avoidance tendencies

Anxious individuals generally avoid perceived threats to reduce levels of fear or anxiety, while depressed individuals show reduced approach and increased avoidance motivation. Two broadband motivational systems are thought to be involved in the development of anxiety and depression (Gray, 1987). In NESDA these were measured using the BIS/BAS self-report questionnaire and the Approach-Avoidance Task (AAT). The AAT is a reaction time task in which participants had to push or pull pictures of various emotional expressions (e.g., angry, happy, fearful) as fast as possible based on the color (yellowish/greyish) of the pictures (Struijs et al., 2017).

2.3.1. Cross-sectional associations with anxiety and depression

Automatic approach-avoidance tendencies showed no consistent association with any psychiatric variable or between individuals with and without disorders (Struijs et al., 2017). In contrast, all patient groups showed medium to large differences in trait avoidance scores compared to individuals without (a history of) anxiety/depression. Whether these associations were independent of differences in neuroticism was not analyzed. BAS scores were largely unrelated to diagnostic status and only showed a small dose-response relationship with depressive symptom severity, in line with the aforementioned role of extraversion.

2.3.2. Longitudinal relationships with anxiety and depression

Stronger trait avoidance tendencies predicted increased risk of recurrence (OR=1.55) and chronicity (OR=1.31) of anxiety disorders also when statistically controlling for demographics and baseline affective disorders (Struijs et al., 2018). Trait avoidance was also associated with the recurrence and chronicity of comorbid disorders (OR=1.29). The associations between stronger trait avoidance tendencies and increased risk of onset and chronicity of depressive disorders were no longer significant when statistically controlling for demographics and baseline affective disorders.

2.3.3. Concluding remarks

Behavioral inhibition seems to be a transdiagnostic feature of affective disorders, and to be more pronounced in anxiety than depression, and predictive of disorder recurrence and chronicity. Computerized performance measures of avoidance tendencies using emotional facial expressions appeared unrelated to outcomes. Finally, we found little evidence for low trait approach tendencies as a risk factor for the development of anxiety and depression.

3. Cognitions

3.1. Repetitive negative thinking and experiential avoidance

Repetitive negative thinking (RNT) comprises repetitive and intrusive thoughts, and a persistent focus on one's problems or negative

experiences (Ehring and Watkins, 2008). Measures of RNT typically focus on disorder-specific content such as worrying about future threats in anxiety, and rumination about past experiences in depression. Experiential avoidance captures unwillingness to remain in contact with aversive private experiences and avoidance of aversive experiences or eliciting cues (Hayes et al., 1996). Experiential avoidance has been associated with psychological constructs such as worry and rumination based on the presupposition that these mechanisms are strategies to avoid the overwhelming affect associated with specific thought content (Borkovec, 1994; Moulds et al., 2008).

3.1.1. Cross-sectional associations with anxiety and depression

RNT and experiential avoidance showed a moderately strong ($r > .5$) interrelationship, and showed cross-sectional relationships with symptoms of anxiety and depression, as well as with other psychological risk factors (e.g., neuroticism) (Spinhoven, Drost, et al., 2016; Struijs, Lamers, Spinhoven, et al., 2018). Moreover, a latent factor that combined RNT with worry, rumination, and perseverative thinking associated with depressive and anxiety disorders and their comorbidity. In concordance with the strong cross-sectional relationship between rumination and depression (Drost et al., 2012; Wiersma et al., 2011) and between worry and GAD (Drost et al., 2012), both independent of neuroticism, the unique portion of rumination showed a significant relationship with MDD and depressive comorbidity, and the unique portion of worry with GAD (Spinhoven, Drost, et al., 2015). Rumination and worry also showed concurrent associations with alcohol dependence (Boschloo et al., 2013), and rumination with evening chronotype (Solis et al., 2017), but not with cortisol awakening response (van Santen et al., 2011)..

3.1.2. Longitudinal relationships with anxiety and depression

In univariate analyses, worry, rumination, and experiential avoidance were risk factors for the onset, persistence, and recurrence of anxiety and depressive disorders over four-year follow-up (Spinhoven et al., 2016, 2017). This predictive effect became greatly attenuated in multivariate analyses statistically controlling for demographics, baseline symptoms, and neuroticism. The predictive properties of rumination and worry were independent of experiential avoidance, whereas the predictive value of experiential avoidance was not independent of rumination and worry (Spinhoven et al., 2016). Moreover, rumination predicted more persistent depression over 2-6 years, while worry was most strongly associated with persistent GAD (Struijs et al., 2018). The predictive power of rumination and worry on different course trajectories of anxiety disorders was also examined using a data-driven method based on life chart data of anxiety and avoidance symptoms (Spinhoven, Batelaan, et al., 2016). Symptoms of anxiety and avoidance persisted in 25% of the participants and slightly increased over six-years follow-up, while 7% reported a severe deterioration of symptoms. These unfavourable course trajectories were predicted by higher baseline levels of worry but not rumination. Yet, worry predicted no incremental variance in affective disorders once neuroticism, extraversion, anxiety sensitivity, and rumination were considered. Finally, rumination but not worry predicted onset of PTSD during a four-year follow-up, also when statistically controlling for demographic and clinical history variables, as well as psychiatric diagnoses at baseline (Spinhoven, Drost, et al., 2015).

3.1.3. Relationships with comorbidity of affective disorders

Longitudinal studies identified RNT or experiential avoidance as predictive of the onset, persistence, and recurrence of both anxiety and depressive disorders, which does not imply that RNT must be a causative factor of (i.e. mediates) their (developing) comorbidity. However, several NESDA studies suggest that high baseline RNT and experiential avoidance are implicated in the increasing comorbidity among anxiety disorders (social anxiety disorder, panic disorder with or without agoraphobia, agoraphobia without panic) and depressive disorders (MDD, dysthymia, GAD) two years later (Spinhoven et al., 2014), and their prospective cross-disorder relationships. Baseline anxiety disorders predicted changes in depressive disorders over four years, which was partly mediated by changes in worry and rumination two years after baseline. The association between baseline depressive disorders and changes in anxiety disorders was mediated by changes in rumination but not by changes in worry (Drost et al., 2014).

Similar results were found when investigating content-independent RNT, with baseline anxiety disorders predicting individual depressive disorders and vice versa over four years, while these prospective associations were significantly mediated by level of RNT as assessed two years after baseline (Spinhoven et al., 2018). Similar analysis with experiential avoidance as putative mediator of comorbidity yielded comparable results with experiential avoidance two years after baseline mediating the prospective association of baseline anxiety disorders with depressive disorders four years later and vice versa (Spinhoven et al., 2014).

3.1.4. Concluding remarks

These NESDA findings strengthen the proposed relevance of negative repetitive thinking and experiential avoidance in the persistence and recurrence of affective disorders. The findings are also consistent with the presupposition that rumination, worry, and experiential avoidance share the tendency to engage in cognitive and behavioral avoidance in order to avoid personally threatening thoughts and accompanying negative emotions. This, common feature is associated with neuroticism and can be seen as a partly independent transdiagnostic risk factor implicated in the onset, course, and comorbidity of anxiety and depressive disorders.

3.2. Cognitive Reactivity

People differ in their probability of developing an anxiety- or depressive disorder in the presence of adversity and chronic stress. One potential explanation comprises ‘anxiety sensitivity’ (AS) and ‘cognitive reactivity’ (CR) to sad mood. AS captures the extent to which emotional or cognitive processes are activated by anxiety-relevant cues, such as bodily sensations. AS was measured with the Anxiety Sensitivity Index (ASI; Peterson and Reiss, 1992; S. E. Taylor and Stanton, 2007). This is an index of ‘reactivity’ – it does not assess the presence of certain thoughts and emotions in general, but their activation in response to a stressor (e.g., “It scares me when my heart beats rapidly”). High AS scores are associated with anxiety disorders (Taylor et al., 2007), suicidality (Capron et al., 2012) and substance abuse (Dixon et al., 2014; Schmidt et al., 2007; Zvolensky et al., 2009).

Cognitive reactivity to sad mood (CR) is the extent to which dysfunctional, depressogenic cognitions are activated by mild states of dysphoria (Teasdale, 1988). CR is typically measured by assessing negative cognitions with the Dysfunctional Attitudes Scales (DAS; Weissman, 1979) before and after the induction of a sad mood. The DAS change score reflects CR (Miranda et al., 1998). However, basic psychometric properties of DAS change scores, such as test-retest reliability, are unknown. Also, the DAS is not very sensitive to change, so mean DAS change scores are typically quite low. To overcome these limitations, the Leiden Index of Depression Sensitivity (LEIDS) was developed (Van van der Does, 2002; Solis et al., 2017) to measure CR without the use of mood induction using conditionally phrased items (e.g., “When I feel down, I am more bothered by perfectionism”), similar to the ASI.

3.2.1. Cross-sectional associations with anxiety and depression

Cognitive reactivity indices are moderately correlated with other psychological risk factors such as neuroticism, extraversion, locus of control and worry ($r = .32$ to $.61$) and were all associated with specific disorders, over and above the variance explained by personality traits neuroticism and extraversion (Drost et al., 2012). AS was specific to panic disorder and social anxiety disorder, whereas the CR subscales

aggression reactivity and rumination were unique to dysthymia and depression (Drost et al, 2012). The finding that recovered-depressed patients have higher LEIDS(-R) scores than never-depressed individuals was already quite robust at the start of NESDA. NESDA showed that chronicity was associated with higher LEIDS-R scores (Wiersma et al. 2011) and that remitted depressed patients with multiple episodes had higher scores than participants who remitted from a single episode (Elgersma et al., 2013). This "dose-response" relationship is consistent with the view that high CR puts people at risk for recurrent depression and is less relevant for the development of an incidental depressive episode.

3.2.2. Longitudinal relationships with anxiety and depression

NESDA showed that in never-depressed individuals, high CR scores predicted the first onset of depression over a period of two years (Kruijt et al., 2013). Furthermore, high scores on the rumination subscale during remission predicted faster recurrence (Figueroa et al., 2015).

Psychological risk factors that theoretically were specific to certain disorders indeed selectively predicted the course of these disorders. AS was associated with chronicity of panic disorder and social anxiety disorder, whereas CR as indexed by the rumination subscale of the LEIDS was associated with chronicity of depression (Struijs et al., 2018). Over a period of nine years, the temporal stability of CR measures was high and comparable to the temporal stability of personality traits such as neuroticism and LoC (Struijs et al., 2020). This pattern of results supports the notion of specific next to transdiagnostic predictors of the course of affective disorders, and is consistent with hierarchical models of psychopathology (Drost et al., 2014; Spinhoven et al., 2017; Spinhoven, Drost, et al., 2015, 2016).

The CR profile (LEIDS-R subscale scores) during remission also associated with the symptom profile during the prior depressive episode. People who were suicidal during their depressive episode, for example, reported more hopelessness during remission than their remitted peers without suicidal thoughts (Antypa et al., 2010). In other words, suicidal thoughts remain especially easily triggered after a depressive episode. This is an important finding for clinicians and patients to be aware of.

3.2.3. Concluding remarks

The finding that CR scores predicted the incidence of depression in never-depressed individuals (Kruijt et al., 2013) is the most novel NESDA finding of this section. It is important both from a clinical and a theoretical perspective. It is one of the first papers to demonstrate a cognitive vulnerability prior to a first depressive episode, in a longitudinal design. The finding that CR seemed especially relevant for the onset of multiple episodes and predictive of a chronic course further underlined its clinical relevance. Cognitive reactivity as indexed by the LEIDS and ASI demonstrated cross-sectional relations with anxiety- and depressive disorders and showed differential predictive validity for the onset, chronicity, and recurrence of both anxiety and depression. Both cognitive reactivity indices share common aspects and strongly suggest that emotional and cognitive processes activated by relevant cues are relevant to understanding affective disorders.

4. Implicit measures

4.1. Disorder-specific self-associations

Dysfunctional self-schemas are assumed to play a causal role in both anxiety disorders and depression (Beck and Haigh, 2014). According to current information-processing models, it is important to differentiate between 'explicit' (self) beliefs and automatic (self) associations (Gawronski and Bodenhausen, 2006). Explicit beliefs stem from the weighting of propositions and their corresponding 'truth' values, while automatic associations reflect more simple associations in memory that are difficult to control and do not require conscious reflection to influence affect, cognition, or behavior. Both types of associations are assumed to have different functional properties and both may be involved in affective disorders.

Thus far, most studies into self-schemas in affective disorders focused on consciously accessible traces of self-schemas and predominantly relied on self-report measures. To complement these 'explicit' findings and more directly tap into self-schemas, NESDA included adapted versions of the Implicit Association Task (IAT; Greenwald et al., 1998) as performance based implicit measures of automatic self-associations (Egloff and Schmukle, 2002). The IAT is a computerized reaction time task designed to measure the relative strengths of automatic associations between two contrasted target concepts and two attribute concepts. The implicit measures proved reliable, as indexed by Spearman-Brown corrected correlations between test halves (between .84 and .92).

4.1.1. Cross-sectional associations with anxiety and depression

Cross-sectional findings provided evidence for disorder-specific automatic and explicit self-associations (Glashouwer and de Jong, 2010). Furthermore, automatic (and explicit) self-anxious/depressed associations partly remained following remittance. Moreover, consistent with the view that automatic and more deliberate self-associations may be play a complementary role in affective disorders, it was found that both types of self-associations showed (partly) independent associations with the severity of symptoms of anxiety and depression (Wave 1: Glashouwer and de Jong, 2010; Wave 3: Jabben et al., 2014).

Automatic self-depressive and self-anxious associations also showed a partly independent relationship with suicidal ideation and attempts (Glashouwer et al., 2010). Although automatic self-associations did not explain additional variance over and above explicit self-beliefs, the interaction between automatic and explicit self-associations did. This suggests that the probability of having suicidal thoughts/attempts was especially high for individuals who had depressive (anxious) self-associations at both the automatic and explicit level.

4.1.2. Longitudinal relationships with anxiety and depression

Both automatic and explicit self-anxious associations and self-depressive beliefs showed predictive validity for the course of anxiety- and depressive disorders. Individuals with relatively strong self-anxious associations showed a reduced chance of remission from anxiety during a two year follow up, whereas individuals with relatively strong self-depressive associations showed a reduced chance of remission from depression (Glashouwer et al., 2012) and a heightened chance for the development of depressive symptoms (Struijs et al., 2013). Explicit self-anxious associations and both explicit and implicit self-depressive associations remained significant when statistically controlling for severity of baseline symptoms.

There was no evidence that relatively strong automatic self-associations preceded the first onset of anxiety disorders at two year follow up (Glashouwer et al., 2011). Automatic and explicit self-anxious associations predicted the recurrence of anxiety disorders within a two year follow up period, but not incremental to baseline measurements of anxiety symptoms and phobic avoidance. Similarly, premorbid automatic and explicit self-depressive associations predicted the first onset of depression within a two-year time window (Kruijt et al. 2013), but not incremental to baseline symptom severity and self-reported cognitive reactivity. Supporting the view that self-depressive associations reflect a malleable risk factor, findings indicated that for those who remitted from depression both automatic and explicit self-depressive associations weakened from baseline to follow up (van Tuijl et al., 2018). Importantly, the (remaining) strength of explicit self-associations after remittance predicted recurrence risk within a four year time window. These associations showed a dose-response relationship (Elgersma et al., 2013; van Tuijl et al., 2018). Thus, self-depressed associations may become stronger following prolonged activation during depressive episodes, which may render individuals increasingly vulnerable for the development of future episodes.

4.2. Affective-evaluative self-associations (self-esteem)

4.2.1. Cross-sectional associations with anxiety and depression

Only the group of comorbid anxiety and major depression disorders showed lowered implicit self-esteem compared to individuals without a history of affective disorders (van Tuijl et al., 2016). This latter group also showed lowest explicit self-esteem. Explicit self-esteem was more generally lowered in individuals with anxiety disorders or depression disorders with scores of remitted/recovered individuals in between the symptomatic groups and the group without a history of affective disorders. Supporting the view that low self-esteem represents a malleable factor, especially for participants with major depression disorder, explicit self-esteem substantially increased following remission (van Tuijl et al., 2020).

4.2.2. Longitudinal relationships with anxiety and depression

Both explicit and implicit self-esteem were significant predictors of anxiety and depression recurrence within a three-year time window. When statistically controlling for baseline symptoms, neuroticism, and history of comorbid depression/anxiety (i.e., adjusted models), specifically implicit self-esteem still showed independent predictive validity for depression recurrence, whereas both low implicit and explicit self-esteem showed independent prognostic value for anxiety recurrence.

4.2.3. Concluding remarks

NESDA provided evidence for dysfunctional disorder-specific (automatic) self-associations in individuals with anxiety and/or depression disorders, whereas lowered implicit self-esteem seems restricted to individuals with comorbid anxiety and depression disorders. Both types of self-associations seem especially relevant for the persistence and recurrence of affective disorders.

4.3. Attentional bias in depression

Cognitive models of depression emphasize the role of biased processing of affective information in the development and chronicity of depression (De Raedt and Koster, 2010; Gotlib and Joormann, 2010). A difficulty to redirect attention away from negative, depression-relevant information (Koster et al., 2005) together with attentional avoidance of positive information (Winer and Salem, 2016) may give rise to a negative, self-reinforcing loop that hampers people's ability to correct overly negative views of themselves and the world. The Exogenuous Cueing Task (ECT) that has been used in previous research to measure attentional bias in depression (e.g., Koster et al., 2005) was also included in NESDA to assess Attentional Bias (AB) for negative (e.g., inferior, worthless) and positive (e.g., valued, powerful) attributes. To test the specificity of AB for depression-relevant negative information, also general threat words were included (e.g., dangerous, pain). To differentiate between early and late processes the ECT covered short and long presentation times (500 and 1250 ms) (cf. Koster et al., 2005). Reaction-time based measures of AB typically show low internal consistency (McNally, 2019). This also yielded for the AB measures in NESDA (with Cronbach's alpha close to zero) which may have hampered their sensitivity as a measure of individual differences.

4.3.1. Cross-sectional and longitudinal relationships with depression and comorbidity

There was no evidence for AB towards negative or away from positive attributes in participants with major depression disorder (without dysthymia or history of AD) or individuals with major depression and a comorbid anxiety disorder (Elgersma et al., 2018), nor for threat adjectives. Yet, there was weak evidence that patients who were remitted from depression did show a differential AB that was restricted to negative attributes for long duration trials (1250 ms). This maintained attention for negative information might reflect a heightened sensitivity for signals related to the impending threat of a new upcoming depressive episode. Longitudinal findings showed that this and other AB were however not associated with the recurrence of major depression disorder or increased depressive symptoms up to four year follow up (Elgersma et al., 2019).

4.3.2. Concluding remarks

There was no consistent evidence for AB towards negative or away from positive adjectives in strictly defined clinical groups with major depression, with or without a comorbid anxiety disorder. Thus, heightened AB for negative or a lowered AB for positive adjectives seems not critically involved in the maintenance of depression. Longitudinal analyses in participants who were remitted from a major depression indicated that AB for negative or positive adjectives is neither critically involved in the recurrence of depression.

5. Discussion

As summarized in Table 3, most psychological risk factors included in NESDA are cross-sectionally associated with both singular anxiety and depressive disorders as well as their comorbidity. The same holds for disorder recurrence and persistence, and to a lesser extent first onset of affective disorders. NESDA identified transdiagnostic factors that may help explain the high comorbidity between affective disorders and overlap in symptoms, and indications for partly overlapping disorder-specific risk factors, which support the relevance of distinct disorder categories and disorder-specific mechanisms. This suggests that treatments could aim at transdiagnostic mechanisms implicated in diagnosis (e.g. neuroticism Barlow et al., 2017; or self-esteem, see Korrelboom et al., 2012), and that such a general approach could be complemented with disorder/diagnosis-specific interventions addressing more specific mechanisms (e.g., mindfulness-based cognitive therapy for cognitive reactivity, see Kuyken et al., 2010). Within NESDA adults with low neuroticism and relatively high levels of extraversion, conscientiousness, agreeableness, and openness were least likely to develop affective problems, in line with the notion of a healthy personality profile (Bleidorn et al., 2020).

5.1. Cross-sectional associations of psychological risk factors with affective disorders

Almost all of the selected self-reported psychological risk showed cross-sectional relationships with the development and chronicity of singular and comorbid anxiety and depression disorders. Replicating earlier cross-sectional findings in this well-powered NESDA study that allowed for selection of well-defined clinical groups, including individuals who were remitted from anxiety and/or depression and/or with a comorbid profile.

As an important asset, NESDA not only relied on self-report measures but also included implicit performance-based measures of constructs that are central to cognitive models of emotional disorders but are not accessible to introspection (Bar-Haim et al., 2007; Beevers, 2005; McCabe et al., 2000). NESDA provided emerging evidence for dysfunctional disorder-specific (automatic) self-associations in individuals with anxiety and/or depression disorders, whereas lowered implicit self-esteem was restricted to individuals with comorbid anxiety and depression disorders. Both types of self-associations seem especially relevant for associations with the persistence and recurrence of affective disorders.

However, in contrast with promising earlier results (Koster et al., 2005) there was no consistent evidence for attentional bias towards negative or away from positive adjectives in strictly defined clinical groups with affective disorders. Also, automatic approach-avoidance of emotional facial expressions showed no relationship with affective disorders. Important results given the fact that both attentional bias and automatic behavioral tendencies never before have been studied on such a large scale in well-defined clinical samples.

Table 2
Psychometric and descriptive details of psychological risk factors assessed within NESDA.

Construct	Description	Measure	Waves	#	Items	CA	Mode
Basic personality dimensions							
Extraversion	Sociability, positive affectivity, energy.	NEO-FFI	1,3,4	21	12	0.78-0.84	SR
Conscientiousness	Disciplined, goal striving, adherence to principles	NEO-FFI	1,3,4	17	12	0.78-0.80	SR
Agreeableness	Likability, trust, cooperation and altruism	NEO-FFI	1,3,4	15	12	0.58-0.83	SR
Openness	Intellectual curiosity, need for variety, and progressive attitudes	NEO-FFI	1,3,4	15	12	0.63-0.78	SR
Neuroticism	Emotional instability, negative affect, doom	NEO-FFI	1,3,4	28	12	0.75-0.90	SR
Locus of Control	Internal (stable) versus external (fate) LOC. Only mastery was assessed.	PM	1,3,4,5,6	9	5	0.87-0.88	SR
Dispositional Optimism	Generalized positive expectations towards the future	LOT-R	4	1	6	0.87	SR
Impulsivity	Disinhibition, Thrill and adventure seeking, experience seeking, boredom susceptibility	SSS	4	1	32	0.56-0.86	SR
Approach and Avoidance		BIS/BAS	4,5	2	11		SR
	Behavioral inhibition	BIS	4,5	2	7		SR
	Behavioral activation	BAS	4,5	2	4		SR
	Approach	AAT	4,5	2			CT
	Avoidance	AAT	4,5	2			CT
Self-esteem	Global Self-esteem	RSES	5,6	2	10	0.92	SR
Cognitions							
Worry	unwanted, uncontrollable, aversive cognitive activity associated with negative thoughts and emotional discomfort (frequency/intensity). Worry engagement scale.	PSWQ	1,2,3,4,5,6	13	11	0.92-0.96	SR
Perseverative thinking	Content-independent measures of repetitive negative thinking	PTQ	5,6	2	15	0.97	SR
Experiential avoidance	Acceptance and Action	AAQ-I	3,4	3	9	0.69-0.74	SR
Hopelessness/Suicidality	reactivity (subscale)	LEIDS-r	1,3,4,5,6	11	5	0.82-0.93	SR
Acceptance / Coping	subscale	LEIDS-r	1,3,4,5,6	5	5	0.56	SR
Aggression	subscale	LEIDS-r	1,3,4,5,6	7	6	0.79	SR
Control / Perfectionism	subscale	LEIDS-r	1,3,4,5,6	6	6	0.61	SR
Risk aversion	subscale	LEIDS-r	1,3,4,5,6	6	6	0.67	SR
Rumination on sadness	subscale	LEIDS-r	1,3,4,5,6	17	6	0.70-0.93	SR
Anxiety sensitivity	Fear of Anx S_x because of beliefs of their perceived harmful physical, social, or cognitive consequences	ASI		7	16	0.87-0.98	SR
	* Physical concerns	ASI-phc	1,2,3,4,5,6	3	8	0.87-0.89	SR
	* Social cognitive concerns	ASI-scc	1,2,3,4,5,6	3	6	0.78-0.80	SR
Cognitive reactivity	Cognitive reactivity to sad mood	LEIDS-r	1,3,4,5,6	5	34	0.93	SR
Implicit measures							
Implicit self-anxious associations	* Self-Anxiety (D-measure)	IAT	1,3	4		.87†	CT
Implicit self-depressive associations	* Self-Depression (D-measure)	IAT	1,3	8		.82†	CT
Explicit self-anxious associations	* Trait-Anxiety	IAT	1,3	4	10	0.94	SR
Explicit self-depressive associations	* Trait-Depression	IAT	1,3	8	10	0.95	SR
Implicit affective self-associations	* Self-esteem (D-measure)	IAT	5,6	2		.85†	CT
Attention bias	Exogenous cueing task: negative, positive, threat, neutral	ECT	3,4	2			CT

Note. #= NESDA studies that used the construct. †= Spearman-Brown corrected correlations between test halves. **Wave 1**=Baseline. **AAT**=Approach Avoidance Task. **ASI**= Anxiety Sensitivity Index. **BIS=**Behavioral Inhibition System. **BAS**=Behavioral Activation System. **CA=** Cronbach Alpha. **CT=** Computerized Task**. ECT**=Exogene Cueing Task. **IAT**= Implicit Association Test. **LEIDS-r**= Leiden Index of Depression Sensitivity – revised. **LOT-R**= Life Orientation Test-Revised. **NEO-FFI**=Neuroticism-Extraversion-Openness Five-Factor Inventory. **PM**= Pearlin Mastery Scale. **PSWQ**= Penn State Worry Questionnaire. **PTQ**= Perseverative thinking questionnaire. **RSES**= Rosenberg Self-esteem Scale. **SR**= Self-report. **SSS**= Sensation Seeking Scale, abbreviated version.

Overall, psychological risk factors showed moderate to strong interrelationships, and most risk factors were associated with either both anxiety and depression or neither (see Table 3), highlighting the similarities rather than the differences between these two seemingly distinct diagnostic entities (Kotov et al., 2017). The NESDA research methodology allowed for important nuances to be made however, such as low extraversion and cognitive reactivity being more specific for depression and social anxiety, and avoidance tendencies being more prominent in anxiety compared to depression (Fricke and Vogel, 2020). Also, certain content-related aspects of repetitive negative thinking were linked to specific disorders (e.g., worry was more strongly related to GAD, whereas rumination was more strongly related to MDD (Spinhoven et al., 2018). Finally, disorder specific self-associations proved to be associated with specific disorders (e.g. self-anxious associations were stronger in anxiety disorders).

Some risk factors showed specific associations with comorbid anxiety and depression, such as higher neuroticism, habitual avoidance, repetitive negative thinking (RNT) and (implicit) self-esteem (ter Meulen et al., 2021), which is consistent with the view that disorder comorbidity may be more than the sum of its parts (Kleiman and Riskind, 2012).

5.2. Longitudinal associations of psychological risk factors with affective disorders

Thanks to the longitudinal design of NESDA it could be established that most of the candidate psychological risk factors were also associated with the development and recurrence/chronicity of singular and comorbid depression and anxiety disorders and corresponding symptoms (for an overview see Table 4). Several results should be highlighted in that regard.

NESDA showed that cognitive reactivity increases the risk of developing one's first full-blown depression episode, and to experience multiple episodes in a chronic course, which underlined its clinical relevance. Additionally, longitudinal NESDA findings suggest that (early and later) negative life events may promote the development of more external locus of control, thereby pointing to the relevance of stress related changes in locus of control as one of the mechanisms that may help explain how stress experiences may heighten the risk for developing (chronic) affective disorders. Furthermore, implicit self-esteem showed independent predictive validity for depression recurrence even when statistically controlling for baseline symptoms, neuroticism, and history of comorbid depression/anxiety, pointing to its relevance as a target for (preventive) interventions. Finally, NESDA showed that repetitive negative thinking is not only a risk factor for singular anxiety and depression disorders but also specifically for the development of comorbidity.

Psychological risk factors typically overlapped in their predictive qualities when simultaneously included in statistical models. However, some risk factors, such as cognitive reactivity, implicit and explicit self-esteem, and implicit and explicit self-depressive associations showed prognostic value for the development of anxiety and depression that was (partly) independent of other risk factors that were included in the models. Yet, although some risk factors failed to show incremental predictive value (over symptom severity and more general negative affectivity), this does not imply that these factors are no (possible) causal risk factors (Kraemer et al., 2001). More generally, statistically controlling for symptoms and general negative affectivity may over-adjust for the role of potential mechanisms in the etiology and course of depression and anxiety, and remove constituent components from the predictors themselves, such as the depression trait in neuroticism (Riese et al., 2016).

5.3. Treatment implications

As most psychological risk factors seem to be associated with affective disorders in general and are moderately to strongly intercorrelated, it can also be questioned whether it is fruitful to target individual psychological vulnerabilities associated with single depression or anxiety disorders. Their high interrelatedness suggests a common etiologic factor (Hong and Cheung, 2015) presenting an avenue for transdiagnostic interventions. The transdiagnostic model focuses on identifying the common psychological processes that underly a broad array of mental disorders (Harvey et al., 2004) and targeting these factors in treatment across disorders (Barlow et al., 2004). Recently Barlow and co-workers (2014) argued that the core psychopathological mechanism or functional relationship in depression, anxiety and related emotional disorders consists of intense negative emotional reactions as manifested by individuals with higher levels of neuroticism, and subsequent efforts to down-regulate these aversive negative emotional experiences. Such individuals may be more likely to engage in avoidant coping strategies (such as rumination, worry, emotion suppression, experiential avoidance, anxiety sensitivity) to manage their emotions, which paradoxically may increase the frequency/intensity of these negative emotions. Preliminary evidence shows that transdiagnostic treatments such as the Unified Protocol (UP) (Barlow, 2017) targeting these core mechanisms are superior to control conditions on anxiety, depression and quality of life (Newby et al., 2015). It is noteworthy, that most of the available evidence-based interventions for anxiety and depression are designed for single anxiety or depression disorder and are directed at modifying presumed specific mechanisms underlying these single disorders. Comparisons of the effectiveness of transdiagnostic with disorder-specific treatments remain rare and their comparative effectiveness in single and combined disorders is not well established.

Table 3
Overview of cross-sectional associations of psychological factors with (comorbid) anxiety and depression diagnoses.

	Outcome		
Construct	Anxiety†	Depression†	Comorbid
Personality dimensions			
Extraversion	+	++	+
Conscientiousness	+	++	+
Agreeableness	+	+	+
Openness	-	-	-
Neuroticism	+	+	+
Locus of Control	+	+	+
Dispositional Optimism	+	+	+
Approach and Avoidance			
BIS	++	+	+
BAS	–	++	–
AAT approach	–	–	–
AAT avoidance	–	–	–
Cognitions			
Worry	++	+	+
Perseverative thinking	+	+	+
Experiential avoidance	+	+	+
Rumination on sadness	+	++	+
Cognitive reactivity	+	++	+
Anxiety sensitivity	+	-	+
Implicit measures			
Implicit self-anxious associations	++	+	+
Implicit self-depressive associations	+	++	+
Implicit self-esteem	–	–	+
Explicit self-anxious associations	++	+	+
Explicit self-depressive associations	+	++	+
Explicit self-esteem	+	+	+
Attention bias		–	–

Note. – = no association found; + = (a majority of) positive result(s). † Whenever positive associations were found for both depression and anxiety, ++ is used to indicate whenever one association was stronger versus the other.

5.4. Limitations

Direct comparison of cross-sectional associations of psychological

Table 4
Overview of longitudinal associations of risk factors with (comorbid) anxiety and depression diagnoses.

	Anxiety			Depression			Comorbid		
Construct	FO	RC	PS	FO	RC	PS	D	RC	PS
Personality dimensions									
Extraversion	+	-/+	+	+	+	+	+	-/+	-/+
Conscientiousness	-/+	-/+	+	+	+	-/+	+	+	+
Agreeableness	-	-	+	+	-	-/+	+	-	-/+
Openness	-	-	-	-/+	-	-/+	-	-	-
Neuroticism	+	+	+	+	+	+	+	+	+
Locus of Control		+	+		+	+			
Dispositional Optimism									
Approach and Avoidance									
BIS		+	+		+	+		+	+
BAS		–	–		–	–		–	–
AAT approach		–	–		–	–		–	–
AAT avoidance		–	–		–	–		–	–
Cognitions									
Worry	+	+	+	+	+	+		+	+
Perseverative thinking		+	+		+	+		+	+
Experiential avoidance	+	+	+	+	+	+		+	+
Rumination on sadness	+	+	+	+	+	+		+	+
Cognitive reactivity				+	+	+			
Anxiety sensitivity			+			–			
Implicit measures									
Implicit self-anxious associations	–	–/+	–/+		–	–			
Implicit self-depressive associations	–	–	–	–/+	–/+	–/+			
Implicit self-esteem		+			+				
Explicit self-anxious associations	–/+	+	+		–	–/+			
Explicit self-depressive associations	–/+	–/+	–	–/+	+	+			
Explicit self-esteem		+			+				
Attention bias					–	–		–	–

Note. FO = First onset. **RC**= Recurrence. **PS** = Persistence. **D**=Development. – = no association found; -/+ = mixed results or association no longer significant after adjustment of covariates; + = (a majority of) positive result(s).

risk factors with affective disorders remained elusive because not all risk factors could be assessed in the same waves (see table 2). In addition, direct comparison is hampered by differences in selected subgroups and outcomes (e.g., symptoms or disorders), follow-up time, and number and type of predictors in the models. The risk factors that were studied showed conceptual overlap, and also, many NESDA research designs contrasted groups of participants with various levels of symptoms (or diagnoses) for (cross-sectional or longitudinal) group differences on the psychological vulnerabilities, which were sometimes implicitly assumed to reflect a causal process despite the notion these differences between groups could well reflect a scar or concomitant mental state (Haeffel et al., 2021). Finally, NESDA has been set-up in such a way that it favours examination of the course of affective disorders versus the onset of disorders by oversampling diagnosed participants at baseline, and some diagnoses of affective disorders (such as OCD and PTSD) were not represented in NESDA.

5.5. Conclusion

This narrative review of NESDA studies examining the specificity and predictive value of important candidate psychological risk factors showed that – barring attentional bias and automatic behavioral tendencies – all proposed risk factors have both cross-sectional and prospective relationships with the development and chronicity of singular and comorbid depression and anxiety disorders and corresponding symptom severity. Mostly transdiagnostic factors were identified such as high neuroticism, low implicit self-esteem and repetitive negative thinking. Additionally, there were indications for partly overlapping disorder-specific risk factors, which support the relevance of distinct symptom clusters and syndrome-specific mechanisms. Overall, results align with hierarchical models of psychopathology, in which conceptually broad psychological risk factors such as personality, repetitive negative thinking and habitual avoidance are grouped in higher order dimensions (e.g., an 'internalizing spectrum') and conceptually more specific risk factors are grouped in lower order syndromes (i.e., disorders, see Kotov et al., 2017, and Haeffel et al., 2021 for a critique). Together, the results point to the relevance of both transdiagnostic and disorder-specific psychological targets for therapeutic interventions.

Author statement

All authors contributed to conceptualization, writing, editing and revision of the manuscript, and all approved the final article. SS, PdJ and PS designed the study, and interpreted the data. SS and BJ prepared the tables.

Data availability

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

Author Disclosure

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Declaration of Competing Interest

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

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Review article

Fifteen years of NESDA Neuroimaging: An overview of results related to clinical profile and bio-social risk factors of major depressive disorder and common anxiety disorders

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ABSTRACT

The longitudinal Netherlands Study of Depression and Anxiety (NESDA) Neuroimaging study was set up in 2003 to investigate whether neuroanatomical and functional abnormalities during tasks of primary emotional processing, executive planning and memory formation, and intrinsic brain connectivity are *i)* shared by individuals with major depressive disorder (MDD) and common anxiety disorders; and *ii*) characterized by symptomatology-specific abnormalities. Furthermore, questions related to individual variations in vulnerability for onset, comorbidity, and longitudinal course could be investigated.

Between 2005 and 2007, 233 individuals fulfilling a diagnosis of MDD, panic disorder, social anxiety disorder and/or generalized anxiety disorder and 68 healthy controls aging between 18 and 57 were invited from the NESDA main sample (n = 2981). An emotional faces processing task, an emotional word-encoding task, and an executive planning task were administered during 3T BOLD-fMRI acquisitions. In addition, resting state BOLD-fMRI was acquired and T1-weighted structural imaging was performed. All participants were invited to participate in the two-year and nine-year follow-up MRI measurement.

Fifteen years of NESDA Neuroimaging demonstrated common morphological and neurocognitive abnormalities across individuals with depression and anxiety disorders. It however provided limited support for the idea of more extensive abnormalities in patients suffering from both depression and anxiety, despite their worse prognosis. Risk factors including childhood maltreatment and specific risk genes had an emotion processing modulating effect, apparently stronger than effects of diagnostic labels. Furthermore, brain imaging data, especially during emotion processing seemed valuable for predicting the long-term course of affective disorders, outperforming prediction based on clinical information alone.

1. Introduction

Affective disorders including Major Depressive Disorder (MDD) and common anxiety disorders (panic disorder, social anxiety disorder, generalized anxiety disorder) are the most prevalent psychiatric disorders and are characterized by considerable heterogeneity in clinical presentation, etiology, and course of the disorders (Malhi and Mann, 2018). Not only is the symptom representation highly variable across individuals within a certain diagnostic category, this is also the case in terms of simultaneously fulfilling the criteria for multiple psychiatric or somatic diagnostic categories. Psychiatric comorbidity is especially high between MDD and anxiety disorders, most notably panic disorder (PD), social anxiety disorder (SAD), and generalized anxiety disorder (GAD) (Gorman, 1996). Comorbidity estimations vary between 10 and 50 per cent (Gorman, 1996; Roy-Byrne et al., 2000), and often the clinical manifestation of the anxiety disorder precedes the onset of the major depressive episode. Because of this high overlap, but also because depression and anxiety respond to the same treatment strategies (e.g. cognitive behavioral therapy and serotonin reuptake inhibitors), it has been suggested that they have overlapping neurobiological underpinnings, including shared abnormal structural and functional brain pathways (Ressler and Mayberg, 2007). In 2003, clinical neuroimaging

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studies were still very few in number and no study had investigated the overlap in structural and functional brain abnormalities associated with MDD and most common anxiety disorders. Also, existing studies in either depression or anxiety disorders were mostly based on small sample sizes, not allowing to control for, or specifically investigate, clinical heterogeneity. Finally, although it was known at the time that comorbidity of MDD and anxiety was associated with a less favorable clinical course, it was unknown if any structural or functional brain abnormalities would be associated with this clinical phenomenon and whether persistence of depression and anxiety would also be associated with 'aggravation' of brain abnormalities over time. These questions were the primary reason to set up a longitudinal Neuroimaging study as an add-on study of the Netherlands Study of Depression and Anxiety (NESDA) in 2003, in alignment with the main objectives of the main NESDA study (Penninx et al., 2008).

2. Design of NESDA Neuroimaging study

Between January 2005 and April 2007, 301 individuals from the NESDA cohort were included for a structural and functional MRI session at one of the participating centers: Amsterdam, Leiden, or Groningen, where a similar type of 3T Philips MRI scanner was operational. We invited participants who were scheduled for the NESDA baseline interview to also participate in the NESDA Neuroimaging study if they fulfilled the DSM-IV criteria for MDD, SAD, PD and/or GAD in the past 6 months, were available for a scanning session within eight weeks following the baseline interview, were not using any other antidepressant medication than selective serotonin reuptake inhibitors, and had non-regular use of benzodiazepines (see van Tol et al. (2010), for a full overview of in- and exclusion criteria for the NESDA Neuroimaging study). Severity of depressive and anxiety symptomatology was assessed again at the time of scanning We chose our functional MRI task-paradigms based on the then brand new neurocognitive model of Mary Philips on the trans-diagnostic importance of emotional processing for psychiatric disorders (Phillips et al., 2003a, 2003b) and the related limbic-cortical neuroanatomical model of depression of Helen Mayberg (1997), both stressing the importance of adequate interaction between 'dorsal' cortical brain areas and 'ventral' limbic brain regions. We administered the parametric Tower of London executive planning task (van den Heuvel et al., 2003) to capture activity in a 'dorsal' executive control network, an emotional face processing task including sad, fearful, angry, happy and neutral facial pictures (adapted from Wolfensberger et al., 2008) to capture activity of a 'ventral' primary emotional processing network, and an emotional implicit word-encoding and -recognition task (Daselaar et al., 2003; de Ruiter et al., 2007) to capture activity in a memory network. Furthermore, following the promising, at the time new insights that resting state functional connectivity could bring (Damoiseaux et al., 2006; Greicius et al., 2007; Raichle et al., 2001), we included an 8-minute resting state BOLD-fMRI acquisition after individuals were instructed to close their eyes and not think of anything in particular[1]. Finally, a 3D-T1 weighted structural image was acquired for volumetric quantification. The order of the acquisitions was 1) BOLD-fMRI during Tower of London, 2) BOLD-fMRI during implicit encoding of emotional words, 3) T1-3D, 4) BOLD-fMRI during recognition of emotional words, 5) BOLD-fMRI emotional faces task and 6) "resting-state" BOLD-fMRI.

At two-year follow-up, we repeated the full MRI-session and included 199 individuals of the original n=301 sample. The same tasks and sequences were employed. At this two-year follow-up, the 6-channel SENSE head coil in Amsterdam was replaced by an 8-channel SENSE head coil. Otherwise, scanner hardware was identical. At 9-year follow-up, we invited all participants who participated in the baseline measurement, and additionally invited 40 patients fulfilling criteria of MDD with a 6 months recency, 40 healthy siblings of participating MDD patients, and 15 additional healthy controls without a first or second degree family member with any psychological problems. This resulted in the inclusion of a total number of 98 MDD patients and 41 HC for the nine year follow-up measurement. During this assessment, a T1-3D structural image, a 10-minute resting state acquisition, a DTI-scan (Heij et al., 2019), and BOLD-fMRI during a task of effortful emotion regulation of positive and negative emotional images (van Kleef et al., in preparation) were acquired. This measurement was completed between September 2013 and September 2016. In Leiden, the 3T Philips Achieva system had been upgraded with a 32-channel SENSE head coil. At this time, the scanner in Amsterdam was being replaced, therefore most participants included in the Amsterdam area traveled to Leiden for their scan (only 30 minutes by train). In Groningen, the same Philips Intera system as during the baseline and two year follow-up was still operational, although now equipped with a 32- channel SENSE coil. See Fig. 1 for an overview of neuroimaging measurements and samples.

The NESDA MRI project was considered a medium to large scale psychiatric neuroimaging initiative at the time, but in the past decade neuroimaging (and genetics) initiatives of a completely different scale have been launched such as the ENIGMA project (Thompson et al., 2014) and the UK Biobank (http://www.ukbiobank.ac.uk/about-biobank-uk). As detailed below, the NESDA consortium is an active member of the global ENIGMA initiative in which data from the NESDA MRI are used in mega- and meta-analytic approaches.

3. Overview of primary and secondary NESDA Neuroimaging analyses

3.1. Comorbidity of depression and common anxiety disorders

One of the main aims of the NESDA study is to investigate depression and anxiety in concert and to integrate biological and psychosocial models of mood and anxiety disorders (see Penninx et al., 2008). We could therefore include patients with MDD, SAD, PD and/or GAD in the past 6 months for the NESDA imaging study. This allowed us to study whether functional and structural MRI-characteristics of individuals suffering from MDD differed from those suffering from an anxiety disorder, or those suffering from both MDD and a common anxiety disorder. The primary analyses focused on comparing groups of patients fulfilling either criteria for MDD (n = 70), anxiety disorders (n = 71), MDD and comorbid anxiety disorders (n = 92), and healthy controls (n = 68).

Structural imaging: Van Tol et al. (2010) showed in their whole-brain voxel-based morphometry (VBM) analysis of 298 high-quality structural T1-weighted scans that abnormally low volume of the pregenual to dorsal-anterior cingulate cortex was generically observable across individuals with MDD and anxiety disorders compared to healthy individuals, supporting the hypothesis of a common neuropathology. Though not included as *a priori* region of interest, anxiety-depression common lower volume of the posterior cingulate cortex was also observed. Disorder-class specific abnormalities were observed as well. Abnormally low volume of the right inferior frontal cortex was only present in individuals with MDD without comorbid anxiety whereas abnormally low volume of the left superior temporal gyrus was specific to individuals with only anxiety disorders. All observations were independent of sex, age, education, current severity of depressive and anxiety symptomatology, and use of antidepressant medication. Additionally, it was observed that MDD patients with an onset of their first episode before the age of 18 displayed lower subgenual anterior cingulate volume than patients who experienced their first depression after their 18th birthday. No effects for time of onset of the first anxiety episode were observed.

Executive planning: The analysis of whole brain voxel-based fMRI-

[1] Of note, the resting state sequence was added to the study 10 months after inclusion of the first participant and therefore was not available for all participants.

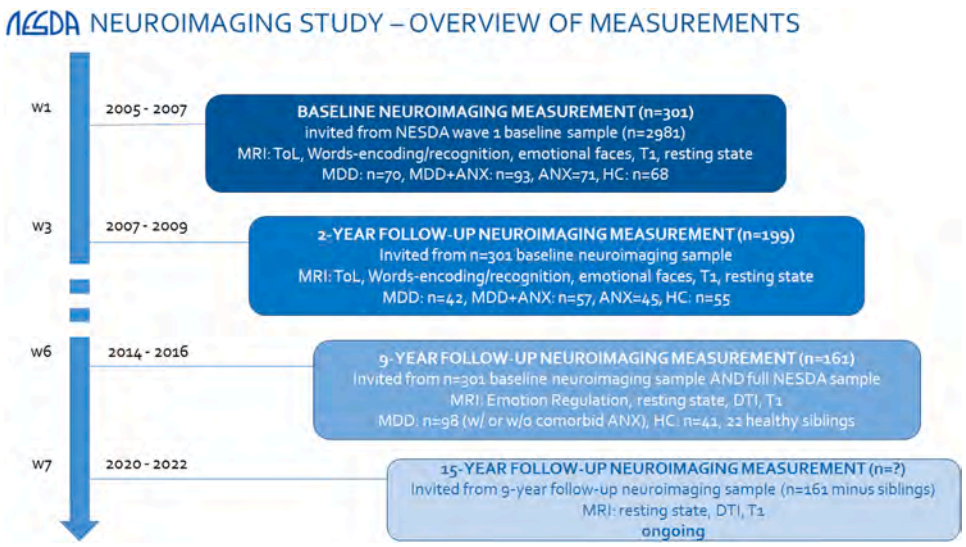

Fig. 1. Summary of NESDA Neuroimaging measurements at NESDA waves 1 (baseline), 3 (2-year follow-up), 6 (9-year follow-up) and 7 (15-year follow-up), including sampling base, type of tasks/MRI-measurements, and sample size per clinical/healthy group.

correlates of executive planning during performance of the parametric Tower of London visuospatial planning task in 211 patients and 63 healthy controls showed marginal support for the hypothesis of abnormalities in the prefrontal cortex associated with MDD symptomatology (van Tol et al., 2011). Analyses indicated slightly elevated activation as a function of increasing planning difficulty in the left dorsolateral prefrontal cortex, which was most pronounced in individuals fulfilling criteria for only MDD (n = 65) and showing moderate to severe depressive symptomatology of depression at the time of scanning. No abnormalities were observed in individuals fulfilling a diagnosis of anxiety disorders only (n = 64). Correction for age, education, sex, and anti-depressant medication use did not change these results. These results suggest that frontal over-recruitment during executive planning is a state characteristic of depression without anxiety.

Emotional face processing: Related to processing of angry, fearful, sad, happy, and neutral faces during a gender-discrimination task including stimuli from the Karolinska Directed Emotional Faces emotional faces set (Lundqvist et al., 1998), no support for abnormal 'ventral' limbic processing was observed in 182 patients with MDD and/or anxiety disorders in response to negative (fearful, sad, angry) face processing compared to healthy controls (n = 56) (Demenescu et al., 2011). Both amygdala response peak height (whole-brain voxel-based) and response shape (of the amygdala region of interest) were investigated. Also, no differences in activation of the amygdala were observed after excluding patients that used antidepressants or when taking current severity of depression or anxiety into account. Instead, hyperactivation of the right dorsolateral prefrontal gyrus in response to positive face viewing was observed in MDD patients, which was interpreted as reflecting an increased demand of resources needed to process the conflict between the stimulus valence and the current mood state. Patients with only anxiety disorders showed elevated responses to happy faces in the lentiform nucleus, explained as defective basal-ganglia linked reward processing previously associated with anxiety disorders. In a follow-up analysis focusing on type of anxiety diagnosis, abnormally low amygdala and lingual gyrus activation to angry, happy, fearful, and neutral faces was observed in PD patients, but not in SAD patients, compared to controls (Demenescu et al., 2013). Presence of co-morbid GAD did not affect this result. Furthermore, in these analyses, the class of anxiety disorder was not associated with abnormal amygdala-seeded connectivity with the medial prefrontal cortex, thought current severity of anxiety symptomatology as measured with the Beck Anxiety Index was associated with increased connectivity during viewing of fearful, but not happy or neutral faces across patients. This suggests that aberrant amygdala responsivity is not common to all anxiety disorders, and may explain the absence of a general anxiety effect in the analyses where all diagnostic classes were pooled. Furthermore, anxiety severity may relate to connectivity with regulatory medial prefrontal brain areas, while not impacting amygdala responsiveness per se.

Implicit word encoding: During the process of implicitly encoding emotional words, it was observed in a whole-brain voxel-wise analysis that patients with depression, anxiety disorders, or both showed abnormally low activation of the right medial hippocampus, which was interpreted as suggestive of abnormal contextual coupling of positive information underlying the vulnerability for both depression and anxiety (van Tol et al., 2012). During implicit encoding of negative words, a depression specific effect of insular hyperactivation was observed in MDD (with [n = 56] and without anxiety disorders [n = 51]) compared to patients with anxiety disorders (n = 56) and healthy controls (n = 49). In the acutely depressed state, additional hyperactivation of the ventrolateral prefrontal cortex and amygdala was observed during negative word encoding, suggesting increased call for attentional resources related to heightened salience detection of negative information. Furthermore, in the acutely depressed state, anterior cingulate cortex hyperactivation was observed during positive word encoding, which was interpreted as being reflective of conflict processing and the need for extra resources to classify mood-incongruent information.

Resting state functional connectivity: In a subset of unmedicated depressed and anxious patients, effects of comorbidity on resting state functional connectivity patterns in four networks of interest were investigated (Pannekoek et al., 2015). Using a probabilistic independent components analysis, group differences between patients with MDD (n = 37), anxiety disorders (n = 30), MDD and anxiety disorders (n = 25) and healthy controls (n = 48) were investigated in *i*) a limbic network encompassing the amygdala, basal ganglia and ventrolateral temporal cortex, *ii*) a salience network encompassing the insula and anterior cingulate cortex extending into the dorsomedial frontal gyrus, *iii*) a sensory-motor cortex encompassing the sensory-motor cortices, and iv) a default-mode network encompassing medial parietal and frontal brain regions. Analyses showed no effects specific to the presence of depression or anxiety. However, abnormal connectivity of the limbic network with posterior regions, including the precuneus and lingual gyrus, and right ventro- and dorso-lateral prefrontal regions was observed in the group of patients suffering from comorbid depression and anxiety

disorders. No effects of illness severity were observed. The authors interpreted the heightened coupling of the posterior visual and parietal regions with the limbic network as reflective of abnormal self-related cognitive processing, and the heightened lateral frontal limbic-network coupling as reflective of abnormal emotion detection present in depression and anxiety. It is important to note that in an earlier analysis connectivity differences were observed between 19 carefully selected unmedicated MDD patients without comorbidity and 19 matched controls. Results by Veer et al. (2010) showed abnormal lower connectivity of the bilateral amygdala with a limbic network, lower connectivity of the frontal poles to an attentional network, and lower connectivity of the lingual gyrus with a medial-visual network was observed. Subtle differences in selected cases, including the healthy controls, could explain the MDD-related non-overlapping results of Veer et al. (2010) and Pannekoek et al. (2015).

Surprisingly, the resting state functional connectivity findings reported by Pannekoek et al (2015) were the only comorbidity-specific finding in all NESDA neuroimaging data-analyses focusing on disorder-common vs. -specific characteristics of depression and/or anxiety disorders. Volumetric and task-related functional abnormalities were not specific to, or more pronounced in, the comorbid group compared to the non-comorbid groups, despite longer illness duration and severity of both depressive and anxiety symptomatology of the comorbid group. Together these findings give little support for the suggestion that functional and structural brain abnormalities are additive in a way that the symptomatology of MDD and anxiety disorders are. Overall, comorbid depression and anxiety seems most closely related to MDD without anxiety disorders, especially during the acutely depressive state. Findings specific for anxiety were observed as well, rarely shared with comorbid depression and anxiety and not with depression without comorbid anxiety. This suggests that anxiety related pathology is either anxiety vulnerability specific, or generically underpinning the vulnerability for affective disorders.

3.2. Course characteristics

Because of the longitudinal design of NESDA and the NESDA Neuroimaging study, questions related to state-dependency of MDD-related brain abnormalities could be addressed for the first time in the context of a naturalistic study where participants were not assigned to a specific treatment regime. This was one of the primary aims of setting up the longitudinal NESDA Neuroimaging study. Furthermore, because of the careful mapping of the course of the depressed psychopathology over a nine-year period and the completion of an MRI-measurement at nine-year follow-up, the relation between course of the depression and functional and structural brain characteristics could be prospectively studied.

Prediction of depressive course: It was observed that at baseline, MDD patients who would not remit in the two year follow-up period (n = 29) showed higher right hippocampal, left amygdala and left insular activation during the encoding of negative words than healthy controls (n = 45) (Ai et al., 2015). Hyperactivation in these regions was not observed in patients who would quickly remit after the baseline measurement (n = 22, remission within one year) or remit but relapse within two-years (n = 23). Also, irrespective of illness severity, right hippocampal activation during negative word encoding at the baseline measurement was found to positively relate to time to remission: the higher the activation, the longer it would take to reach remission. The authors concluded that higher activation in the left insula could serve as a neural marker of a naturalistic non-remitting course, whereas higher hippocampal activation is associated with delayed remission. Related to processing of emotional faces, higher rostral anterior cingulate activation during positive face processing at baseline was associated with symptomatic remission, compared to patient who would not remit over the two-year interval (Opmeer et al., 2016).

In addition to unimodal associations with clinical state a two-year follow-up, multimodal multi-variate pattern recognition was applied to investigate whether neuroimaging data could improve the prediction of the course of the depressive disorder over the use of known clinical predictors (including illness severity, duration and comorbidity) alone. Schmaal et al. (2015) grouped 118 MDD patients based on their clinical trajectory over the two-year period into chronically depressed patients (n = 23), gradually improving patients (n = 36), and fast remitters (n = 59). Using a Gaussian process classifier approach, it was shown that chronic patients could be discriminated from gradual recovering and fast remitting patients based on the emotional face processing fMRI-data with 73% accuracy, but not from structural MRI and fMRI related to executive planning. This accuracy was higher than predicting outcome from clinical data alone, which suggests that neural responses, especially during emotional processing tasks, could improve clinical outcome prediction. In a follow-up analysis, generative embedding was used to predict individual course trajectories based on the effective connectivity estimates derived from dynamic causal modeling of signal from the bilateral occipital face area, fusiform face area and the amygdalae during the emotional face processing task (Frässle et al., 2020). Using this approach, chronic patients could be distinguished from fast remitting patients with 79% accuracy. Gradually improving patients could be distinguished from fast remitting patients with 61% accuracy. This predictive approach significantly outperformed more traditional approaches (i.e. support vector machine based classification) based on activation or functional connectivity of the regions of interest. This suggest that more elaborative prediction methods can even further improve prediction accuracy.

State-characteristics: Ai et al (2019) observed in 39 MDD patients that the difference in activation of the left anterior hippocampus, extending into the amygdala, between the baseline and two-year follow-up measurement during encoding of positive and negative words, increased when symptomatic change over the two-year period was larger. This increase in activation was suggestive of normalization. During processing of emotional faces, a decrease in activation of the bilateral anterior insula and amygdala was observed in patients who remitted over the two-year period, most notably during processing of positive faces (Opmeer et al., 2016). Additionally, an increase in activation of the parahippocampal gyrus extending to the fusiform gyrus, the dorsolateral prefrontal cortex, and the post-central gyrus during positive face processing was observed with remission during emotional face viewing. Results were independent of any therapy. These results suggest that activation of typical emotion processing areas, including the anterior hippocampus, amygdala and insula, but also areas associated with processing of social emotional cues, responds in a state-dependent manner, indicating activation in these areas may serve as treatment response markers.

Time spent with depression: Time spent with depression in the two-year interval following baseline was not associated with activation differences during emotional word encoding. This suggests that regional brain activation is not subject to 'functional scarring' owing to prolonged presence of depressive symptomatology (Ai et al., 2019). During processing of positive faces, an increase in anterior insula activation over time was trend-wise associated with time spent with depression in the two-year interval (Opmeer et al., 2016). Finally, cortical thickness of medial orbitofrontal cortex (mOFC) and rostral anterior cingulate cortex (ACC), and hippocampal volume estimates were investigated in relation to burden of the disease between baseline and two-year follow-up, but no changes in brain volume or thickness were related to disease burden (or change in depression severity) (Binnewies et al., 2021). Together these results do not provide firm support for the idea that prolonged depression results in structural and functional 'scars', that could explain the heightened vulnerability associated with recurrent and more enduring depression, though subtle changes may characterize regions associated with integrating emotional and cognitive processes as a function of longer duration of the depressed state.

Antidepressant response: About one-third of the included sample

used anti-depressant medication in the form of SSRI's, which was the only allowed type of medication. While modest, this proportion is likely representative of the outpatient sample in the Netherlands. This allowed us to explore whether medication affected the observations by either omitting the SSRI-users in a sensitivity analysis, or adding SSRI-use (yes/no) as a dummy variable to the within-patient analysis. Excluding SSRI-users or controlling for it statistically had no major effect on the results (van Tol et al., 2010, 2011, 2012; Demenescu et al., 2013). Because we did not specifically investigate effects of SSRI use, by comparing SSRI-using patients with non-using patients, we could not report on regional brain activation or morphometry that is related to antidepressant medication use.

Nevertheless, in an exploratory analysis, it was investigated whether functional connectivity patterns during resting state were predictive of antidepressant non-response as a proxy for treatment-resistance (Geugies et al., 2019). MDD patients from the NESDA Neuroimaging sample that were prescribed at least two types of antidepressant medication (n = 17) were compared to MDD patients that kept the same type of medication (n = 32) and carefully matched healthy controls (n = 19). Using an independent component analysis, lower connectivity of the insula with the salience network was observed in 'treatment resistant' patients compared to the 'responders', and follow-up explorations indicated this was related to switching from a task-positive to a task-negative network mode. This might suggest that insula connectivity could potentially serve as a marker of treatment non-response.

3.3. Symptom related associations

Anxiety Distress Specifier: Over the course of the NESDA study, novel ways of accounting for anxiety symptoms were being proposed to characterize the clinical heterogeneity of MDD. The DSM-5 introduced anxious distress as a specifier to recognize the clinical significance of anxiety for depressed patients, as anxious distress was found to be associated with poorer functioning and outcome (Zimmerman et al., 2019). In the NESDA cohort, it was shown that amygdala responses towards emotional faces were higher in MDD patients who presented with anxious distress (ADS) than in MDD patients without ADS and healthy controls (Nawijn et al., in preparation), but no differences in amygdala-seeded functional connectivity during rest were associated with ADS presence. Furthermore, presence of ADS was associated with lower integrity of the white matter of the anterior thalamic radiation, which was observed independent of presence of a comorbid anxiety disorder, as observed in the 9-year follow-up DTI data (Heij et al., 2019). Also, severity of anxiety distress was negatively related to white matter integrity of the uncinate fasciculus and cingulum pathways. Involvement of these frontolimbic white matter tracts may underpin the maladaptive emotional functioning associated specifically with anxiety symptomatology.

Social dysfunction: MDD is frequently associated with impaired social function, which may persist even after full remission of depressive symptoms. Social dysfunction may hamper occupational and social reintegration, thereby adversely affecting overall prognosis, but its neural substrate is poorly understood. Saris et al. (2020) studied associations between social dysfunction and default mode network connectivity in 74 MDD patients, showing that social dysfunction was linked to diminished default mode network connectivity, in particular within the prefrontal cortex. Whereas the authors considered this finding to be preliminary, it nevertheless may serve as a starting point for more extensive (e.g., multimodal) investigations of the role of the default mode network in social dysfunction (Saris et al., 2020).

Suicidality: Suicidal behaviors, including suicidal ideation and attempting suicide, are common in patients with MDD. It has been proposed that suicidal behavior results from a complex cascade, progression through which is moderated by psychological, environmental and neurocognitive factors (Jollant et al., 2011; O'Connor and Kirtley, 2018). In patients with MDD, Ai et al. (2018) studied the relation between suicidal ideation and attempts, the strongest predictors of suicidal acts, and the fMRI-correlates of emotional face processing and executive planning to understand the potential moderating role of emotion processing and executive control in the occurrence of suicidal acts. One-hundred-three MDD patients were included in the analyses, of whom 49 reported suicidal behavior (n = 18 reported a history of suicidal attempts; n = 31 reported current suicidal ideation) at the time of the NESDA interview. MDD patients with a history of attempts showed lower activation of the bilateral fusiform face area than ideators and patients without suicidal attempts or ideation, and healthy controls, activation that was positively correlated to amygdala activation. Effects were unconfounded by presence of current ideation, a history of childhood maltreatment, symptom severity, or current SSRI- or psychotherapy use. No activation differences were observed during performance of the executive planning task. The authors conclude that neural mechanisms underpinning emotional face processing might differentiate between current thoughts from past suicidal behavior that might facilitate the occurrence of suicidal acts, while non-emotional cognitive control seems relatively intact in suicidal patients.

Biotypes: Dinga and colleagues (2019) attempted to replicate earlier findings by Drysdale et al (2017) identifying biologically meaningful subtypes of depression based on resting state functional connectivity characteristics. In a sample of 187 patients with MDD and/or anxiety disorders, the relation between resting state functional connectivity and symptoms was investigated and it was tested whether reliable subgroups could be identified. However, no significant relations with symptoms nor any reliable subtype could be distinguished. Therefore it was concluded that the evidence for the existence of distinct depressive subtypes based on resting state functional connectivity data should be treated with caution, in view of methodological caveats in the earlier study.

3.4. Aetiological factors

Although understanding the comorbidity of depression and anxiety and the variable and heterogeneous clinical course of both depression and anxiety disorders were the primary aims of the NESDA Neuroimaging study, the wealth of available data related to clinical, environmental and biological characteristics also made the NESDA Neuroimaging study a favorable point of departure to explore the neurocognitive basis of this heterogeneity. Over the last decade, researchers within NESDA have sought to explore functional and morphological brain correlates of individual symptoms and possible etiological factors, including early life stress, personality, and a family history of psychiatric disorders.

Childhood maltreatment: van Harmelen and coworkers investigated the effects of childhood trauma, in particular childhood emotional maltreatment (CEM) on regional brain morphology and emotion processing. CEM was found to be associated with lower dorsomedial prefrontal cortex volume, even in the absence of physical and/or sexual trauma, and irrespective of psychiatric status (van Harmelen et al., 2010). These findings indicated that sustained inhibition of growth or structural damage can occur after exposure to CEM in an area critically involved in emotion regulation, thus providing an important link in understanding the increased emotional sensitivity in individuals reporting CEM. Similar findings were obtained using functional imaging: CEM was associated with enhanced bilateral responsiveness of the amygdala to emotional faces (van Harmelen et al., 2013) and lower medial prefrontal activation during encoding and recognition of neutral and emotional words (van Harmelen et al., 2014). The authors concluded that CEM may increase vulnerability to developing psychopathology on different processing levels in the brain, including enhanced automatic/lower order emotion processing and blunted medial prefrontal cortex activation during higher order cognitive processing. Of note, these CEM-related variations in brain volume and responsivity were also observed in the healthy control participants,

suggesting a stress-exposure related characteristic that does not suffice to explain the development of affective psycho-pathology when counteracted by "resilience-promoting" mechanisms. Also in the NESDA sample, van der Werff et al. (2013) showed that CEM was associated with decreased resting-state functional connectivity (RSFC) between the right amygdala and bilateral precuneus and left insula, as well as with decreased RSFC between dorsal ACC and precuneus. The authors concluded that CEM may profoundly alter RSFC in regions associated with episodic memory encoding and retrieval as well as self-referential processing, which may increase the likelihood for developing affective disorders.

Personality factors: Neuroticism is a personality factor associated with the vulnerability for experiencing negative affect and a known risk factor for developing affective disorders. Therefore, its structural and functional associations have been studied in the NESDA healthy control participants to understand vulnerability factors that might contribute to the development of affective disorders. During viewing of emotional faces, neuroticism was found to positively correlate with right amygdala-dorsomedial prefrontal cortex coupling and negatively with left amygdala-ACC coupling, associated with self-referential processing and top-down control, respectively (Cremers et al., 2010). Neuroticism was also associated with higher amygdala-precuneus resting-state functional connectivity in 50 healthy control participants, again suggesting a link with self-referential processing (Aghajani et al., 2014). On the 'protective' side of the personality spectrum, extraversion, but not neuroticism, was found to be positively correlated with amygdala and orbitofrontal gray matter volume in 65 healthy control participants, which was interpreted as reflecting variable sensitivity to positive, pleasant information (Cremers et al., 2011). This might modulate the extent to which an individual is guarded against stress in the face of negative events. Of note, ACC volume was positively correlated to extraversion in males but not in females, suggesting that the ACC in males is included in the same extraversion mediating regulatory network, thereby providing stronger protective effects against mood disorders (Cremers 2012). Of course, structural variations in healthy control participants should not be interpreted as functional abnormalities, but may predispose to network dysfunctions that may have clinical relevance. In NESDA patients, personality factors have not been extensively studied, though extraversion, used as an inverse proxy of (lack of) negative affect, was found to modulate MDD-related functional connectivity of the ventral striatum, medial prefrontal cortex, and ventrolateral prefrontal cortex, during encoding of emotional words (van Tol et al., 2013). Neuroticism had no effect on depression related task-related functional connectivity in this analysis (van Tol et al., 2013).

Together these results suggest that a vulnerability for negative affect, as indicated by higher levels of neuroticism, relates to functional coupling of primary emotional processing areas with regulatory areas in self-related processing. Extraversion, on the other hand, may modulate both the volume and functional connectivity of areas implicated in reward processing and regulatory control, which may contribute to a higher likelihood of experiencing an enduring negative mood when faced with stressful events.

Cognitive vulnerability: It has been proposed that an imbalance in activation of frontal and limbic structures during processing of negative affective cues underpins the vulnerability for the persistence of negative thinking about oneself, the world, or the future, characteristic of a depression (Disner et al., 2011). Groenewold et al. (2015) investigated in 112 NESDA participants whether the relation between cognitive vulnerability and a fronto-limbic imbalance during processing of negative emotional faces differed between healthy control participants and unmedicated patients with a diagnosis of MDD and/or an anxiety disorder, or was moderated by recent life stress as measured with the list of threatening events (Brugha et al., 1985). Cognitive vulnerability estimates were derived from a set of measures assessing cognitive reactivity, negative attribution styles, and explicit negative self-associations. It was observed that cognitive vulnerability was associated with increased activation of the superior parietal cortex extending to the precuneus during negative vs. positive emotional faces, which was found to be specific for the healthy control participants. No specific associations were observed for the experience of recent life stress. Contrary to expectations, no relation between cognitive vulnerability and amygdala activation during processing of negative stimuli was observed. The authors concluded that these associations may reflect increased efforts needed to ignore irrelevant negative emotional information. Given that the association was only observed in the control participants, increased parietal activation related to increased cognitive vulnerability may suggest compensatory cognitive control in order to maintain a healthy status. The lack of such an association in patients may point to a failed engagement of such compensatory mechanisms.

Family history of alcohol use disorders: A family history of alcohol dependence enhances susceptibility for mood and anxiety disorders and the neurocognitive basis for this predisposition has been studied within NESDA on both functional and structural levels. Sjoerds et al. (2013) demonstrated slower performance and increased dorsal prefrontal activation during planning, and altered insula activation when processing positive emotional words in MDD patients with a family history of alcohol dependence compared to those without, suggesting that the presence of family history contributes to the neurophysiological risk profile of mood/anxiety disorders via affecting cognitive control and processing of positive material. Furthermore, it was observed that MDD patients with a positive family history of alcohol dependence showed lower volume of the right parahippocampal gyrus, also when controlled for severity of current symptomatology, childhood emotional maltreatment and a family history of depression and/or anxiety disorders (Sjoerds et al., 2013). Similar results have been observed in drinking and non-drinking adolescents with a family history of alcohol dependence (Benegal et al., 2007; De Bellis et al., 2005). Therefore, the findings of Sjoerds et al (2013) suggest that abnormal parahippocampal volume represents a biologically persistent vulnerability for alcohol use disorders, and is not the result of neurotoxic effects of alcohol or delayed brain maturation.

3.5. *Biological characteristics: stress, genetic variation and immunometabolic dysregulation*

The combination of extensive biological as well as phenomenological data has allowed the NESDA Neuroimaging project to explore brain correlates of several biological factors and processes postulated to be involved in the pathophysiology of depression, in particular of a number of genes, but also of immunometabolic factors and oxidative stress. More recently, the NESDA MRI longitudinal data has also been used to study the concept of increased brain aging in affective disorders, results which will be published soon.

4. GWAS approach: role of the PCLO gene

PCLO: In 2009, involvement of the presynaptic protein piccolo in the psychopathology of MDD was suggested and confirmed in a genome wide association study (GWAS; Bochdanovits et al., 2009; Sullivan et al., 2009) based on amongst others samples from the NESDA study and the Netherlands Twin register. This GWAS implicated the polymorphism rs2522833 in the piccolo (*PCLO*) gene—involved in monoaminergic neurotransmission—as a risk factor for MDD. Subsequently, the relation of this single nucleotide polymorphism with brain functioning during emotional and cognitive processing was studied (Woudstra et al., 2012). In a sample of 118 patients with MDD and 41 healthy controls, the *PCLO* risk allele was found to be specifically associated with altered emotional face processing, but not with executive dysfunction (Woudstra et al., 2012). In *PCLO* risk allele carriers, increased left amygdala during processing of angry and sad faces was observed compared to non-carriers, independent of psychopathological status. During

processing of fearful faces, the *PCLO* risk allele was associated with increased amygdala activation in MDD patients only. It was suggested that this may represent a link between genotype and susceptibility for depression via altered processing of fearful stimuli.

Also, Woudstra et al (2013) explored the effects of the PCLO risk allele on emotional word encoding and retrieval in 89 MDD patients and 29 controls. They observed lower activation of the insula during negative word encoding in PCLO risk-allele carriers, independent of diagnostic status. In addition, depressed risk-allele carriers showed lower dorsal striatal activation during negative word encoding than non-risk carriers, an effect that was not observed in controls. There was also a blunted amygdala response during identifying new positive words among known positive words in healthy risk allele carriers and all MDD patients. No differential effects during recognition of neutral or negative words were observed. In line with the study on face processing, it was suggested that the *PCLO* risk allele may increase vulnerability for MDD by modulating brain functioning with regard to responsiveness to salient stimuli and their processing. In addition, depression-specific effects of PCLO, i.e. altered dorsal striatal activation during negative word encoding and blunted amygdalar responsivity to novel positive information led the authors to suggest a potential role of PCLO in symptom maintenance in MDD.

5. Candidate gene approach: BDNF, COMT, NPY, and DISC-1

In addition to informing our analyses by the GWAS results, we studied the effects of a number of candidate genetic polymorphisms putatively involved in affective disorders. These included the val66met polymorphism on the BDNF gene, the val158met polymorphism on the gene coding for COMT, the Ser704Cys polymorphism on the Disrupted-in-Schizophrenia -1 (DISC-1) gene, and the NPY-gene.

BDNF: Molendijk et al (2012) used structural and functional MRI data to examine the effect of the BDNF val66met polymorphism on hippocampal volume and encoding related activity of emotional words in 126 patients with affective disorders and 31 healthy controls. Importantly, the NESDA data allowed them to take factors such as childhood emotional maltreatment and psychiatric status into account. They found, controlled for psychiatric status and childhood maltreatment, smaller hippocampal volume in carriers of the met allele. For the encoding task the picture was somewhat different. Controlled for psychiatric status, carriers of the met allele showed increased activation during encoding of negative words compared to non-carriers, but only in those participants without childhood abuse. The authors speculated that the higher levels of encoding activity after exposure to childhood abuse in the non-carriers may reflect a gene-environment interaction.

COMT: The val158met polymorphism of the COMT gene causes altered activity of the COMT enzyme. The COMT enzyme is responsible for the breakdown of catecholamines, including dopamine and norepinephrine, and can be mainly found in the prefrontal cortex and temporal areas. Alternations in catecholaminergic neurotransmission may contribute to disturbed emotional and cognitive processing, probably via altered cortico-subcortical interactions, and may be involved in MDD. The val158met COMT polymorphism was found to be associated with abnormal prefrontal cortex activation during both emotional processing and working memory in healthy controls (see Opmeer et al. (2013) for an overview of studies). Because a direct association between the val158met COMT polymorphism and MDD had never been established, Opmeer et al. (2013) examined this using prefrontal and amygdala activation during an executive planning task and an emotional face processing task as an endophenotype. They included 97 MDD patients and 28 healthy control participants with complete Tower of London executive planning task and face processing fMRI data. An interaction between number of met-alleles and presence of MDD diagnosis was found in the ventrolateral prefrontal cortex during negative emotion processing, with higher activation in risk-(met)-allele carriers in healthy controls. In MDD patients, no relation to the number of risk-alleles was found, but all patients were found to show somewhat higher responsivity of this part of the ventrolateral prefrontal cortex. During the executive planning task, met-alleles were associated with increased dorsolateral prefrontal gyrus activation, but with no modulatory effect of MDD diagnosis. There were no behavioral effects on the two tasks. Together, it was suggested that the COMT risk-allele contributes to compensatory recruitment of lateral prefrontal brain areas during both emotional processing and executive control, but that during emotional processing this was potentially obscured in MDD patients due to the effect of the current depressive state.

NPY: Building on work demonstrating the impact of childhood emotional maltreatment (CEM) on the stress-response system and on brain structure and reactivity, in particular increased amygdala responsiveness, Opmeer et al. (2014) investigated the effects of the c/c/ genotype of neuropeptide Y (NPY) in 85 unmedicated NESDA-patients and 33 healthy controls. NPY has been shown to play an important role in adequate stress-responses and is abundantly expressed in several brain regions, in particular in the amygdala. Previous work found an increased vulnerability for developing psychopathology after CEM in subjects with the C/C genotype. The aim of the study by Opmeer et al., in which baseline data from the implicit emotional face processing task was used, was to investigate whether NPY genotype influenced activity of brain areas involved in emotion processing and whether CEM and presence of affective psychopathology could influence the effect of NPY genotype on the amygdala. It was hypothesized that the combined effect of carrying the risk genotype (i.e. C/C-carriers) and a history of CEM would be associated with the highest amygdala activation. Results only showed interactions between genotype and CEM, irrespective or type of facial emotion displayed. Higher amygdala activation across emotional expressions and less activation of the posterior cingulate cortex, as well as faster behavioral responses, was observed in individuals with CEM and the risk genotype. This effect was consistent with the notion that the combination of risk genotype and CEM may cause hypervigilance, potentially contributing to the increased vulnerability for developing affective disorders after CEM in the carriers of the risk allele.

DISC-1: Finally, the last candidate gene for (vulnerability for) affective disorders examined within the NESDA MRI project was the Disrupted-In-Schizophrenia-1(DISC1) gene (Opmeer et al., 2015). Previous studies found associations suggesting that the DISC1-genotype Ser704Cys (with the Cys-allele as risk-allele) was involved in functioning and structure of hippocampal, ACC and prefrontal regions, regions of major interest for affective disorders. However, no previous study examined associations for the various regions at the same time. Opmeer et al. (2015) therefore studied the effects of Ser704Cys-genotype on function and structure of the ACC, dorsolateral prefrontal cortex, and hippocampus in both patients and controls from NESDA. It was hypothesized that Cys-carriers would show smaller grey matter volumes and less activation in these regions of interest during executive planning and episodic memory. During visuospatial planning, healthy Cys-carriers showed smaller bilateral (para)hippocampal volumes compared with Ser-homozygotes, and lower activation in the ACC and dorsolateral prefrontal cortex (Opmeer et al., 2015). Interestingly, in anxiety patients, these effects were reversed: Cys-carriers showed larger (para)hippocampal volumes and more ACC activation during visuospatial planning. In depressive patients, however, no effect of genotype was observed. The authors concluded that Ser704Cys-genotype influences (para)hippocampal structure and functioning of the dorsal prefrontal cortex during executive planning, but most prominently in unaffected controls, with the presence of anxiety disorders having moderating effects, at least for the aspects examined in this study.

6. Immunometabolic factors and oxidative stress

Immunometabolic dysregulation: Chronic psychological stress has been shown to disrupt the homeostasis of various physiological stress systems, including the immune-inflammatory system and the

hypothalamus-pituitary adrenal (HPA)-axis (see review by Epel (2009)). Prolonged dysregulation of these systems results in systemic low-grade inflammation and metabolic dysregulation. These dysregulations have been associated with the onset and more severe course of multiple psychiatric disorders. Previous work suggested this to be partly due to neuroanatomical changes and impaired neuroplasticity. However, previous neuroimaging studies had not examined multiple markers of immunometabolic dysregulation together, did not correct for lifestyle factors or had modest sample sizes. Since this information was available in NESDA for a fairly large group of patients and controls (n = 283), the effects of multiple markers of immunometabolic dysregulation on the amygdala and ACC, key structures involved in psychological and physiological stress-regulation, were examined by van Velzen et al. (2017a). Interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a), c-reactive protein (CRP), triglyceride levels and HDL-cholesterol levels were determined in peripheral blood and genomic profile risk scores (GPRS) for immunometabolic dysregulation were calculated. They performed covariate-adjusted linear regression analyses to examine the relationship between immunometabolic dysregulation and brain volume/thickness across included participants. Triglyceride levels and severity of immunometabolic dysregulation were found to be associated with lower rostral ACC thickness across all participants. IL-6 was inversely associated with hippocampal and amygdala volume in healthy controls only. GPRS for immunometabolic dysregulation, however, were not associated with brain volume or cortical thickness. The authors interpreted these findings as showing different serum, but not genetic immunometabolic factors having similar mechanisms of affecting structural properties of the ACC.

Oxidative stress: Oxidative stress is a biological process that may lead to oxidative damage to lipids, proteins, and DNA and ultimately cell death. Studies in rodents showed that brain regions, particularly the amygdala and hippocampus, are sensitive to oxidative stress, but studies on the association between oxidative stress and brain morphology in humans were lacking at the time. In NESDA the association between two robust measures of oxidative damage in plasma (8-OHdG and F2-isoprostanes) and volume of the hippocampus and amygdala was examined in the complete sample of individuals with and without MDD and/or anxiety (N = 297) (van Velzen et al., 2017b). In secondary analyses, van Velzen et al. examined differential effects in patients and controls. 8-OHdG and F2-isoprostanes plasma levels were determined using liquid chromatography tandem mass spectrometry and volume of the hippocampus and amygdala and hippocampal subfields was determined. Authors found no association between plasma markers of oxidative stress and subcortical volume across participants or in the separate patients and control groups. These findings suggest that exposure to oxidative stress is not associated with lower subcortical brain volume and cannot explain the often observed lower volume of the hippocampus in depression (Schmaal et al., 2016).

7. Comment

This paper summarized the research findings from the NESDA Neuroimaging with relevance for understanding the heterogeneity in clinical presentation, course trajectories, and etiology of MDD and common anxiety disorders, that have been published since 2010. Bringing together all these study results brings to light a number of observations. In this section, these observations will be discussed in the light of various neuroanatomical models of depression, including the models of Mayberg (1997) and Phillips et al. (2003) on which the NESDA study was based, but also newer models resulting from meta-analytic findings of the numerous neuroimaging studies published since the '90s.

8. Common characteristics, but no additive effects of depression and anxiety disorder

In NESDA, it was shown for the first time that individuals diagnosed with MDD, a common anxiety disorder (SAD, PD, and/or GAD), or with both MDD and a common anxiety disorder, are characterized by lower volume of the pregenual cingulate cortex, a region critical for integration of emotional and cognitive processing (van Tol et al., 2010). Also, lower volume of the posterior cingulate cortex was observed across diagnostic groups, though at the time of analysis this region was not included as *a priori region* of interest and therefore this result was not emphasized. Additionally, it was observed that hippocampal hypo-activation during the encoding of positive words was characteristic of both MDD and anxiety disorders, or the comorbid condition (van Tol et al., 2012).

However, comorbid depression and anxiety was not associated with more pronounced abnormalities in brain regions associated with emotion processing and cognitive control. Given that comorbidity is often characterized by early onset of either disorders, longer and more burdensome episodes, poorer treatment response and a less favorable clinical course (ter Meulen et al., 2021), it was expected that this clinical severity would be reflected by greater or more extended neurocognitive alterations. However, abnormalities in the comorbid group were often shared with either the patients diagnosed with only MDD or a common anxiety disorder, or both. Examples are the elevated dorsolateral prefrontal cortex and insula responsiveness during executive planning (van Tol et al., 2011) and encoding of negative words (van Tol et al., 2012), respectively, which were found in MDD with and without comorbid anxiety. The only finding that was specific to the comorbid group of patients diagnosed with both MDD and one or more anxiety disorders, was made during a task-free period, where the intrinsic connectivity between networks commonly associated with affective-, self-referential- and cognitive processing were studied (Pannekoek et al., 2015). It was observed that a limbic network showed increased connectivity with regions in self-referential- and executive control networks in patients with both depression and anxiety, unrelated to severity of current symptoms. This suggests that a higher propensity to exchange signals between brain regions involved in networks associated with emotional processing, self-referential processing, and executive control may heighten the vulnerability for enduring affective symptomatology. Increased connectivity between networks may suggest lower network segregation and specialization, that may result in an inefficient network organization. This hypothesis however deserves further testing using a graph theoretical approach that allows testing for network properties.

9. Relevance of 'ventral'/limbic circuitry for depression and anxiety

Notably, no solid support for general increased activation of the amygdala in response to emotional stimuli associated with the presence of a recent diagnosis of MDD or anxiety disorders was provided. This increased activation was predicted from the 'limbic-cortical' emotion processing models of Phillips (2003b) and Mayberg (1997). Nevertheless, other risk factors or current symptom characteristics were associated with abnormal amygdala activity. During emotional face viewing, it was found that higher levels of anxiety symptoms as defined in the anxiety distress specifier, but not comorbid anxiety disorder, were associated with elevated amygdala responsiveness (Nawijn, in prep). Also, type of anxiety disorder appeared to affect amygdala responsivity, and therefore lumping all anxiety disorders might obscure these effects (Demenescu et al., 2013). It was also observed that anxiety severity, independent of anxiety diagnosis, may result in higher amygdala – medial prefrontal cortex connectivity (Demenescu et al., 2013), which suggests that anxiety related symptomatology may moderate both amygdala responsivity and connectivity. Also, presence of childhood maltreatment (van Harmelen et al., 2013), or the PCLO (Woudstra et al., 2012) and NPY risk allele (Opmeer et al., 2014) appears to result in higher amygdala responses to emotional faces, suggesting that higher vulnerability for depression and anxiety may be mediated by increased amygdala responsivity. During encoding of negative emotional words,

higher amygdala response was observed in depressed patients in an acutely depressed state, not in recently remitted patients (van Tol et al., 2012). Independent of anxious comorbidity, higher insula activation during negative word encoding was observed in MDD patients independent of illness severity (van Tol, 2012). No functional and structural 'scarring' related to persistence of the disorder or oxidative stress were observed in the limbic regions (Binnewies, 2021, Ai et al., 2017; Opmeer, van Velzen). This suggests that limbic hyperactivity is involved in the perpetuation of the current episode, rather than in the general vulnerability for the depressive disorder. Nevertheless, neural characteristics during the episode may contain information relevant for the course of the disorder. For example, in the acute phase increased activation of the amygdala during negative processing at baseline, corrected for current illness severity, was found predictive of the depressive course trajectory over the following two years. Amygdala/anterior hippocampal and insula hyperactivation during negative word encoding was found in individuals who failed to remit in the ensuing two years, whereas individuals who would show remission within this period did not show increased responsivity (Ai et al., 2015). Also, using more complex multi-variate prediction methods, face processing data was able to reliably predict disorder status at two-year follow up (Schmaal et al., Frässle). It should be noted here that this result is likely not related to amygdala reactivity only, but was based on whole brain responsivity (Schmaal et al., 2015) or effective connectivity of the amygdala with other regions in face processing (Frässle et al., 2020).

10. Relevance of dorsal/cortical circuitry for depression and anxiety

Using the Tower of London executive planning paradigm, we aimed to test whether abnormal recruitment of the lateral prefrontal cortex, supposedly involved in regulatory control of emotional states, showed abnormalities during non-emotional (visuospatial) task performance. This would inform on the propensity of the frontal cortex to exert regulatory control when needed in the face of stressful or emotional events. We did not find support for a common abnormality across individuals with MDD and anxiety, but showed that slightly elevated dorsolateral prefrontal cortex responsiveness was common to individuals with a diagnosis of MDD, and was most pronounced in acute depressed patients (van Tol et al., 2011). This suggests that lateral prefrontal regions are engaged during solving complex problems that require sustained attention, mental flexibility, and working memory manipulation, and the observed subtle over-recruitment during the acute state may indicate inefficient control mechanisms that may fall short when more stressful conditions are present. This hypothesis could however not be tested because of the non-emotional nature of the task.

During emotional tasks, frontal hypoactivation was not observed in our sample (van Tol et al, 2012; Demenescu 2011). Instead, ventrolateral prefrontal cortex hyperactivation during negative word encoding was observed in acutely depressed patients, irrespective of anxiety comorbidity. This suggests compensatory need for regulatory control when processing negative emotional material. Also, dorsal ACC and dorsolateral prefrontal cortex hyperactivation was observed in the depressed state during processing of positive words and faces, respectively (van Tol et al., 2012; Demenescu et al., 2011). This suggests that increased frontal resources are needed to deal with emotional conflict when content does not match the current mood state. Together with the depression and anxiety common observation of altered hippocampal involvement during positive word encoding, this suggests that altered regulatory control is involved in the perpetuation of the current disorder state.

Additionally, we observed lower volume of the right ventrolateral prefrontal cortex in patients suffering from depression only (van Tol et al., 2010). Given the role of the ventrolateral prefrontal cortex in an emotion regulation circuitry, specifically in signaling the need for regulatory control (Dixon et al., 2017; Kohn et al., 2014), this finding suggests that the propensity to regulate emotions is altered in MDD. Currently we are preparing a manuscript on involvement of prefrontal regions during effortful emotion regulation as a function of nine-year load of depression (van Kleef, in prep) that could shed light on the state vs. trait abnormalities the prefrontal cortical functioning during implicit and effortful regulation of emotions.

Moreover, we did not find support for a role of prefrontal regions in the long-term course of depression, as no associations with persistent depression (Ai et al., 2019; Binnewies et al., 2021; Opmeer et al., 2016), oxidative stress (van Velzen et al., 2017b) or prediction of course was observed (Ai et al., 2015). Nevertheless, medial 'dorsal' prefrontal regions seem to be involved in the general primary vulnerability for developing depression and anxiety disorders, as both structural and functional impairments in the medial prefrontal cortex (van Harmelen et al., 2010, 2014) and resting state connectivity of the dorsal ACC with the default mode network (van der Werff et al., 2013) were associated with the experience of childhood emotional maltreatment, independent of current psychopathological status. See Fig. 2 for an updated ventral-dorsal model of depression, highlighting involvement of components that were supported by structural and functional neuroimaging results from the NESDA Neuroimaging study.

11. Revisiting the limbic-cortical models of depression and anxiety

Paradigms of the NESDA Neuroimaging studies were chosen based on the neuroanatomical models of Mayberg (1997) and Philips et al. (2003a/2003b) in order to test whether these models applied similarly to both depression and anxiety, and whether more pronounced abnormalities in implicated regions could explain comorbidity of depression and anxiety disorders and associated worse clinical profile. The limbic-cortical dysregulation model of Mayberg (1997), informed by studies into secondary depression occurring in neurological disorders, unipolar 'primary' depression, and treatment studies, concerns the general neuroanatomy underpinning sadness in health and depression. In this model, a 'dorsal compartment', including reciprocally connected neocortical and midline limbic structures, is linked to cognitive, attentional and self-initiation disturbances associated with depression. A 'ventral compartment', composed of paralimbic cortical (subgenual ACC), subcortical structures and brainstem regions is associated with vegetative and somatic aspects of the disorder. In this model, the pregenual cingulate cortex has a special position as connector hub responsible for adequate regulatory interaction between ventral and dorsal systems. It is acknowledged that depression is not the result of dysfunction of any of these single brain regions, but of a failure of coordinated interaction between subcomponents of each compartment, or between compartments. Mayberg (1997) recognizes that evidence for consistent involvement of the ventral component is lacking in 'primary' depression, and that large variability in findings could be explained by differences in symptom profiles that need to be studied.

Philips et al. (2003a/b) presented an elegant transdiagnostic two-systems model explaining the occurrence of mood states in health and disease. It used concepts of appraisalist theory to explain how ventral-dorsal contributions and interactions underpin emotion perception, production of affective states, and regulation thereof, and how abnormalities in these two systems could give rise to psychiatric symptoms, including a persistent abnormal mood typical for depression. In short, it suggested that elevated limbic reactivity to emotional material together with lowered involvement of prefrontal regulatory areas, would give rise to a mood that was dominated by the limbic-regions mediated immediate appraisal without being corrected by cognitive reappraisal, mediated by the prefrontal cortex.

Our findings, consistent with many reports following ours (including the voxel-based meta-analysis of Arnone et al., 2016), support the special position of the pregenual ACC in the neuroanatomy underpinning the vulnerability for depression, independent of current symptomatology (also in line with meta-analytic findings of Schmaal et al., 2017;

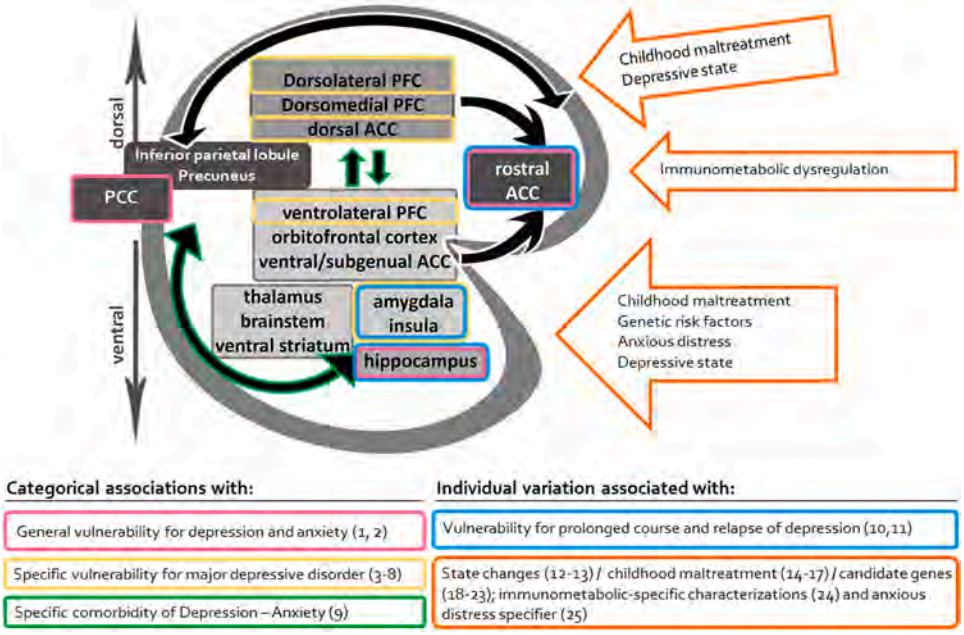

Fig. 2. Summary of NESDA Neuroimaging findings of structural and functional task- and rest-related results, overlaid on an integrated neuroanatomical model including components incorporated in neuroanatomical models of depression (e.g., Mayberg, 1997; Phillips et al., 2003b; Hamilton et al., 2012; Kaiser et al., 2015).
Associations of diagnostic status:
In pink:depression – anxiety common effects: 1) lower pregenual and posterior cingulate cortex volume (van Tol et al., 2010) and 2) lower hippocampus activation during encoding of positive words (van Tol et al., 2012);
In yellow:associations specific for depression: 3) lower ventrolateral prefrontal cortex volume (van Tol et al., 2010); 4) higher ventrolateral prefrontal cortex activation during negative word encoding (van Tol et al., 2012); 5) higher dorsolateral prefrontal cortex activation as a function of increasing planning load (van Tol et al., 2011); 6) increased dorsal ACC activation during encoding of positive emotional words (van Tol et al., 2012) and 7) positive faces (Demenescu et al., 2011); 8) increased insula and amygdala activation during encoding of negative emotional words (van Tol et al., 2012);
In green: effects specific for comorbid depression-anxiety: 9) abnormal limbic-precuneus/posterior cingulate cortex and limbic-lateral prefrontal cortex connectivity during rest (Pannekoek et al., 2015).
Associations of individual variations in course, symptom severity and risk-factors:
In blue: associations with longitudinal course: 10) heightened hippocampus, insula, amygdala activation during negative word encoding was associated with non-remission and longer time to remission (Ai et al., 2015); 11) lower pregenual ACC activation during positive face processing (Opmeer et al., 2016);
In orange: associations with intra-individual changes in depressive state: 12) state-dependent activation in the amygdala and hippocampus during emotional word encoding (Ai et al., 2019) and 13) in the insula, amygdala and dorsolateral prefrontal cortex during positive face viewing (Opmeer et al., 2016); associations with inter-individual difference in the experience of childhood emotional maltreatment: 14) lower volume of the dorso-medial prefrontal cortex (van Harmelen et al., 2010); 15) lower activation of the dorso-medial prefrontal cortex during emotional word encoding (van Harmelen et al., 2014); 16) higher amygdala activation during emotional face viewing (van Harmelen et al., 2013); 17) lower amygdala - precuneus and amygdala – insula/hippocampus connectivity and lower dorsal anterior cingulate cortex – precuneus connectivity during rest (van der Werff et al., 2013); Associations with candidate genes: 18) higher activation amygdala negative faces in PCLO risk-allele carriers (Woudstra 2012); 19) lower insula activation during negative encoding in PCLO risk-allele carriers (Woudstra et al., 2013); 20) lower hippocampal volume in BDNF val66met carriers and higher hippocampus activation during negative word encoding in BDNF val66met carriers, only in individuals who experienced childhood maltreatment; 21) ventrolateral prefrontal cortex activation was associated with number of COMT met-alleles in non-depressed individuals and lower dorsolateral prefrontal cortex activation during executive planning associated with COMT met-alleles (Opmeer et al., 2013); 22) higher amygdala and lower posterior cingulate cortex activation during emotional face processing in NPY risk-allele carriers who experienced childhood maltreatment (Opmeer et al., 2014); 23) lower anterior cingulate and dorsolateral prefrontal cortex activation during planning in healthy DISC-1 risk-gene carriers, no effect inpatients; associations with immunometabolic risk factors: 24) higher dysregulation was associated with lower pregenual ACC thickness (van Velzen et al., 2017a); associationswith anxiety distress: 25) Higher anxiety distress specifier scores related to diminished integrity within the anterior thalamic radiation, uncinate fasciculus and cingulum pathways (Heij et al., 2019). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Goodkind et al., 2015, for parts of the ACC). It also fits the meta-analytic finding of abnormal activation of the pregenual ACC in depression linked to biased emotional processing and cognitive control (Diener et al., 2012). Also, we observed that insular hyperactivation to emotional words was associated with depressive symptomatology independent of depression severity, that was furthermore associated with the longitudinal course (Ai et al., 2015). We did not find additional support for the proposed increased ventral-limbic responsivity and lower lateral prefrontal responsivity to negative emotional stimuli of the Phillips (2003b) model.

Later meta-analytic results of increased limbic responsivity (McTeague et al., 2020; Hamilton et al, 2012), decreased prefrontal control responsivity (Groenewold et al, 2013 for the prefrontal hypo-activation; Hamilton et al., 2012) support the ventral-dorsal model (Philips et al., 2003a/b). However, involvement of the ventral or dorsal component in depression (and anxiety) could not be confirmed by all (Müller et al., 2017; McTeague et al., 2017; Groenewold et al., 2013 for limbic involvement). Variations in anxiety symptomatology, genetic and etiological factors, and course heterogeneity of the disorders observed in our studies, could explain variability in published reports for the ventral compartment. Related to involvement of the hippocampus, abnormal responsivity to positive material (van Tol et al., 2012) does suggest state- and symptomatology independent involvement of this limbic structure, particularly when confronted with mood-incongruent material. This finding does not match the meta-analytic results of Muller et al. (2017) who find no support for memory related abnormalities in depression. However, this discrepancy could relate to the fact that working- and episodic memory tasks were lumped for the Müller meta-analysis, a consideration that was highlighted by Barch and Pagliaccio (2017). Though not observed at the set threshold in our sample (van Tol et al., 2010), lower volume of the hippocampus has been observed consistently in depression (see meta-analysis of Schmaal et al., 2016; Goodkind et al., 2015) and hyperactivation of the amygdala/hippocampus to negative emotional material in anxiety disorders and MDD (McTeague et al., 2020). Recently, multi-modal meta-analytic work provides support for spatial divergence in involvement of the hippocampus and amygdala (and subgenual ACC and putamen) in depression (Gray et al., 2020). Together these results support the involvement of the pregenual ACC, and of 'ventral' hippocampus, amygdala and insula in the psychopathology of depression, whereas no solid support for abnormal reactivity

of medial and lateral prefrontal regions in the context of emotion processing and executive control could be provided. A similar picture emerged from jointly discussing the NESDA neuroimaging reports focusing on a recent diagnosis of MDD (See Fig. 2). Of note, whereas Mayberg (1997) places the hippocampus in the ventral-limbic compartment because of its anatomical connections, Phillips (2003a) labels the hippocampus as part of the dorsal-regulatory component because of its role in effortful regulation of behaviour. This positioning is also based on the role-description provided by Gray and McNaughton (2003), indicating the hippocampus as a general purpose comparator, mainly tasked with resolving goal-conflict in goal-directed behaviour.

12. Updated models of depression

Hamilton and colleagues (2012) refined the limbic-cortical models following an integration of baseline activation- and emotional-task induced responsivity data in a whole-brain voxel-wise meta-analysis. They observed consistent *i*) elevated baseline pulvinar activation and *ii*) increased activation of the amygdala, insula and dorsal ACC and decreased activation in the caudate nucleus and dorsolateral prefrontal cortex in response to negative emotional stimuli. They suggest that the combination of pulvinar activation and limbic reactivity potentiates these parts of the brain's salience circuitry to negative stimuli. Because of earlier reported low striatal dopamine levels associated with depression and the critical role of striatal dopamine in relaying information through the caudate to the dorsolateral prefrontal cortex, they basically suggest that the prefrontal cortex goes uninformed about the need for regulatory control when faced with negative emotional stimuli. This oblivion of the prefrontal cortex then results in the lack of back-projection to the cortical-striatal-pallidal-thalamic circuitry. Though this model elegantly explains the context/valence dependent abnormalities in limbic and cortical response patterns and therefore matches our findings of relative intact prefrontal responsivity during neutral executive planning tasks, our and later meta-analytic findings (Müller et al., 2017; McTeague, 2017) do not solidly support lower caudate and prefrontal reactivity and higher salience-circuitry reactivity to negative emotional stimuli, though subtle hyperactivation of the insula was observed by us (van Tol et al., 2012, which was found to be relevant for the longitudinal course of the depressive disorder (Ai et al., 2015).

At around the same time, Disner et al. (2011) presented their model of depression, integrating the cognitive theory of Aaron Beck (1967) with a review of neuroanatomical and neurophysiological findings. They proposed detailed circuitry models explaining maladaptive cognitive processing involved in generating and maintaining depressive symptomatology, including attentional bias, emotional processing, emotional memory, ruminative tendencies, and dysfunctional attitudes about oneself resulting from the activation of depressive self-referential schemas. Their model in general supports the notion of increased limbic 'bottom-up' reactivity, and attenuated cognitive control over these bottom-up regions, in line with models primarily developed to explain affective dysregulation (e.g. Mayberg, 1997; Phillips et al., 2003b). The Disner model attempts to both explain vulnerability and maintenance of depressive symptomatology, and the occurrence of specific and thus heterogeneous symptomatology, in line with the Research Domain Criteria (NIH) approach. Our paradigms would fit the study of emotional processing, both during the emotional faces and word encoding task, which would support the involvement of higher responsivity of limbic responsivity in the acutely depressed state (van Tol et al., 2012) and long term course of the disorder (ai), though not consistently as no amygdalar abnormalities were observed during face processing (Demenescu et., 2011) but instead elevated dorsolateral prefrontal responsivity when processing mood-incongruent faces (i.e., happy). Overall, recent well-powered meta-analytic findings do not fully support the general idea of heightened bottom-up and decreased top-down processing during emotional processing (Müller et al., 2017, McTeague et al., 2020). Futures studies should investigate how especially the circuitry proposed for maladaptive cognitive functioning is mechanistically involved in ruminative processing and dysfunctional belief underpinning the vulnerability for depressive symptomatology, as proposed by the Disner model (2011).

One component seems to be missing in all discussed models: posterior parietal regions involved in the *default mode network*, a network of posterior and anterior midline and lateral parietal regions (Raichle, 2001) that has gained considerable attention since 2001. It has been linked to self-referential processing, which is highly relevant for internally directed processing modes characteristic of depression and anxiety disorders (See Spreng (2012) for an overview). In the context of depression, it was first mentioned by Greicius et al (2007) who observed that patients with MDD showed elevated functional coupling of the subgenual cingulate cortex and thalamus with the default mode network. The default mode network is also referred to as the task-negative network (Fox et al., 2005), because regions in this network tend to de-activate during execution of an external task, and are activated during rest or self-referential processing. This could explain why these regions are typically not reported when studying task related activation. However, reconceptualizations of the default mode network being critical for goal-directed behavior place the function of this network in a different perspective (Spreng et al., 2014). Nevertheless, numerous resting state functional connectivity focused on depression related intrinsic connectivity differences, though using a variety of methods. We for example did not observe abnormalities in the default mode network in patients with MDD without anxiety using independent component analyses (Veer et al., 2010; Pannekoek et al., 2015), but observed abnormal connectivity between regions of the default mode network with a limbic network in patients suffering from both depression and anxiety (Pannekoek et al., 2015). Kaiser et al (2015) meta-analyzed 25 seed-based resting state fMRI studies, and proposed a neurocognitive network model of depression based on their findings. In this model, it is stated that abnormalities in within-network and between-network connectivity in networks associated with self-referential processing, executive and attentional control, and salience processing may result in perpetuation of current depressive episodes. Specifically, the model describes dysfunctions in multiple networks that may predispose to ruminative thinking: 1) lower functional connectivity among fronto-parietal regions, which may underlie abnormalities in cognitive control, 2) higher functional connectivity between regions in the default mode network, associated with self-referential processing and the frontoparietal network, and 3) lower functional connectivity between the frontoparietal network and a dorsal attentional network, which may bias towards ruminative thoughts at the cost of attending to the outside world. Next, lower functional connectivity in a limbic affective network with midline prefrontal cortical may underpin impairments in regulating emotional states. Finally, abnormal functional connectivity in a ventral attentional network with posterior regions may underpin abnormal salience processing, in particular enhanced processing of predominantly negative emotional material.

In light of recent task-related meta-analysis of cognitive and emotional tasks (Müller et al., 2017; McTeague et al., 2017, 2020), this would suggest that the extent to which depressed individuals engage the prefrontal cortex when instructed to, is unaffected, but that the altered intrinsic connectivity of frontal and parietal regions at rest predisposes to lower engagement when confronted with emotional stimuli. Next, together with higher connectivity to default mode regions, this may result in a bias towards self-related ruminative thoughts, while less attention is paid to the outside world and thus corrective (positive) events may be missed. However, higher regulatory control is needed in the face of salient, negative internal or external stimuli. These salient stimuli are processed to a higher extent, both because of higher responsivity of limbic regions to emotional material (McTeague et al., 2020) and because of lower intrinsic connectivity between limbic regions and medial prefrontal regions (Kaiser et al., 2015), thereby

diminishing automatic regulation. This would suggest that strengthening the intrinsic connectivity between frontal and parietal regulatory areas is key when treating depression, thereby lowering the self-referential processing bias, and also between lateral prefrontal and midline prefrontal areas in order to strengthen emotion regulation capacity, while lowering the responsivity of limbic regions associated with threat and salience detection in order to lower the need for regulatory control.

The brain regions involved in the network-hypothesis and their supposed functionality as proposed by Kaiser et al. (2015), are highly relevant for understanding inadequate emotion regulation that is generally associated with affective disorders and is a target of many effective psychological interventions. Adequate emotion regulation depends on functioning of lateral prefrontal, medial frontal and limbic brain areas (Buhle et al., 2014). Meta-analytic results indeed support that abnormalities in a distributed network of midline parietal and cingulate areas, the insula, lateral prefrontal regions, the putamen, cerebellum and precentral gyrus during emotion regulation are associated with depression and anxiety disorders (Picé-Pérez et al., 2017). Abnormal activation of limbic regions other than the insula was not observed in this meta-analysis, which does not fully support the network model of Kaiser et al. (2015) and ventral-dorsal models, which would suggest abnormalities in both frontal and limbic structures. In the NESDA study, an emotion regulation task was included in the nine-year follow-up MRI-measurement, results of which have not yet been published. This will allow us to study whether neural underpinnings of emotion regulation are associated with the long-term course of depression, but also the task-related connectivity of brain regions in multiple brain networks and thus how the resting-state Kaiser et al model holds for the automatic and instructed regulation of mood states.

Future models of depression need to take into account morphological features, baseline activity and connectivity characteristics, to fully understand the off-set from where stimulus-related activation and connectivity changes emerge. Finally, recent explorations of the time-varying nature of network organization, as also explored NESDA by Geugies et al. (2019), make it evident that also the dynamic nature of the network reconfiguration is an important aspect of understanding both the depressive state related abnormalities involved in perpetuation of the current disorder, as well as the time-varying dynamics on the clinical level including recovery, relapse in newer episodes, and development of comorbid disorders.

12.1. General comments

Even though many neuroimaging studies focused on depression followed the original NESDA neuroimaging studies, the observations are still relevant. Not only have findings been replicated and have original data been fed into larger meta-analytic endeavors (Arnone et al., 2016; Schmaal et al., 2016; 2017), there are still only a limited number of studies out there that studied depression and anxiety disorders in common, and were able to specifically control for the comorbidity. Also, due to the careful clinical longitudinal characterization, the relevance of cross-sectional findings of illness severity for understanding state vs. trait abnormalities could be tested using the longitudinal neuroimaging data (Opmeer et al., 2016; Ai et al., 2019; Binnewies et al., 2021). However, the set-up of the NESDA Neuroimaging study predates the Research Domain Criteria approach and focused on the explanatory power of diagnostic labels rather than symptom dimensions across diagnostic labels. Nevertheless, because of the detailed clinical phenotyping, we were also able to take a dimensional approach (i.e. anxious distress) or symptom focused approach (suicidality). However, these all concern secondary analyses.

Overall, at the start of the NESDA Neuroimaging study, it was expected that we would observe massive effects and large blobs of brain activation or morphology differences given the projected sample sizes. We quickly learned that though the main effects of task were indeed very robust, effects of clinical variations were far more subtle, reflecting a trend in the recent neuroimaging literature. Even in the huge meta-analyses that were performed in the context of the ENIGMA MDD-project in thousands of individuals, it became apparent that solely the label of MDD does not explain a lot of variance, although stable associations have been observed (e.g. Schmaal et al., 2020, 2017, 2016).

Similar conclusions can be drawn from the candidate-gene genetic-neuroimaging approach, chosen by NESDA researchers. We report on significant but small effects of several single nucleotide polymorphisms on the BDNF-, NPY-, COMT, DIS1C, and PCLO-genes on activation during emotional and cognitive processing. We observed main effects of the risk-genotypes, as well as interaction effects of gene and diagnosis, or gene and early life stress. Many effects were observed in the limbic regions, that also were defined of regions of interest. Although these results contributed to theorizing on mechanisms linking the genes to psychopathology, new insights led to the conclusion that much larger samples are necessary to explore genetic variations, as well as using other genetic approaches such as polygenic risk scores (PGRS), or approaches that take into account genetic interactions or correlations among traits with a shared genetic basis.

Some limitations, that have been mentioned in most NESDA Neuroimaging papers, should be mentioned here. Earlier papers based on the NESDA Neuroimaging sample not always adhered to current rigorous standards for multiple comparison correction when reporting results, which should therefore be interpreted with caution. Also, owing to the use of multiple scanners which underwent various upgrades over time, scanner variability potentially resulted in an underestimation of true effects. However, we always controlled for scanner site, and patients and controls were randomly distributed over scanner sites so that no systematic site x group error could have occurred. Furthermore, the clinical severity of the NESDA Neuroimaging sample overall was modest, though a substantial proportion showed moderate to severe symptom severity. Finally, it should be mentioned that the NESDA Neuroimaging data from the baseline measurement was used in many publications, and therefore if any systematic bias occurred in sampling of the population or in the measurements, this bias will have affected many results. Also, many statistical tests have been performed, which would in an experimental set-up require appropriate correction for multiple comparisons. However, various analyses were set-up to explore effects of clinical and etiological variations, that could be considered hypothesis generating in nature and ideally need replication in independent samples. This specifically holds for the candidate-gene approach papers, an approach popular in the first 15 years of the 21th century, but which also often showed low reproducibility. Genome Wide Association studies made evident that a single gene variation is usually unlikely to explain a large part of the complex psychopathology of common mental disorders, making the candidate-gene neuroimaging approach, or exploring gene-behavior associations, in smaller samples rather obsolete. More recent candidate-gene neuroimaging studies typically use larger samples and more sophisticated approaches, with the candidate gene neuroimaging study often being part of a comprehensive set of studies investigating various aspects of the candidate gene such as gene-environment interactions (Gottschalk et al., 2019), intermediate phenotypes and treatment response. Nevertheless, our findings from our neuroimaging genetics studies contributed to advancing this field, and could still provide insight from a neural mechanisms point of view (Meyer-Lindenberg and Weinberger, 2006).

Finally, the NESDA study included paradigms focusing on primary emotional processing and non-emotional cognitive control, but did not include paradigms relevant for reward learning and motivation (Keren et al., 2018). This however is an important aspect of understanding the development and maintenance of depression, as motivational problems are a core component of depression, predictive of an unfavorable course. Recently, the need to frame cognitive dysfunction in the light of goal-directed behavior and motivation and not on its own is elegantly presented by Grahek et al. (2018, 2019), which we recognize as an

important advancement in the field.

12.2. Outlook

Though many papers have been written on the NESDA neuroimaging study, several remaining questions are still being addressed. For example, whether executive planning related neural correlates change upon symptomatic remission or are predictive of the longitudinal course. Also, currently we are investigating the effects of depressive persistence and burden over a nine-year period on white matter integrity, resting state functional connectivity, and correlates of effortful emotion regulation. Results of these analyses are expected in the coming year. Because the number of longitudinal studies related to white matter integrity and resting state connectivity in MDD is limited, we are currently performing the fourth MRI-measurement in which we will attempt to invite all individuals that participated in the nine-year follow-up measurement. During this measurement, T1-weighted structural imaging, DTI acquisition and a BOLD-fMRI acquisition during the resting state will be performed that allow for the characterization of changes in intrinsic functional and structural connectivity and morphology over a 15 year period, when many of the NESDA participants will have also reached ages over 65. This will allow exploring the hypothesis whether affective disorders and associated biological dysregulation results in accelerated aging of the brain in a longitudinal manner, and to explore whether for example persistent psychological rigidity is associated with progressive rigidity of functional brain connectivity.

Availability of NESDA Neuroimaging data

The NESDA Neuroimaging project welcomes requests for collaborations on data-analysis, either as a stand-alone project, or by including NESDA Neuroimaging data in a larger analyses, for example for independent replication. Please contact the authors for further information.

Author statement

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Declaration of Competing Interest

None.

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Supplementary materials

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Research paper

The 9-year clinical course of depressive and anxiety disorders: New NESDA findings

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ABSTRACT

Background: In longitudinal research, switching between diagnoses should be considered when examining patients with depression and anxiety. We investigated course trajectories of affective disorders over a nine-year period, comparing a categorical approach using diagnoses to a dimensional approach using symptom severity.
Method: Patients with a current depressive and/or anxiety disorder at baseline ($N = 1701$) were selected from the Netherlands Study of Depression and Anxiety (NESDA). Using psychiatric diagnoses, we described 'consistently recovered,' 'intermittently recovered,' 'intermittently recurrent', and 'consistently chronic' at two-, four-, six-, and nine-year follow-up. Additionally, latent class growth analysis (LCGA) using depressive, anxiety, fear, and worry symptom severity scores was used to identify distinct classes.
Results: Considering the categorical approach, 8.5% were chronic, 32.9% were intermittently recurrent, 37.6% were intermittently recovered, and 21.0% remained consistently recovered from any affective disorder at nine-year follow-up. In the dimensional approach, 66.6% were chronic, 25.9% showed partial recovery, and 7.6% had recovered.
Limitations: 30.6% of patients were lost to follow-up. Diagnoses were rated by the interviewer and questionnaires were completed by the participant.
Conclusions: Using diagnoses alone as discrete categories to describe clinical course fails to fully capture the persistence of affective symptoms that were observed when using a dimensional approach. The enduring, fluctuating presence of subthreshold affective symptoms likely predisposes patients to frequent relapse. The commonness of subthreshold symptoms and their adverse impact on long-term prognoses deserve continuous clinical attention in mental health care as well further research.

1. Introduction

Longitudinal research is essential to validate diagnostic classifications and tailor treatment plans for optimal effectiveness and efficiency for patients with affective disorders (Gillis et al., 1995; Kendell and Jablensky, 2003; Kraepelin, 1921; Lorenzo-Luaces et al., 2017; McGorry et al., 2016; Penninx et al., 2011). In longitudinal research, depressive and anxiety disorders should be investigated synchronously considering that major depressive disorder (MDD) and anxiety disorders often co-occur (Angst et al., 2009; Giandinoto and Edward, 2015; Hayden and Klein, 2001; Howland et al., 2009; Kessler et al., 2005; Kleiboer et al., 2016; Lamers et al., 2011; Moffitt et al., 2007; Rush et al., 2006), and as time passes, one disorder will often switch over to the other ("diagnostic switching") (Gregory et al., 2007; Hovenkamp-Hermelink et al., 2016; Scholten et al., 2016). For example, those recovered from MDD may then meet criteria for generalized anxiety disorder (GAD) and still experience functional impairment and a decreased quality of life (Angst et al., 2009; Maj et al., 2002; Wells et al., 1992). Patients may also switch over to dysthymic disorder, the more chronic but milder form of depression (Klein et al., 2008; Rhebergen et al., 2012).

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The selected observation period may also reveal crucial insights into the course of depressive and anxiety disorders. A shorter window of less than two years has led to relatively positive findings with regard to prognosis (Gilchrist and Gunn, 2007; Hendriks et al., 2013; Richards, 2011; Steinert et al., 2014). For example, previous research has shown that more than half (50 – 70%) of patients recovered within one year from MDD (Richards, 2011; Steinert et al., 2014), and approximately half (43 – 73%) of patients recovered within two years from anxiety disorders (Hendriks et al., 2013). However, when extending the observation window, lower levels of recovery were found, which may be due to diagnostic switching (Caspi et al., 2020; Gregory et al., 2007; Hovenkamp-Hermelink et al., 2016; Plana-Ripoll et al., 2019; Scholten et al., 2016), relapse (Hardeveld et al., 2010; Mueller et al., 1999; Scholten et al., 2013; Verduijn et al., 2017), or continuous subthreshold or subclinical symptoms (Ormel et al., 1993; Wagner et al., 2000).

The course of depressive and anxiety disorders can be and have been described using two clinically-relevant approaches: with psychiatric diagnosis criteria according to the Diagnostic Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013) (i.e., categorical approach) or scores on symptom severity scales (i.e., dimensional approach) (Wardenaar et al., 2014). Use of DSM diagnoses allows us to examine participants who (continue to) meet full DSM criteria over time, whether these are comorbid diagnoses or transitions to other diagnoses. Alternatively, symptom severity scores are regularly used throughout the treatment follow-up process to assess change of symptoms over time, such as in routine outcome monitoring (ROM) (e.g., de Beurs et al., 2011). Using symptom severity scores may also help reveal and describe the heterogeneity in (sub)clinical symptom profiles (Brunoni, 2017; Fried and Nesse, 2015a). Considering that depression and anxiety DSM-diagnoses can be viewed as discrete categorical syndromes imposed on a continuum of depressive or anxiety symptoms of varying severity and duration (Kendler and Gardner, 1998; Klein et al., 2006, 2008; Torpey and Klein, 2008), comparing both approaches is relevant. Latent class growth analysis (LCGA) with both depressive and anxiety symptoms would allow us to examine how symptoms change over time as a dimensional approach and to compare the outcome to the categorical approach with DSM diagnoses.

The present study aimed to describe and compare course trajectories of depressive and anxiety disorders over a nine-year period using a categorical approach for DSM-diagnosis trajectories and a dimensional approach for symptom pathways using LCGA. We considered depressive and anxiety comorbidity, switching to other diagnoses over time, and switching to other trajectories over time. We specified how participants intermittently recover and relapse over a nine-year period and how the DSM diagnoses concur with fluctuating symptom scores. For the categorical approach, we hypothesized that those with baseline comorbid depressive and anxiety disorders, compared to those with baseline depression or anxiety disorder, would have higher levels of chronicity at nine-year follow-up (Hendriks et al., 2013; Richards, 2011; Steinert et al., 2014). Likewise, for the dimensional approach, we hypothesized that those with higher baseline symptom levels would coincide with a more chronic course. Finally, we hypothesized that the trajectories according to the categorical approach would correspond highly with the dimensional symptom pathways.

2. Method

2.1. Study sample and procedure

Data were used from the Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2021), an ongoing longitudinal cohort study examining the course of depressive and anxiety disorders (for the extensive protocol, see Penninx et al., 2008). At baseline (2004–2007), a total of 2981 participants aged between 18 and 65 years were recruited from community (19.0%), primary care (54.0%), and specialized mental healthcare (27.0%). After baseline, face-to-face follow-up assessments were conducted at two years (87.1%, $n = 2596$), four years (80.6%, $n = 2402$), six years (75.5%, $n = 2256$), and nine years (69.4%, $n = 2069$). The nine-year follow-up was completed in 2016.

For the present study, we selected a total of 1701 participants with MDD, dysthymic disorder, and/or anxiety in the six months prior to baseline (i.e., a current six-month diagnosis) (see below).

2.2. Measures

2.2.1. Categorical course trajectories

To determine the categorical trajectories, we examined the presence of depressive (MDD, dysthymic disorder) and anxiety disorders (panic disorder, social phobia, generalized anxiety disorder (GAD), and agoraphobia) according to the DSM-IV criteria at each assessment. The disorders were assessed in person using the Composite Interview Diagnostic Instrument (CIDI) version 2.1 by trained research personnel (Wittchen, 1994; Wittchen and Nelson, 1996). To extrapolate whether the CIDI diagnoses were consistently present during follow-up periods, we examined the continuous presence of diagnosis-related symptoms reported in the Life Chart Interview (LCI; Lyketsos et al., 1994) for that same follow-up period. More information regarding the instruments can be found in the **Supplementary Material**.

Using the CIDI, participants were first divided into subgroups at baseline: 1) depression only (single or any combination of MDD and/or dysthymic disorder); 2) anxiety only (single or any combination of panic disorder, social phobia, GAD, and agoraphobia); and 3) comorbid depression-anxiety (any combination of both depressive and anxiety disorders). The following "primary" categorical diagnosis trajectories were then described at two-, four-, six-, and nine-year follow-up for the total group and for each of the subgroups by examining whether participants had any CIDI diagnosis at each following assessment after baseline: *'consistently recovered'* (fixed diagnosis-free period at each assessment), *'intermittently recovered'* (variable diagnosis-free period preceded by a diagnosis-present period with or without discontinuous LCI symptoms), *'intermittently recurrent'* (variable diagnosis-present period with discontinuous LCI symptoms), and *'consistently chronic'* (fixed diagnosis-present period at each assessment with continuous LCI symptoms). The trajectories of 'intermittently recovered' and 'intermittently recurrent' allowed us to explore the ebb and flow of diagnoses across the nine-year period. At nine-year follow-up, we defined three "comparison" trajectories, where each percentage was aggregated at each subsequent assessment point: *'recovered'* (diagnosis-free period), *'recurrent'* (diagnosis-present period with discontinuous LCI symptoms), and *'chronic'* (diagnosis-present period with continuous LCI symptoms). This allowed us to compare our results to Verduijn et al. (2017), who examined the six-year follow-up NESDA data. An extended description of the trajectories can also be found in the **Supplementary Material** (see "Description of categorical trajectories"). The specific differences with Verduijn et al. (2017) are also outlined in the **Supplementary Material** (see "Comparison with previous NESDA study").

2.2.2. Dimensional course trajectories

To determine dimensional trajectories, we used depressive and anxiety symptom severity measures. For depressive symptom severity, we used the Inventory of Depressive Symptomatology – Self-Report (IDS-SR; Rush et al., 1996; Trivedi et al., 2004). For anxiety symptom severity, we used the Beck Anxiety Inventory - Self-Report (BAI; Beck et al., 1988; De Ayala et al., 2005; Muntingh et al., 2011; Steer et al., 1993); the Fear Questionnaire (FQ; Marks and Mathews, 1979; Oei et al., 1991); and the Penn State Worry Scale (PSWQ; Meyer et al., 1990; Salarifar and Pouretemad, 2012; Verkuil and Brosschot, 2012). Finally, we examined functional (dis)ability, which was measured using the World Health Organization Disability Assessment Schedule (WHO-DAS-II; Chwastiak and Von Korff, 2003). More information regarding these instruments can be found in the **Supplementary Material**.

2.3. Statistical analyses

Sociodemographic characteristics. We reported baseline characteristics as percentages or as means with standard deviations (*SD*). We inspected baseline symptom severity scores for clinically-relevant threshold levels (IDS > 13; BAI > 7; approximations FQ > 30; PSWQ > 48) (Gillis et al., 1995; Rush et al., 1996).

Categorical approach using diagnoses. For the categorical approach, we described the "primary" DSM-diagnoses trajectories using variable and aggregated percentages and "comparison" DSM-diagnoses trajectories using aggregated percentages. We also examined the trajectories without any missing CIDI data at all follow-up assessments. Moreover, we conducted a contingency table analysis with adjusted residuals (Beasley and Schumacker, 1995; García-Pérez and Núñez-Antón, 2003), to test whether there was an association between baseline diagnostic subgroup (i.e., depression only, anxiety only, and depression-anxiety) and the four course trajectories at nine-year follow-up.

Dimensional approach using symptom severity. For the dimensional approach, we used latent class growth analysis (LCGA), a type of mixture modeling with latent class analysis, to identify subgroups of participants with distinct patterns of change in their longitudinal symptom severity assessments, relative to baseline (using the 'hlme' function of the 'lcmm' package in R version 3.6.1) (Proust-Lima et al., 2017). In LCGA, participants are clustered into classes representing trajectories with similar mean levels and mean-level changes of symptom severity by modeling a latent categorical variable. Unlike conventional growth mixture modeling (GMM), the analysis was conducted with the variance of the latent slope and intercept fixed to zero within class, thus limiting the heterogeneity within the latent classes, allowing us to identify course-trajectory classes that were optimally differentiated from each other (Armour et al., 2012; Asparouhov, 2006; Berlin et al., 2014; Cicchetti and Rogosch, 1999; Curran and Hussong, 2003; deRoon-Cassini et al., 2010; Jung and Wickrama, 2008; Muthén and Muthén, 2000; Nylund et al., 2007). For more information, see "Description and interpretation criteria of the latent class growth analysis" and the checklist for the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS; van de Schoot, 2015) in the **Supplementary Material.**

Comparison of categorical and dimensional approaches. We compared the outcome of both the categorical and dimensional approaches at nine-year follow-up. Hereafter, we examined the overlap across the identified dimensional symptom severity pathways and the "primary" and "comparison" DSM-diagnosis trajectories at nine-year follow-up. For the "comparison," trajectories, where a 3 × 3 contingency table was possible, we tested the level of agreement between the categorical and dimensional approaches with the Kappa statistic as a complete-case analysis, where 0.01–0.20 = none to slight/very poor, 0.21–0.39 = minimal, 0.40–0.59 = weak, 0.60–0.79 = moderate and 0.80–0.90 = strong (Cohen, 1960; de Raadt et al., 2019; McHugh, 2012). We then examined the average functional (dis)ability scores across the identified dimensional symptom severity pathways.

To further compare the symptom severity pathways with the DSM-diagnoses trajectories, we examined the trends of symptom severity per questionnaire across the assessment points based on baseline diagnosis subgroups and functional (dis)ability across the assessment points. We split the IDS-SR, BAI, FQ, PSWQ, and WHO-DAS-II scores into quartiles based on the baseline total score of that particular questionnaire and used mixed model regression analysis to yield marginal mean values at each follow-up assessment per questionnaire. Given that depression and anxiety frequently emerge in younger adulthood (Caspi et al., 2020; Ernst and Angst, 1992; Moffitt et al., 2007), we tested whether there was a potential effect of age and gender on depressive, anxiety, fear and worry severity symptoms. Age was split into quartiles, or four age groups. We then examined these trajectories over the nine-year follow-up.

Statistics programs for the analyses. The descriptive analyses and categorical approach analysis were conducted using IBM SPSS version 25.0. For the dimensional approach, we used R statistical software (R version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria, 2016. URL: https://www.R-project.org/). The mixed-model analyses were also conducted using R software using the 'lme4' package. Alpha was set at 0.05, except for the chi-square post hoc contrasts, where alpha was set to 0.0042 after a Bonferroni correction.

Table 1
Baseline Socio-Demographic and Clinical Characteristics ($N = 1701$).

Age, years, mean (*SD*)	41.3 (*12.4*)
Sex, female,% (*n*)	67.0 (*1140*)
Education, years, mean (*SD*)	11.8 (*3.3*)
Married or life partner, yes,% (*n*)	65.3 (*1110*)
Single depressive disorder,% (*n*)	19.9 (*339*)
Comorbid depressive disorders,% (*n*)	3.4 (*57*)
Severity of depressive symptoms (IDS-SR), mean (*SD*)	27.6 (*11.6*)
Severity of anxiety symptoms (BAI), mean (*SD*)	12.1 (*8.9*)
Severity of fear symptoms (FQ), mean (*SD*)	21.7 (*16.8*)
Severity of worry symptoms (PSWQ), mean (*SD*)	29.3 (*15.7*)
Severity of functional disability (WHO-DAS-II), mean (*SD*)	31.6 (*16.0*)
Single anxiety disorder,% (*n*)	22.6 (*384*)
Comorbid anxiety disorders (2 to 3),% (*n*)	9.3 (*159*)
Severity of depressive symptoms (IDS-SR), mean (*SD*)	21.9 (*9.8*)
Severity of anxiety symptoms (BAI), mean (*SD*)	14.7 (*9.5*)
Severity of fear symptoms (FQ), mean (*SD*)	31.1 (*18.5*)
Severity of worry symptoms (PSWQ), mean (*SD*)	29.7 (*14.4*)
Severity of functional disability (WHO-DAS-II), mean (*SD*)	25.1 (*15.4*)
Comorbid depression and anxiety,% (*n*)	44.8 (*762*)
Severity of depressive symptoms (IDS-SR), mean (*SD*)	34.2 (*13.1*)
Severity of anxiety symptoms (BAI), mean (*SD*)	20.8 (*11.5*)
Severity of fear symptoms (FQ), mean (*SD*)	38.8 (*21.9*)
Severity of worry symptoms (PSWQ), mean (*SD*)	32.4 (*18.2*)
Severity of functional disability (WHO-DAS-II), mean (*SD*)	41.1 (*17.2*)

Note. Depression only = depressive disorders such as major depressive disorder or dysthymia. Anxiety only = anxiety disorders such as social phobia and generalized anxiety disorder. Comorbid depression and anxiety = MDD, dysthymic disorder and anxiety disorders. *IDS-SR* = Inventory of Depressive Symptomatology – Self-Report; *BAI* = Beck Anxiety Inventory; *FQ* = Fear Questionnaire; PSWQ = Penn State Worry Scale; WHO-DAS-II = World Health Organization Disability Assessment Schedule (standardized).

3. Results

3.1. Baseline sociodemographic information

Table 1 shows the baseline characteristics of the study sample ($N = 1701$). Participants were on average 41.3 years old ($SD = 12.4$), 67.0% were female ($n = 1140$), and 65.3% had a spouse or partner ($n = 1110$). The mean total IDS-SR and BAI scores were 31.5 ($SD = 10.9$) and 18.3 ($SD = 10.6$), respectively, reflecting a moderate level of depressive and anxiety symptom severity at baseline. Nearly half of our participant sample (44.8%) had comorbid depression and anxiety at baseline.

3.2. Categorical approach using depression and anxiety diagnoses

Fig. 1 presents four stacked bar charts showing the proportions of participants at each follow-up assessment who were 'consistently recovered,' 'intermittently recovered,' 'intermittently recurrent,' and 'consistently chronic,' divided by baseline diagnostic status. Over the course of nine years, the prognosis of each group was relatively positive: the percentage of participants who recovered increased, and the percentage of those with consistently chronic diagnoses decreased. Specifically, at nine-year follow-up, across all groups, between 51.9 and 68.6% had recovered from any disorder (when combining both consistent and intermittent recovery) and between 2.9 and 11.8% maintained consistently chronic disorders. Approximately one-third of participants experienced intermittent recurrence across all groups at four-, six- and nine-year follow-up. Looking specifically at nine-year follow-up, baseline diagnostic status was significantly associated with course, χ^2 (6, $N = 966$) = 61.5, $p < .0001$, with a lower proportion of participants with

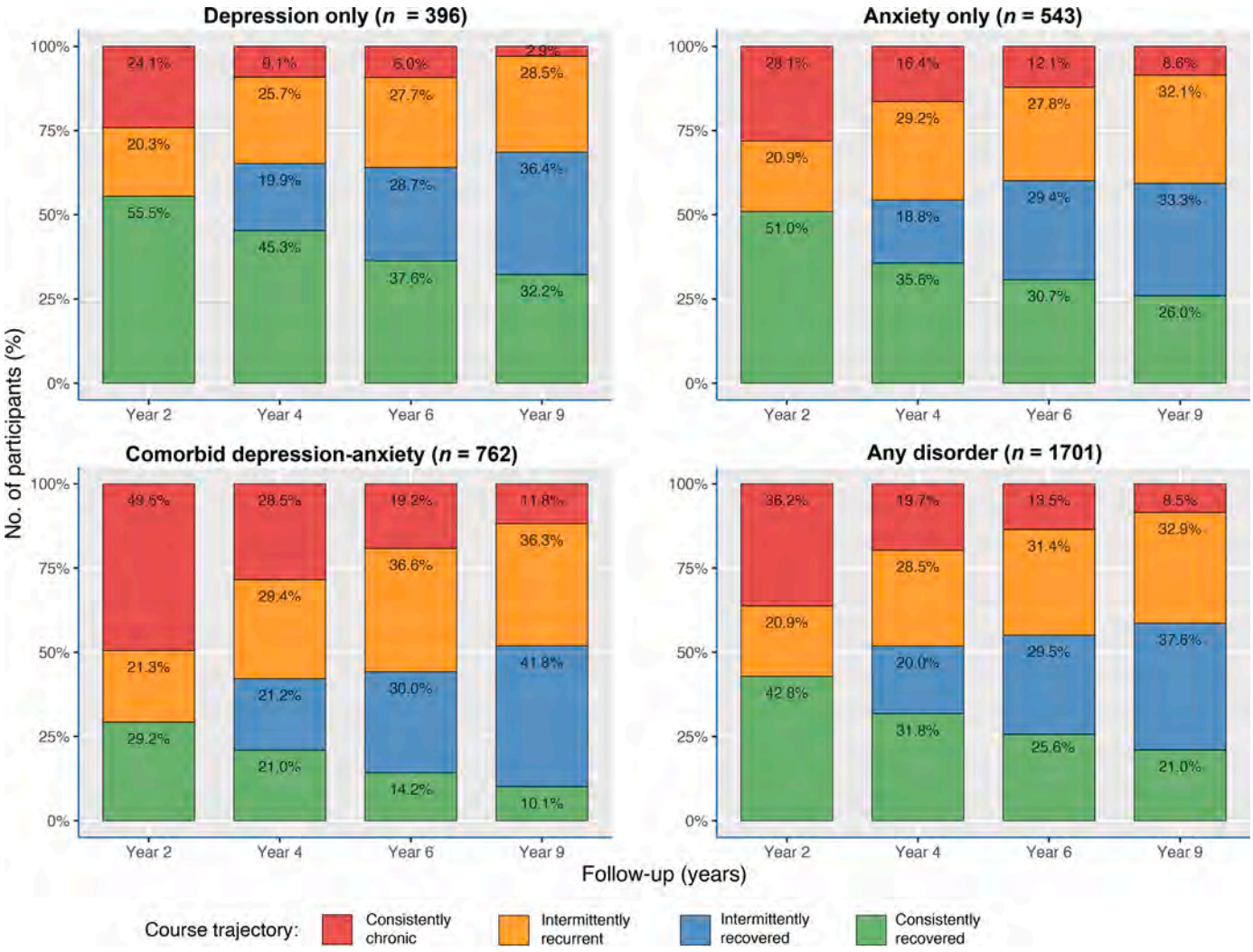

Fig. 1. Categorical trajectories of diagnoses at two-, four-, six-, and nine-year assessments, based on any CIDI affective disorder and LCI data. Depression only = depressive disorders such as major depressive disorder or dysthymia. Anxiety only = anxiety disorders such as social phobia and generalized anxiety disorder.

baseline depression-anxiety comorbidity experiencing consistent recovery than participants with baseline depression ($p < .0001$), and a higher proportion of participants with depression-anxiety comorbidity experiencing consistent chronicity than participants with baseline depression ($p = .0012$). Additionally, when examining recovery more closely at nine-year follow-up, only 10.1% of participants with baseline comorbid depression-anxiety were consistently recovered, 26.0% of the anxiety-only group were consistently recovered, and 32.2% of the depression-only group were consistently recovered. Lastly, for the total group with any disorder, 21.0% were consistently recovered. When using a sample without missing CIDI diagnoses at any follow-up assessment ($N = 956$), we found the same pattern as in the primary categorical trajectories. For comparison with trajectories of Verduijn et al. (2017), see Figure A and "Comparison with previous NESDA study" in the **Supplementary Material**. The main finding of the comparison trajectories is that 78.5% of participants with any disorder experienced recurrence over a nine-year period.

3.3. Dimensional approach using symptom severity

Table 2 shows the fit indices resulting from the log-linear LCGA with one- to six-classes.

Table 2
Fit Indices of One- to Six-Class Latent Class Growth Analysis over a Nine-Year Follow-Up ($N = 1693$).

Classes	Log-Likelihood	AIC	BIC	SA-BIC	Entropy	Percentage of Individuals in Class					
						1	2	3	4	5	6
1	−5735.8	11,477.6	11,493.9	11,484.3	1.00	100	–	–	–	–	–
2	−4827.9	9667.8	9700.5	9681.4	0.71	22.1	77.8	–	–	–	–
3	−4598.8	9215.6	9264.5	9235.9	0.69	7.5	66.6	25.9	–	–	–
4	−4505.9	9035.9	9101.1	9063.0	0.62	4.7	14.1	18.9	62.4	–	–
5	−4452.1	8934.2	9015.7	8968.1	0.65	2.4	7.6	62.3	19.5	8.2	–
6	−4427.9	8891.8	8989.7	8932.5	0.66	1.2	2.4	61.4	7.5	19.8	7.8

Note. AIC = Akaike Information Criterion (Akaike, 1987); BIC = Bayesian Information Criterion (Schwartz, 1978); SA-BIC = sample-size-adjusted BIC (Sclove, 1987); Entropy (Ramaswamy et al., 1993).

Taking all fit indices into account, the three-class model was considered the optimal solution. The AIC and SA-BIC values showed a marked drop between one-, two- and three-class models (see elbow plots in **Fig. B** in **Supplemental Material**), and hereafter, the differences in AIC and SA-BIC values were smaller, suggesting that the addition of more classes did not further improve the model. Also, solutions with four to six classes had very small numbers of participants (<5%) in some classes. Examining the entropy value of the three-class model (0.69) indicated that a moderate to high proportion of participants were correctly classified. The grid search also confirmed a three-class model.

Fig. 2**A** delineates the three latent classes that were identified using pooled standardized mean severity scores of depressive, anxiety, fear,

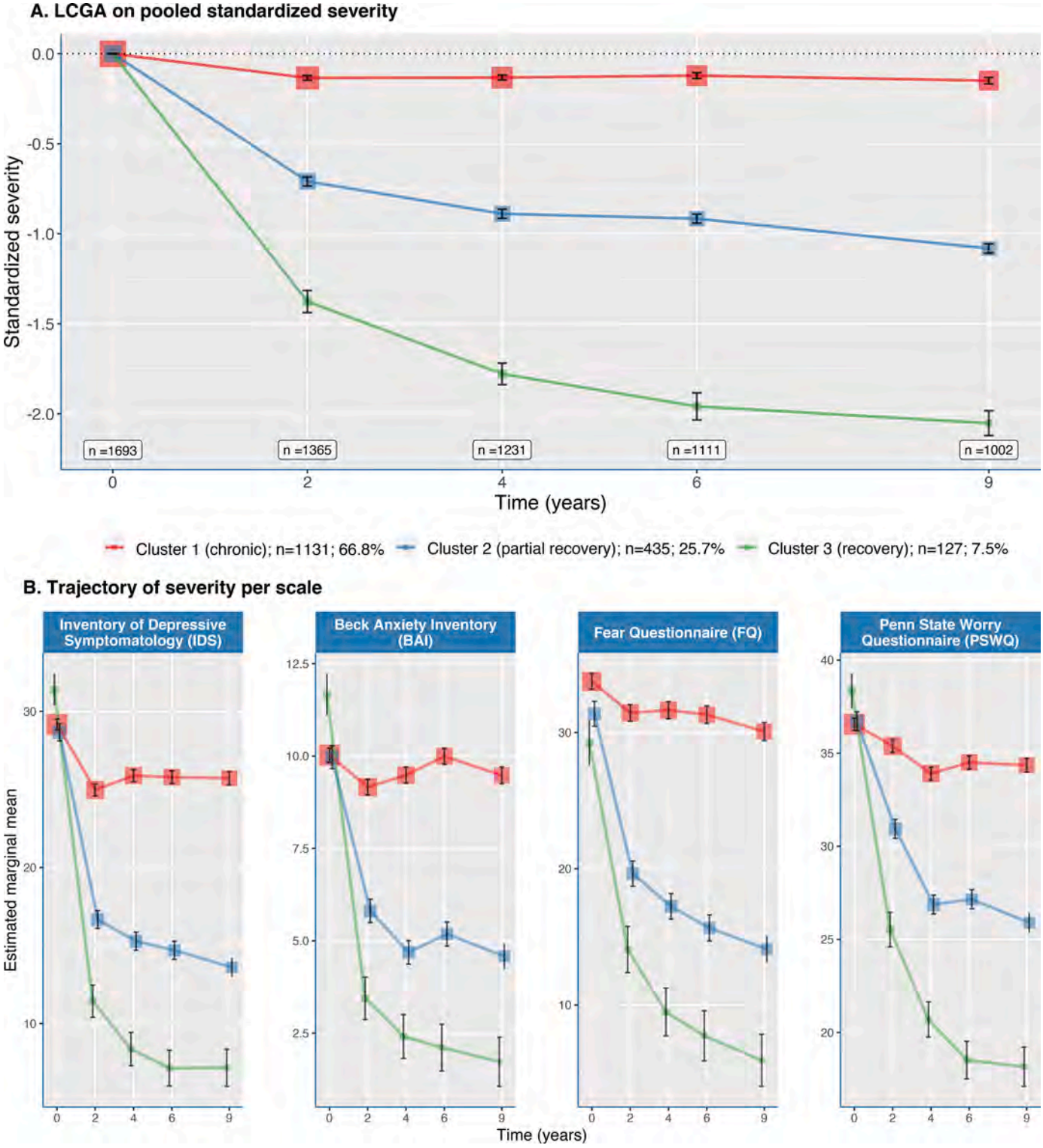

Fig. 2. Three latent class solution of pooled standardized mean severity scores of depressive, anxiety, fear, and worry symptoms (LCGA: latent class growth analysis). Panel A shows the average change in standardized severity over time as compared to baseline severity, and Panel B shows the standardized severity scores per scale over time. Error bars represent standard errors, and the box size is proportional to the number of participants.

and worry symptom questionnaires: class 1: *chronic* (66.8%); class 2: *partial recovery* (25.7%); and class 3: *(sustained) recovery* (7.5%). Class 1 (red) remained stable and severe; whereas symptom levels decreased moderately in class 2 (blue) and markedly in class 3 (green). This was consistent with the latent classes of pooled symptom severity for depression, anxiety, fear, and worry symptom levels, viewing each questionnaire separately (see Fig. 2**B**): the group with the highest symptom levels maintained high symptom levels throughout the nine-year period; the moderate level group showed slow decline and intermittent increases in anxiety and worry; and the lowest symptom level group showed a larger and steady decline. Moreover, inspection of the classes, or symptom pathways, showed that there was a relatively greater change in symptom severity between baseline and the first follow-up, after which the course showed less change between follow-up assessments and began to stabilize, suggesting that the log-linear function best described these symptom pathways. For a comparison with alternative models, see "Alternative models using latent class growth analysis" in the **Supplementary Material**. Recomputing the model without any missing data and comparing these to the abovementioned classes resulted in highly corresponding models: 94.9% similarity for class 1 (chronicity), 89.9% similarity for class 2 (partial recovery), and 100% similarity for class 3 (recovery).

3.4. Comparison of categorical and dimensional approaches

We compared the diagnosis trajectories of the total sample using the categorical approach at nine-year follow-up with the three identified symptom severity pathways of the dimensional approach. The 'intermittently recurrent' trajectory and the 'partially recovered' pathway corresponded relatively well (32.9% versus 25.7%). However, the percentages of the '(consistently) chronic' and '(consistently) recovered' trajectories did not align. In the categorical approach compared to the dimensional approach, chronicity was lower (8.5% versus 66.8%), and (combined) recovery was higher (58.6% versus 7.5%). The 'recovered' dimensional pathway appeared to correspond more to the 'consistently recovered' diagnosis trajectory (10.1%) at nine-year follow-up.

We then compared the primary and comparison DSM-diagnosis trajectories and three identified symptom severity pathways using cross-tabulation at nine-year follow-up (see Table 3).

First, we looked at the four primary DSM-diagnosis trajectories. Participants who were 'consistently recovered,' 'intermittently recovered,' and 'intermittently recurrent' from a DSM diagnosis were spread across all three symptom severity pathways. No clear pattern of correspondence emerged. Second, we looked at the three comparison DSM-diagnosis trajectories with the symptom severity pathways, and the overlap of was low, with very poor agreement, $\kappa = 0.02$. Participants from the categorical 'recovered' trajectory, for example, were also allocated to the 'partially recovered' and 'chronic' dimensional pathways. Regarding functional disability, participants in the 'chronic' symptom severity pathway experienced the highest functional disability, followed by the 'partial recovery', then 'recovered' pathway.

Finally, we tested whether there was a potential effect of age (in quartiles) and gender on depressive, anxiety, fear, and worry severity symptoms (see **Fig. C** in **Supplemental Material**). There were age group and gender differences, with age having a slightly higher effect on severity symptoms. Fig. 3 presents the trends of depressive (A), anxiety (B), fear (C), and worry (D) severity symptoms for subsamples of participants with depression only, anxiety only, or comorbid depression-anxiety, based on baseline severity scores split into quartiles. These were adjusted for the effects of age and gender. However, the adjusted mixed model regression analyses resulted in similar trajectories as the non-adjusted analyses.

Throughout the nine-year period, those with the highest baseline severity levels (red line) on average maintained the highest severity scores, remaining above clinically-relevant threshold levels. In general, all baseline quartiles had trends that ran rather parallel over time and remained stable after an initial drop in severity at two-year follow-up. Furthermore, comparing the three subsamples, those with comorbid depression-anxiety at baseline appeared to have the highest scores across all symptom measures compared to the depression only and anxiety only groups.

Finally, to assess the trends of functional disability, we reviewed the WHO-DAS-II scores at each follow-up assessment over the nine-year period for subgroups of depression only, anxiety only, and comorbid depression-anxiety based on baseline total scores split into quartiles (see Fig. 2**E**). Those with comorbid depression-anxiety appeared to have higher disability than those with depression only or anxiety only.

Table 3
Comparison of the Three Identified Dimensional Symptom Severity Pathways of the Latent Class Growth Analysis (LCGA) with the Primary and Comparison Categorical Diagnosis Trajectories based on Overlap and Disability at Nine-Year Follow-Up.

Categorical diagnoses trajectories[a]	Dimensional symptom severity pathways orLCGA classes		
	Recovered	Partially Recovered	Chronic
Consistently Recovered	33	92	78
% within categorical trajectories	16.3%	45.3%	38.4%
% within LCGA classes	52.4%	29.7%	13.2%
Intermittently Recovered	25	135	203
% within categorical trajectories	6.9%	37.2%	55.9%
% within LCGA classes	39.7%	43.5%	34.2%
Intermittently Recurrent	5	75	238
% within categorical trajectories	1.6%	23.6%	74.8%
% within LCGA classes	7.9%	24.2%	40.1%
Consistently Chronic	0	8	74
% within categorical trajectories	0.0%	9.8%	90.2%
% within LCGA classes	0.0%	2.6%	12.5%
Categorical diagnoses trajectories[b]			
Recovered	**33**	92	78
% within LCGA classes	40.7%	24.3%	9.0%
% within categorical trajectories	16.3%	45.3%	38.4%
Recurrent	48	**278**	715
% within LCGA classes	59.3%	73.5%	82.5%
% within categorical trajectories	4.6%	26.7%	68.7%
Chronic	0	8	**74**
% within LCGA classes	0.0%	2.1%	8.5%
% within categorical trajectories	0.0%	9.8%	90.2%
Disability (WHO-DAS-II), mean (*SD*)	5.3 (7.9)	13.9 (12.6)	28.8 (17.6)

[a] 4 primary trajectories of the categorical approach, $N = 966$.
[b] 3 comparison/aggregated trajectories of the categorical approach, $N = 1326$.
In **bold** = overlap between the comparison/aggregated categorical trajectories and dimensional pathways.
WHO-DAS-II = World Health Organization disability assessment schedule.

4. Discussion

Our findings show that using DSM diagnoses alone fails to fully capture the persistence of depressive and anxiety symptoms over time. The categorical trajectories using diagnoses were not congruent with results of the identified dimensional pathways using symptom severity, further emphasizing the need to better capture clinical course (Batelaan et al., 2014). In other words, diagnostic recovery was not equivalent to symptomatic recovery. When using the categorical approach with any depressive or anxiety diagnosis, approximately 8% were consistently chronic, 33% had intermittently relapsed, 38% had intermittently recovered, and 21% remained consistently recovered at nine-year follow-up, showing a higher estimation of recovery compared to the dimensional approach. However, when we examined participants with baseline comorbid depression and anxiety, only 10.1% remained consistently recovered at nine-year follow-up, which paralleled the 7.5% who were recovered using the dimensional approach.

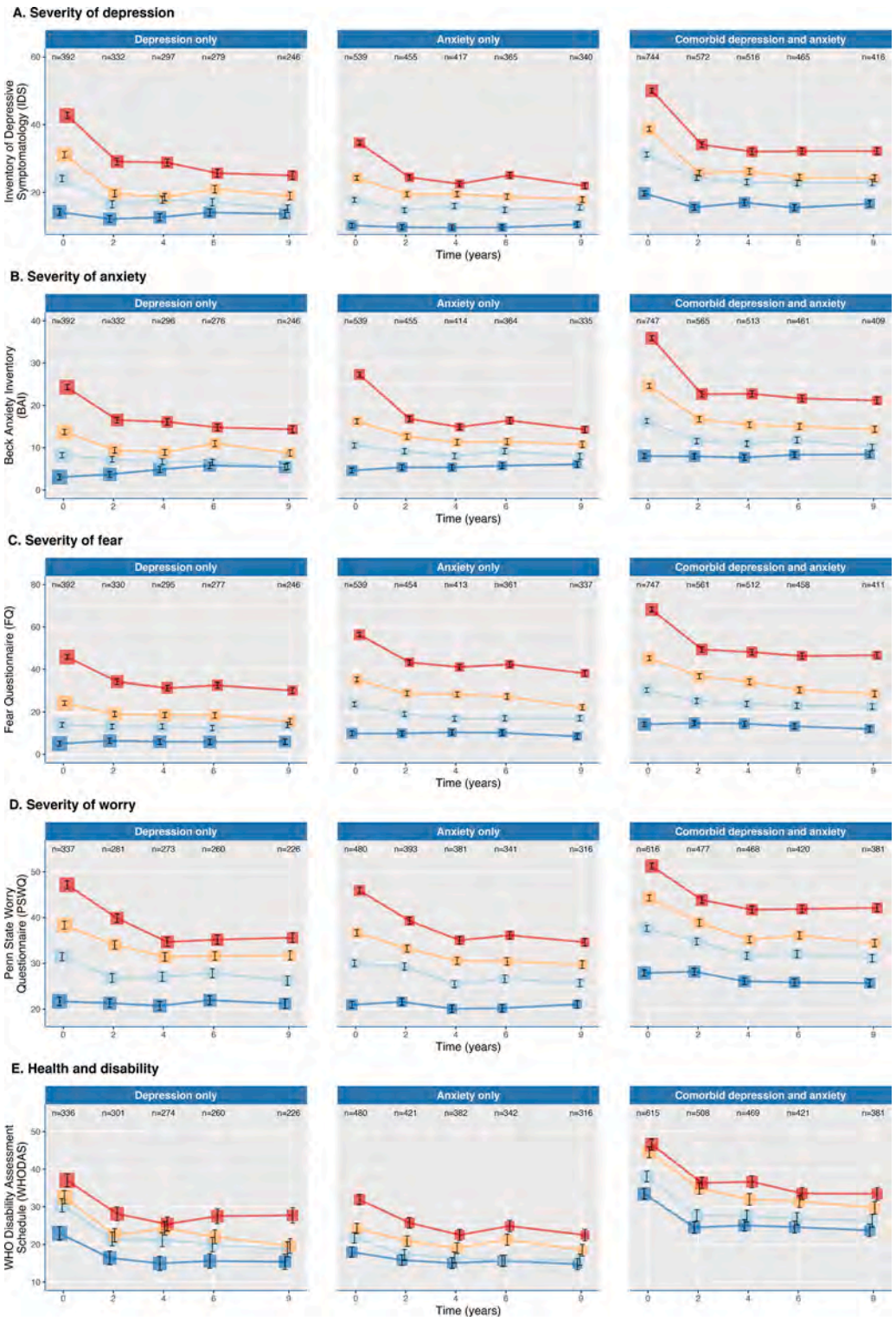

Fig. 3. Trajectories of depressive, anxiety, fear, and worry symptoms, controlled for the effect of age and gender. Error bars represent standard errors, and the box size is proportional to the number of participants.

Additionally, compared to the categorical trajectories of comorbid depression and anxiety, the chronicity of the dimensional symptom severity pathway was much higher (11.8% versus 66.8%). When using aggregated trajectories, we found that 78.5% of participants with any disorder experienced recurrence over a nine-year period. This was much higher than the 25.7% who were partially recovered when using the dimensional approach.

The discrepancy between the trajectories could be explained by the following reasons. First, the discrepancy may be due to the inherent differences of the methods used to assess the dimensional versus the categorical outcomes. Specifically, the dimensional approach used self-report questionnaires to determine the change in symptom severity over time while the categorical approach used a structured interview to establish DSM diagnoses and examine them over time. Although the self-

report questionnaires encompassed the same symptoms as the depression and anxiety syndromes in the structured interview, the questionnaires assessed a shorter duration period of one to two weeks. For the diagnoses, we allowed a longer recency period of six months. The diagnosis, therefore, may not have been present at the moment of assessment and might have been present up to five and a half months ago. Moreover, in the structured interview, the trained interviewer examined the number of symptoms, duration of the symptoms, and the patient's level of functioning. Thus, if a patient had the required number of symptoms yet a higher level of functioning, a DSM diagnosis was not recorded. At the outset, due to the specific diagnostic criteria, using a categorical approach with DSM diagnoses may be less inclusive when compared to the dimensional approach, which may have resulted in higher recovery rates and lower chronicity. Because of the inclusion of the functional disability criterion, we consider DSM diagnoses to be a better indicator of psychological suffering than self-report questionnaires. Second, the discrepancy in results could be due to enduring, fluctuating subthreshold affective symptoms and the higher prevalence of individuals experiencing recurrence of diagnoses. Those with remitted affective diagnoses, for instance, may still suffer from subthreshold disease (e.g., minor depression), or they could have been assessed during a short period in which affective symptoms had slightly receded (Batelaan et al., 2014; Torpey and Klein, 2008). Previous research has shown that, compared to those without symptoms, those with subthreshold symptoms relapsed sooner (Cuijpers and Smit, 2004; Fawcett, 1994; Judd et al., 1998; Karsten et al., 2011) and were found to suffer more chronic episodes and fewer symptom-free weeks (Arnow and Constantino, 2003; Judd and Akiskal, 2000). Other studies have also found a recurrent course with (non)chronic episodes in at least 50% of participants (Bobes et al., 2018; Bruce et al., 2005; Scholten et al., 2016, 2013; Verduijn et al., 2017; Yonkers et al., 2003) and up to 80% (Judd, 1997).

Furthermore, when using the categorical approach, as expected, those with comorbid depressive and anxiety disorders had a relatively poorer long-term course when compared to those with baseline depressive disorders only. This finding is in line with previous research examining anxiety and (comorbid) depressive disorders (Batelaan et al., 2014; Bruce et al., 2005; Rhebergen et al., 2011; ter Meulen et al., 2021). According to Batelaan et al. (2014), however, baseline severity, duration of symptoms, and disability appear to be better indicators of a poor prognosis than DSM-categories.

4.1. Clinical significance of the results

Kraepelinian nosology (Kraepelin, 1921) emphasizes that course, functional outcome, and etiology support a dimensional approach of depression and anxiety. In light of our findings, the question arises whether we should view individuals with comorbidity as having two or more distinct DSM disorders or as having a single dimensional disorder, or symptoms on a continuum, in which myriad etiological factors may result in diverse syndromes that are modified with time and environmental exposures (Angst and Wicki, 1991; Cardno et al., 2002; Hyman, 2010; Kendler et al., 1992; Krueger and Markon, 2006). Previous studies (Fried and Nesse, 2015b; Fried et al., 2014; Lux and Kendler, 2010; van Eeden et al., 2019) have identified risk factors, such as neuroticism and baseline chronicity, that affected individual depressive symptoms to varying degrees, suggesting that depression is not one unified latent construct. On the other hand, abandoning the current DSM criteria would reduce reliability and leave psychiatry without a common language (Kendell and Jablensky, 2003; Patten, 2015). Therefore, until a better dimensional model is proposed, we suggest the integrative use of diagnostic classification, symptom severity, symptom duration, and levels of impairment (Batelaan et al., 2014; Hyman, 2010; Patten, 2015). An example is the Activity, Cognition, and Emotion (ACE) model that groups symptoms commonly present in mood disorders like depression and bipolar disorder according to functional domains (Malhi et al., 2018). Another option is the symptom-based framework which looks at individual symptoms and how they influence each other (Fried, 2015). However, more research is needed to confirm whether a dimensional symptom-oriented tool will lead to more accurate symptom-specific tailored treatment plans and better outcomes. Moreover, clinicians may consider the adoption of longer-term treatment strategies (Vos et al., 2004) that may include relapse prevention strategies and psychiatric rehabilitation (i.e., functional recovery) for those with high levels of subthreshold symptoms and a high risk of recurrence of disorders over nine years. Well-designed interventions studies looking into the types and effectiveness of relapse prevention strategies are warranted.

4.2. Strengths and limitations

This study has some noteworthy strengths. First, NESDA was designed to gain more insight into the long-term clinical course of depression and anxiety in a large cohort study with access to the full range of depression and anxiety disorders from primary and secondary care. Patients were rigorously diagnosed using diagnostic interviews and followed over a nine-year time period with multiple assessment points. Moreover, rather than investigating the course of single MDD or anxiety disorders, we examined variable course categories that allowed comorbidity and diagnostic switching, which may be more ecologically and clinically relevant. To strengthen our conclusions, we used the data-driven LCGA method, to distinguish groups with similar symptom severity trajectories, which handles missing data rather well. The findings were further confirmed by inspecting symptom severity scores, diagnoses, and functional (dis)ability. Additionally, we compared our models to those without missing data, and results were not significantly altered.

With regard to our study limitations and research recommendations, the following may be mentioned. First, the current study used data from NESDA, which concerns DSM-IV criteria rather than the newest DSM-5 criteria. In the DSM-5, there is a duration criterion for social phobia and agoraphobia, which could be useful in excluding patients with only transient fears (Batelaan et al., 2014). Second, NESDA was set up as an observational, naturalistic study, and therefore, the effects of treatment on outcomes could not be examined (e.g., due to confounding by indication effects). While general data were collected regarding medication use, treatment duration, and setting (e.g., primary or secondary care, or psychotropic use), data on the specifics of type, duration, and intensity of psychotherapeutic interventions were not collected. Third, to maximize our sample, we selected participants with a diagnosis in the six months prior to baseline, a period during which some participants may have remitted. Fourth, NESDA did not include participants with obsessive compulsive disorder (OCD), bipolar disorders, or other common mental disorders, which participants may also be experiencing, thereby potentially increasing prevalence rates of chronicity. Fifth, our sample included participants recruited from the community, primary care and specialized mental health care, resulting in a heterogenous cohort (Patten, 2015; Regier et al., 1998). Thus, our results may not be generalizable to each population. Sixth, at each follow-up there was a selective loss of participants, which were those with the highest baseline severity levels. Thus, chronicity may have been underestimated. Seventh, the Life Chart Interview (LCI), which relies on the recall of past memories, was used to establish the continuity of symptoms between assessment points in the categorical approach. Recall error of autobiographical information may have had an impact on the accuracy of the sustained recovered or consistently chronic categorical trajectories (Drasch and Matthes, 2013; Reimer and Matthes, 2007). Although the LCI uses an event history calendar with landmark events, which has been shown to be an effective tool for the reliable retrieval of older memories (Belli, 1998; Belli et al., 2001; Drasch and Matthes, 2013; Vaart and Glasner, 2011), memory is not always reliable, and any results using retrospective recall should be carefully considered (Glasner and

Vaart, 2009; Patten et al., 2010). Eighth, NESDA used the CIDI to diagnose DSM-IV disorders. However, there is an alternative semi-structured clinical interview, namely the Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology (SPIKE) (Angst and Dobler-Mikola, 1985; Angst et al., 2009; Angst and Wicki, 1991; Ernst and Angst, 1992), which has a lower threshold than the CIDI to meet diagnostic criteria. The strict criteria of the CIDI may make it less inclusive, potentially leading to an underestimation of chronicity levels in the current study. Ninth, LCGA classes were calculated primarily with log-linear functions and with too few assessments. Therefore, our dimensional approach may not have been able to fully describe the "waxing and waning" of symptom severity. However, examining alternative models with other shape trajectories corresponded highly with the log-linear primary model. Tenth, while we did examine the functional disability in the dimensional approach using mixed-model regression analyses, functional disability was not included in the main LCGA due to bias. Future research using a longitudinal design and a dimensional approach that includes both rater-based versus self-rated symptom scales would be of value and may help improve the prediction of the clinical course.

5. Conclusion

This study showed that, when taking comorbidity, switching between diagnoses, and symptom duration into consideration to examine the long-term course of depression and anxiety, using categorical diagnoses alone to describe clinical course led to a high estimation of recovery, low estimation of chronicity, and appeared to inadequately capture the persistence of affective symptoms. Discrepancies in the clinical course using DSM-categories or symptom severity could be explained by the enduring, fluctuating presence of subthreshold affective symptoms that do not meet diagnosis criteria but still may lead to recurrence of disorders. The commonness of subthreshold symptoms and their adverse impact on long-term prognoses deserve continuous clinical attention in mental health care as well further research.

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Data availability statement

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

CRediT authorship contribution statement

Ericka C. Solis: Formal analysis, Writing – original draft. **Albert M. van Hemert:** Writing – review & editing. **Ingrid V.E. Carlier:** Writing – review & editing. **Klaas J. Wardenaar:** Writing – review & editing. **Robert A. Schoevers:** Writing – review & editing. **Aartjan T.F. Beekman:** Writing – review & editing. **Brenda W.J.H. Penninx:** Writing – review & editing. **Erik J. Giltay:** Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest to report.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.08.108.

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Research paper

Common and specific determinants of 9-year depression and anxiety course-trajectories: A machine-learning investigation in the Netherlands Study of Depression and Anxiety (NESDA).

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ABSTRACT

Background: Given the strong relationship between depression and anxiety, there is an urge to investigate their shared and specific long-term course determinants. The current study aimed to identify and compare the main determinants of the 9-year trajectories of combined and pure depression and anxiety symptom severity.

Methods: Respondents with a 6-month depression and/or anxiety diagnosis (n=1,701) provided baseline data on 152 sociodemographic, clinical and biological variables. Depression and anxiety symptom severity assessed at baseline, 2-, 4-, 6- and 9-year follow-up, were used to identify data-driven course-trajectory subgroups for general psychological distress, pure depression, and pure anxiety severity scores. For each outcome (class-probability), a Superlearner (SL) algorithm identified an optimally weighted (minimum mean squared error) combination of machine-learning prediction algorithms. For each outcome, the top determinants in the SL were identified by determining variable-importance and correlations between each SL-predicted and observed outcome (ρ_{pred}) were calculated.

Results: Low to high prediction correlations (ρ_{pred}: 0.41-0.91, median=0.73) were found. In the SL, important determinants of psychological distress were age, young age of onset, respiratory rate, participation disability, somatic disease, low income, minor depressive disorder and mastery score. For course of pure depression and anxiety symptom severity, similar determinants were found. Specific determinants of pure depression included several types of healthcare-use, and of pure-anxiety course included somatic arousal and psychological distress.

Limitations: Limited sample size for machine learning.

Conclusions: The determinants of depression- and anxiety-severity course are mostly shared. Domain-specific exceptions are healthcare use for depression and somatic arousal and distress for anxiety-severity course.

1. Introduction

Both depression and anxiety generally follow chronic-intermittent course-trajectories (Verduijn et al., 2017) but considerable course heterogeneity exists (Musliner et al., 2016). Prospective studies of long-term (≥6 years) depression course indicate that patients can have recurrent episodes (Brodaty et al., 2001; Kennedy et al., 2003), never reach full remission (e.g., Angst & Volrath, 1991; Angst, 1996; Keller et al., 1992; Piccinelli & Wilkinson, 1994; Chen et al., 2000) or have persistent residual symptoms (Judd et al., 1998; Kennedy et al., 2004; Rhebergen et al., 2011), all of which is associated with higher costs (McIntyre & O'Donovan, 2004), healthcare use (e.g., Pettit et al., 2009) and impairments (e.g., Judd et al., 2000a;(Fichter et al., 2008). Prospective studies of long-term anxiety course have also shown high persistence over time (Cowley et al., 1996; Bruce et al., 2005; Keller, 2002; 2003; Wittchen & Fehm, 2003; Katschnig & Amering, 1998), although anxiety-disorder diagnoses may change over time (Hovenkamp-Hermelink et al., 2016). Often, depression and anxiety

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disorders co-occur (e.g., Clark & Watson, 1991), which is associated with a less favourable course (e.g., Bruce et al., 2005; Rhebergen et al., 2011).

Both for clinical and public-health purposes, identifying the baseline determinants of the long-term course of depression and anxiety is of strong interest. Prospective studies have shown that baseline clinical characteristics such as comorbidity (Coryell et al., 2012), severity, number of previous episodes (Steinert et al., 2014), residual symptoms (Judd et al., 2000b), psychosis (Coryell et al., 1996), suicidality (Moos & Cronkite, 1999), as well as psychological characteristics (Surtees & Wainwright, 1996, Struijs et al., 2018; Hovenkamp-Hermelink et al., 2019) are associated with increased risk of long-term chronicity and/or recurrences. In addition, physical and health-related variables, such as increased triglyceride, decreased HDL cholesterol (Virtanen et al., 2017), lower birth weight, older age at first standing/walking (Colman et al., 2007), and pain intensity, duration and severity (Gerrits et al., 2015) were found to predict long-term depression persistence.

For anxiety, studies have found baseline clinical characteristics, including comorbidity (Hovenkamp-Hermelink et al., 2021; Keller, 2003; Bruce et al., 2005), young age of onset (Angst & Vollrath, 1991; Rubio et al., 2007), anxiety duration (Spinhoven et al., 2016), severity, parental history (Beesdo-Baum et al., 2012), personality traits (Angst & Vollrath, 1991; Schopman et al., in press), mental functioning and negative life events (Schopman et al., in press) to predict long-term persistence. So far, there has been little evidence for biological predictors (Hovenkamp-Hermelink, 2021).

Although informative, previous work has had limitations. First, most studies defined course based on presence or absence of discrete diagnoses over time, whereas mental health is a continuous phenomenon (e.g., Kendell & Jablensky, 2003; Clark & Watson, 1991). The use of course outcomes based on trajectories on continuous severity measurements (e.g., Rhebergen et al., 2011; Olino et al., 2010) could better capture naturally-occurring course variations, but studies using such outcomes have been scarce. Second, most studies focused either on the determinants of depression or anxiety course, whereas these domains are known to be strongly related (Goodwin, 2015; Kotov et al., 2020). Indeed, the few studies that looked at the combined course of depression and anxiety found considerable overlap between their determinants (e.g., comorbidity, neuroticism, childhood adversity; Rhebergen et al., 2011; Fichter et al., 2010; Merikangas et al., 2003). Importantly, some domain-specific course-determinants have also been found. For instance, a parental history of anxiety was found to predict a chronic anxiety course from an early age (<14 years); Olino et al., 2010). This aligns with the theory that both shared and domain-specific mechanisms underlie depression and anxiety (Clark & Watson, 1991). Third, studies have so far each investigated the predictive association of different and relatively small sets of baseline determinants, hampering identification of all potentially relevant (combinations of) course determinants.

Given the above, investigating the shared and domain-specific determinants of depression and anxiety course trajectories using a large number of baseline variables from different domains would be an ideal approach. For such purposes, machine-learning (ML) is ideal as it can handle larger numbers of variables and more complex associations than traditional regression (e.g., Smith, 2018). However, there are many different ML-algorithms that can each yield different results depending on their suitability for a given problem, with the optimal choice seldom being clear a priori. To navigate this problem, a Superlearner (SL) approach (van der Laan et al., 2007; van der Laan & Rose, 2011; Rose, 2013) is recommended, in which multiple ML-algorithms are estimated and 'stacked' in a SL that weights these algorithms as to obtain optimal predictions. This approach was previously shown useful in psychiatric studies (Kessler et al., 2014; Rosellini et al., 2018a; 2018b; 2020; Webb et al., 2020).

The current study aimed to use a SL to address the above-described knowledge gaps with regard to the shared and specific determinants of long-term course of dimensional anxiety and depression, using data from a large 9-year cohort study. This dataset contains many baseline predictor variables (n=152), which in combination with the SL allowed for estimation of prediction models incorporating most of the determinants that had previously not been studied or only in separate studies. Using this approach, as much information as possible was used to obtain optimal predictions for the 9-year course trajectories of (1) general psychological distress, (2) pure depression, and (3) pure anxiety symptom severity. The main baseline course determinants were compared between (a) pure depression and anxiety trajectories to evaluate overlap and (b) between the pure depression/anxiety and psychological distress trajectories to evaluate the degree of overlap between domain-specific and general psychological distress determinants.

2. Methods

2.1. Participants and procedures

Data came from the Netherlands Study of Depression and Anxiety (NESDA) cohort study (Penninx et al., 2008). Participants were recruited from the general population, primary care, and secondary care centres. The baseline sample (n=2,981) consists of adults aged 18-65 years (mean age: 41.6 years; 1,979 (66%) women). Of the participants, 652 (22.9%) had no lifetime diagnosis, and 2,329 (78.1%) had a lifetime diagnosis of a depressive and/or anxiety disorder at baseline. All participants had a detailed assessment at baseline and were followed up after 2, 4, 6 and 9 years. Exclusion criteria at baseline were: not being fluent in Dutch, a primary diagnosis of a psychotic, obsessive-compulsive disorder, bipolar disorder or severe addiction disorder. The detailed objectives and rationales of NESDA are given in Penninx et al. (2008). The Ethical Review Boards of all participating universities approved the study protocol. All participants signed informed consent. This study used data from participants with a diagnosis of dysthymia, major depressive disorder (MDD) or an anxiety disorder within 6 months before baseline (n=1,701; see **Figure S1**).

2.2. Measurements

The baseline assessment consisted of a face-to-face interview including a structured psychiatric interview by a trained research assistant, self-report questionnaires, biological measurements and a blood-draw. In total, 152 baseline variables (**Table S1**) were used as determinants. At 2-, 4-,6- and 9-year follow-up assessments were repeated. Longitudinal anxiety- and depression-severity self-report assessments were used to construct course outcomes.

2.2.1. Determinants

2.2.1.1. Demographics. Age, gender, relationship status, employment status, income, living situation, having children (yes/no), and having siblings (yes/no) were assessed in the interview.

2.2.1.2. Psychiatric and psychological variables. The Composite International Diagnostic Interview (CIDI; World Health Organization [WHO] v2.1) was used to establish DSM-IV diagnoses of depressive (minor depression, dysthymia and MDD) and anxiety disorders (Generalized Anxiety Disorder [GAD], Social Phobia, Agoraphobia, Panic Disorder [PD] with and without Agoraphobia). For all disorders, the lifetime, 6-month and 1-month presence were established. Also, comorbidity, number of comorbid disorders and first age of onset of any disorder were assessed.

Health-related disability and its subdomains ('cognition', 'mobility', 'self-care', 'getting along', 'life activities' and 'participation') were assessed with the WHO Disability Assessment Schedule (WHODAS; Üstün et al., 2010). The symptoms dimensions of General Distress, Anhedonic Depression and Anxious Arousal were measured with the

adapted Mood and Anxiety Symptoms Questionnaire (MASQ-D30; Wardenaar et al., 2010). Symptoms of mania or hypomania were assessed with the Mood Disorder Questionnaire (MDQ, Hirschfeld et al., 2000). Suicidal thoughts and occurrence of a lifetime suicide attempt were assessed with the Beck Scale for Suicide Ideation (BSSI; Beck et al., 1979). Insomnia severity and presence of sleep problems (dichotomized at IRS>9) were assessed with the Insomnia Rating Scale (IRS; Levine et al., 2003). Psychological distress and somatization were assessed with the Four-Dimensional Symptoms Questionnaire (4DSQ, Terluin et al., 2006). Loneliness was assessed with the de Jong-Gierveld Loneliness Scale, using the total, social and emotional loneliness subscales (de Jong Gierveld & Kamphuis, 1985). Big five personality traits were assessed with the Neuroticism-Extraversion-Openness-Five Factor Inventory (NEO-FFI, Costa & McCrae, 1992). Locus of control was assessed with the mastery scale (Pearlin & Schooler, 1978). Daily stressful events were assessed with the daily pressure and rejection subscales of the Daily Hassles questionnaire (Kanner et al., 1981). Threatening life events were assessed using the List of Threatening Events-Questionnaire (LTE-Q; Brugha et al., 1985), using both the occurrence and number of life events. Childhood trauma before the age of 16, was assessed with the NEMESIS-childhood trauma questionnaire (de Graaf et al., 2002) and used to calculate a childhood life event index (0-2) and trauma index (0-4; Hovens et al., 2010).

2.2.1.3. Medication use. Participants brought medication packaging/containers to the interview to be recorded. Medication was classified according to the WHO Anatomical Therapeutic Chemical system. Dichotomous medication variables were used for anxiolytics, antidepressants (selective serotonin reuptake inhibitors, tricyclic antidepressants, other [e.g., serotonin–norepinephrine reuptake inhibitors]), antihypertensive drugs and diabetes medication (see Licht et al., 2008 for details).

2.2.1.4. Lifestyle and somatic health. Current smoking, drugs consumption (cannabis, ecstasy, heroin, cocaine, LSD and speed), and the presence of ≥1 somatic diseases (e.g., diabetes, asthma) were assessed during the interview. The presence of the metabolic syndrome (MS) according to the (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001) (ATP-III) criteria, was assessed based on biological and medication-use measurements. Abdominal circumference was measured (in cm) with a tape measure and systolic and diastolic blood pressure were measured in supine position using an electronic Omron sphygmomanometer. The MS was considered present if ≥3 of the following criteria were met: (1) abdominal circumference >102 cm (men) or >88 cm (women), (2) triglyceride level ≥1.7 mmol/L, (3) high-density lipoprotein (HDL) cholesterol <1.03 mmol/L (men) or <1.30 mmol/L (women), (4) blood pressure ≥130/85 mm Hg or use of antihypertensive drugs, and (5) fasting plasma glucose ≥6.1 mmol/L or use of diabetes medication. Variables for the MS (yes/no) and for each separate component were used. Alcohol-use problems were assessed using the Alcohol Use Disorders Test (AUDIT; Saunders et al., 1993). Physical activity was assessed using the International Physical Activity Questionnaires (IPAQ; Craig et al., 2003). Pain was assessed using the Chronic Graded Pain Scale, using the intensity and disability subscales (von Korff et al., 1992).

2.2.1.5. Need and use of healthcare. Healthcare use and needs were assessed using the Perceived Need of Care Questionnaire (PNCQ; Meadows et al., 2000). Variables were created for the use of different healthcare types in the 6 months before baseline: homecare, alternative care, self-help group, hospital, physician, medical specialist, occupational physician, psychologist, mental healthcare [MH] institute, substance-use care, independent psychiatrist/psychotherapist, physiotherapist.

2.2.1.6. Cardiovascular measurements. Activity of the cardiac autonomic nervous system during the interview was assessed in sitting position with an ambulatory monitoring system (VU-AMS; de Geus et al., 1995). The VU-AMS continuously registers time series of inter-beat intervals (IBI) and impedance cardiograms (ICG) during rest and test conditions during the interview. Raw data were processed as described elsewhere (de Geus et al., 1995; Riese et al., 2003). IBIs assessed during rest and test conditions were used to derive mean heart rate and heartrate variability (HRV) indices (the Root-mean square of successive differences (RMSSD, in ms) and standard deviation of NN-intervals (SDNN, in ms), Respiration Rate (RR, in breaths per/min) and Respiratory Sinus Arrhythmia (RSA, in ms) were used. ICG signal assessed during test-conditions were used to derive mean Pre-Ejection Period (PEP, in ms).

2.2.2. Blood markers

Before the interview (between 8:00 and 9:00 AM), venous blood was drawn after an overnight fast. Routine assays of the blood samples were run in local labs. Within an hour after the draw the remaining samples were spun down to serum and plasma and stored at -80°C. The routine assays included markers of metabolic function (HDL [mmol/L], LDL [mmol/L], triglycerides [mmol/L], glucose [mmol/L], free thyroxine [pmol/L]), liver function (aspartate aminotransferase [ASAT-GOT; U/L], γ-glutamyl transferase [Gamma-GT, U/L], alanine aminotransferase [ALAT-GPT; U/L]), kidney function (creatinine; mg/dL) and haematological markers (haematocrit [L/L], haemoglobin [mmol/L] and erythrocyte count [$*10^{12}$/L]). Plasma Interleukin-6 (IL-6; mg/L) levels were measured in duplicate using a high sensitivity enzyme linked immunosorbent assay (ELISA) (PeliKine Compact TM ELISA, Sanquin, Amsterdam, The Netherlands). Tumor necrosis factor-alpha (TNF-α; pg/mL) plasma levels were assayed in duplicate with a high-sensitivity solid phase ELISA (Quantikine® HS Human TNF-α Immunoassay, R&D systems Inc, Minneapolis, MN, United States). C-reactive protein (CRP; mg/L) was measured in duplicate by an in-house ELISA, based on purified protein and polyclonal anti-hsCRP antibodies (Dako, Glostrup, Denmark). Tryptophan (μmol/L) and kynurenine (μmol/L) concentrations were assayed by an automated online solid phase extraction-liquid chromatographic-tandem mass spectrometric (XLC-MS/MS) method. Brain-derived neurotrophic factor (BDNF; ng/L) levels were measured in serum using the Emax Immuno Assay system from Promega (Madison, WI, USA).

2.2.3. Course outcome measures

Course outcomes were based on the longitudinal data collected with the Inventory of Depressive Symptomatology-Self Report (IDS-SR; Rush et al., 1996), the Beck Anxiety Inventory (BAI, Beck et al., 1988), the Fear Questionnaire (Marks & Matthews, 1979) and the Penn State Worry Questionnaire (Meyer et al., 1990). General psychological distress severity was calculated as the average of the standardized IDS-SR, BAI, FQ and PSWQ scores (**Table S2** gives scale correlations).

2.3. Analyses

2.3.1. Outcome trajectory classes

Outcomes for the current study were all based on LCGAs of the longitudinal course measures. In a previous study (Solis et al., submitted), LCGA had been run on the general psychological distress measure. For the current study, LCGAs were also run with (1) only the IDS-SR and (2) the BAI scores to identify pure-depression and pure-anxiety course trajectories, respectively.

Prior to analysis, all repeated outcome scores were standardized to zero mean and unit variance and baseline values were subtracted from the follow-up values to focus the LCGAs on change rather than baseline differences. LCGA was used rather than growth mixture modelling as the latter allows for more within-class heterogeneity, making the classes less suitable as differentiated outcome categories. Inspection of the pre-

processed data revealed that most change occurred between baseline (all values are 0) and the first follow-up, after which changes were more stable. To model this pattern of change, a log-linear function was chosen for the LCGA (i.e. outcomes were log-transformed).

LCGA models with increasing numbers of classes were fitted to the data. The best model was selected using the Bayesian and Akaike Information Criteria (BIC and AIC), with lower values indicating better fit. Also all model classes were required to have a size of n>100 to ensure that they would be usable in the subsequent prediction analyses. All models were estimated using Maximum Likelihood estimation, using each participant's non-missing data. One-hundred random starts were used to prevent solutions at local maxima. LCGAs were conducted with package *'lcmm'* (Proust-Lima et al., 2017) in R (R core team, 2020). In subsequent analyses, the continuous posterior class-probabilities rather than discrete class membership (based on highest posterior class-probability) were used if class-allocation involved too much uncertainty as indicated by model entropy<0.8 (Clark & Muthén, 2009).

2.3.2. Prediction modelling

2.3.2.7. Data pre-processing. All categorical variables were recoded to dichotomous variables, coded as 0/1. Continuous variables were Z-transformed. Overall, only 1.7% of the data were missing: 66/152 determinants had ≥1 missing value (range: 5.9%-15.8%; **Table S1**). These were imputed once using predictive mean matching with the '*mice*' R-package (van Buuren and Groothuis-Oudshoorn, 2011). See supplement for some complete-case analyses.

2.3.2.8. Super Learner. SL analyses were performed with the '*sl3*' R-package (Coyle et al., 2020) to identify the optimal prediction model for each outcome-trajectory. The mean squared error (MSE) of predicted versus observed outcomes was used to determine prediction accuracy. In the SL method, a number of individual ML-algorithms (*'base learners'*; leDell et al., 2016) are run. Base-learners were selected that can work with continuous outcomes and large numbers of correlated determinants: Elasticnet (Zou & Hastie, 2005), Random Forests (Breiman 2001), Gradient Boosting (Friedman, 2001), and Support Vector Machines (details: **Table S3**). Each base-learner was run with 10-fold cross validation (CV) to limit the risk of overfitting. We chose 10-fold CV in favour of a single hold-out sample as the former is more efficient (all subjects are included in training and validation) and yields MSEs with less random variation (Hastie et al., 2009; James et al., 2013). Next, a stacked SL-model formula, weighting each of the individual learners' predictions as to minimize the SL MSE (MSE_{SL}) was estimated in the whole sample using a Non-Negative Least Squares (NNLS, van der Laan et al., 2007) estimator, which was set to yield a convex solution with the learners' weights summing to one. This yields SL predictions that improve upon any of the stack's base-learners (van der Laan et al., 2007). The resulting SL formula was then used to generate predictions based on the base-learners that were fit to the complete dataset, and the MSE_{SL} was evaluated. See Rose (2013) for details. Although the MSE_{SL} is a good measure of precision, is hard to interpret on its own. Therefore, the Spearman correlation between SL-predicted and observed scores (ρ_{pred}) and its squared value (ρ^2_{pred}: coefficient of determination) were also calculated and evaluated using the following performance cut-offs: ρ_{pred}<0.2 (negligible: less than practically significant), 0.2≥ρ_{pred}<0.5 (small), 0.5≥ρ_{pred}<0.8 (moderate) and ρ_{pred}≥0.8 (strong; Ferguson, 2009). Finally, SL performance was compared to performance of Ordinary Least Squares (OLS) regression with the identified top 15 important determinants (see below).

2.3.3. Determinant importance

For each outcome, the importance of each determinant in the SL was investigated by evaluating the change in the MSE_{SL} (i.e. MSE difference) when the given determinant's data were randomly scrambled (Coyle et al., 2020). For each outcome's SL, this resulted in a list of determinants' MSE-differences, with higher values indicating higher importance. For each outcome, the top 15 important determinants were listed and Spearman correlations between each determinant and the model-predicted score were calculated to gain insight into the determinants' roles in the SL.

3. Results

3.1. Sample characteristics

The baseline sample characteristics are given in **Table 1**. The mean age was 41.3 years and the majority was female (67.2%). Most participants had an MDD diagnosis (65.4%) and a majority of these also had comorbid anxiety (68.0%). Of participants, 23.3% and 32.0% had only a depressive or anxiety disorder, respectively.

3.2. LCGA

3.2.1. General psychological distress

LCGA identified three classes with different severity trajectories: a 'chronic' (n=1,131), 'partial recovery' (n=435) and 'full recovery' trajectory (n=127) (Solis et al., submitted).

3.2.2. Pure depression and anxiety

The preprocessed IDS-SR and BAI data showed a moderate relationship (Spearman ρ=0.64; p<0.001). In the LCGAs (**Table 2**), for both domains, the BIC decreased little when adding a 4th class and for both outcomes, the 4-class model contained classes that were too small (n<100). For depression, the selected model had a 'chronic' (n=1,078), 'partial recovery' (n=502) and 'full recovery' (n=112) class. For anxiety, the model had a 'full recovery' (n=236), 'partial recovery' (n=1,306), and 'increasing severity' (n=151) class (**Figure S2** gives the trajectories). Because entropy was <0.8 for both models, the posterior class-probabilities were used as outcomes (See **Table S4** for distributions).

Table 1
Study sample characteristics (n=1,693)

Variable	*Sample*
Demographics	
Age (in years), mean (sd)	41.3 (12.4)
Women, n (%)	1,137 (67.2%)
Years of education	11.8 (3.3)
Unemployed, n (%)	597 (35.3%)
Partner, n (%)	1,107 (65.4%)
6-month CIDI diagnoses, n (%)	
MDD	1,108 (65.4%)
Dysthymia	303 (17.9%)
GAD	460 (27.2%)
PD with Agoraphobia	421 (24.9%)
PD without Agoraphobia	245 (14.5%)
Social phobia	665 (39.3%)
Agoraphobia	187 (11.0%)
Pure depressive disorder(s), n (%)	394 (23.3%)
Only anxiety disorder(s), n (%)	542 (32.0%)
Comorbid depression and anxiety, n (%)	757 (44.7%)
Ever a suicide attempt, n (%)	283 (16.7%)
Severity scales, median (IQR)	
Depression severity (IDS-SR)	29 (20-38)
Anxiety Severity (BAI)	15 (9-24)
Worrying (PSWQ)	37 (30-44)
Fear/Phobia (FQ)	30 (17-46)

Note: CIDI= Composite International Diagnostic Interview; MDD=Major Depressive Disorder, GAD=Generalized Anxiety Disorder, PD=Panic Disorder, IDS-SR=Inventory of Depressive Symptomatology - Self Report; BAI=Beck Anxiety Inventory; PSWQ=Penn State Worry Questionnaire; FQ=Fear Questionnaire; IQR=interquartile range.

Table 2
latent class growth analysis (LCGA) results to explain variation in the 9-year course of (A) depression severity and (B) anxiety severity over 9 years.

Outcome	Classes	Degrees of freedom	AIC	BIC	Entropy	Class sizes
Depression (n=1,692)[a]	1	3	15241.3	15257.6	1.00	1692
	2	6	13821.9	13854.5	0.69	1357, 335
	3	**9**	**13378.5**	**13427.4**	**0.65**	**502, 112, 1,078**
	4	12	13214.2	13279.4	0.67	70, 102, 1169, 351
Anxiety (n=1,693)[b]	1	3	15402.0	15418.3	1.00	1693
	2	6	13971.3	14003.9	0.68	340, 1353
	3	**9**	**13507.2**	**13556.1**	**0.70**	**151, 1306, 236**
	4	12	13161.8	13227.0	0.70	80, 361, 96, 1156

Note: IDS-SR=Inventory of Depressive Symptomatology - Self Report; BAI=Beck Anxiety Inventory; PSWQ=Penn State Worry Questionnaire; FQ=Fear Questionnaire; AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion. Bold print indicates the model that was selected in this study.
[a] Based on the IDS-SR.
[b] Based on the BAI.

3.3. Prediction modelling

3.3.1. Prediction of general psychological distress course

Prediction performance indices are given in Table 3 (all ρ_{pred}: $p<0.001$). The 'chronic' class probability was predicted with MSE=0.150-0.159 across base learners and MSE_{SL}=0.148, with a strong ρ_{pred}=0.91 (ρ^2_{pred}=0.83). 'Partial-recovery' was predicted with MSE=0.118-0.131 across base learners and MSE_{SL}=0.118 with a small ρ_{pred} of 0.41 (ρ^2_{pred}=0.17). 'Full-recovery' was predicted with MSE=0.054-0.056 across base learners and MSE_{SL}=0.054 with a moderate ρ_{pred} of 0.70 (ρ^2_{pred}=0.50). SL-based ρ_{pred} were all higher than small OLS-based ρ_{pred} (0.18-0.27).

Figure 1 shows the top determinants. Age, age of onset, RR, WHODAS participation, somatic disease, low income, 1-M minor depression and mastery score were among the most important overall determinants. Prediction correlations showed that age and somatic disease were positively correlated with predicted 'chronic' course and negatively with 'partial' and/or 'full recovery', whereas age of onset, RR, WHODAS participation, mastery and minor depression were positively correlated with 'partial' and/or 'full recovery'.

3.3.2. Prediction of pure depression course

'Chronic' course probability was predicted with MSEs=0.133-0.137 across base learners (Table 3) and MSE_{SL}=0.131, with a strong ρ_{pred}=0.81 (ρ^2_{pred}=0.66). 'Partial-recovery' was predicted with MSE=0.114-0.121 across base learners and MSE_{SL}=0.114 with a strong

Table 3
10-fold cross-validated prediction performance of individual learners and of the total sample Super Learner in predicting the probability of different course trajectories of joint depression and anxiety.

	Learners	Probability of 'Chronic course'			Probability of 'Partial recovery'			Probability of 'Full recovery'		
		MSE[a]	SE	SL Weight	MSE[a]	SE	SL Weight	MSE[a]	SE	SL Weight
General psycho-pathology severity course[c]	Elasticnet	0.152	0.004	0.18	0.118	0.003	0.68	0.054	0.004	0.19
	Random forest (100)[b]	0.151	0.003	0.11	0.120	0.003	0.00	0.056	0.004	0.00
	Random forest (250)[b]	0.150	0.003	0.01	0.120	0.003	0.00	0.055	0.004	0.08
	Random forest (500)[b]	0.150	0.003	0.30	0.119	0.003	0.00	0.055	0.004	0.00
	Gradient Boosting	0.151	0.003	0.09	0.119	0.003	0.32	0.055	0.004	0.00
	Support Vector Machine	0.159	0.004	0.31	0.131	0.005	0.00	0.055	0.005	0.73
	SuperLearner	0.148	0.003	-	0.118	0.003	-	0.054	0.005	-
		Probability of 'Chronic course'			Probability of 'Partial recovery'			Probability of 'Full recovery'		
		MSE[a]	SE	SL Weight	MSE[a]	SE	SL Weight	MSE[a]	SE	SL Weight
Pure depressive symptom severity course[d]	Elasticnet	0.133	0.003	0.37	0.114	0.003	0.56	0.049	0.004	0.21
	Random forest (100)[b]	0.136	0.003	0.10	0.117	0.003	0.00	0.050	0.004	0.08
	Random forest (250)[b]	0.137	0.003	0.00	0.116	0.003	0.03	0.050	0.004	0.00
	Random forest (500)[b]	0.137	0.003	0.00	0.116	0.003	0.10	0.050	0.004	0.00
	Gradient Boosting	0.134	0.003	0.16	0.116	0.003	0.07	0.050	0.004	0.00
	Support Vector Machine	0.137	0.004	0.37	0.121	0.004	0.24	0.050	0.005	0.71
	SuperLearner	0.131	0.003	-	0.114	0.003	-	0.049	0.004	-
		Probability of 'Increasing severity'			Probability of 'Partial recovery'			Probability of 'Full recovery'		
		MSE[a]	SE	SL Weight	MSE[a]	SE	SL Weight	MSE[a]	SE	SL Weight
Anxiety severity course[e]	Elasticnet	0.058	0.004	0.37	0.117	0.004	0.63	0.096	0.005	0.11
	Random forest (100)[b]	0.059	0.004	0.00	0.118	0.004	0.16	0.097	0.004	0.00
	Random forest (250)[b]	0.058	0.004	0.04	0.118	0.004	0.00	0.096	0.004	0.00
	Random forest (500)[b]	0.058	0.004	0.00	0.117	0.004	0.20	0.096	0.004	0.29
	Gradient Boosting	0.058	0.004	0.32	0.119	0.004	0.00	0.095	0.005	0.43
	Support Vector Machine	0.062	0.005	0.26	0.130	0.005	0.00	0.102	0.006	0.17
	SuperLearner	0.057	0.004	-	0.116	0.004	-	0.095	0.005	-

Note: IDS-SR=Inventory of Depressive Symptomatology - Self Report; BAI=Beck Anxiety Inventory; PSWQ=Penn State Worry Questionnaire; MSE=mean squared errors; SL weight= NNLS estimated weight (range: 0-1) of the algorithm in the Super Learner.
[a] The average of the MSEs obtained in each test fold;
[b] Numbers between parentheses indicate number of trees in the *ranger* package.
[c] Based on the IDS-SR, BAI, PSWQ and FQ
[d] Based on the IDS-SR
[e] Based on the BAI

Figure 1. Variable importance for the course of general psychopathology severity, expressed as the percentage of change in the mean squared error if the given determinant is removed from the model ('MSE difference (%)' on x-axis). For added interpretability, the Spearman correlations of the determinants with the predicted probabilities of the Super Learner (SL) are printed behind each determinant's bar. A green bar indicates a positive correlation and a red bar indicates a negative correlation with the SL-predicted score.

ρ_{pred}=0.82 (ρ^2_{pred}=0.67). 'Full-recovery' was predicted with MSE=0.049-0.050 across learners and MSE_{SL}=0.049 with a moderate ρ_{pred}=0.60 (ρ^2_{pred}=0.36). SL-based ρ_{pred} were larger than the OLS-based ρ_{pred} (0.22-0.31).

Figure 2 shows the top-15 determinants, which were age, youngest age of onset, mastery, visiting an occupational physician, physiotherapist or MH institute, somatic disease, extraversion and WHODAS participation score. Age was positively correlated with the probability of a 'chronic' course and negatively with 'partial' and 'full recovery', whereas age of onset, mastery and visiting a MH institute showed the reversed pattern.

3.3.3. *Prediction of pure anxiety course*

An 'increasing-severity' probability was predicted with MSE=0.058-0.062 across learners (Table 3) and MSE_{SL}=0.057 with a moderate ρ_{pred}=0.53 (ρ^2_{pred}=0.28). 'Partial-recovery' was predicted with MSE=0.117-0.130 across learners and MSE_{SL}=0.116, with a high ρ_{pred}=0.88; ρ^2_{pred}=0.77). 'Full-recovery' was predicted with MSE=0.095-0.102 across learners and MSE_{SL}=0.095 with a moderate ρ_{pred}=0.73; ρ^2_{pred}=0.53). The SL-based ρ_{pred} were much higher than negligible OLS-based ρ_{pred} (0.12-0.20).

Figure 2 shows that MASQ-D30 Anxious Arousal, 4DSQ Somatic, 4DSQ Distress, WHODAS participation, 1-M minor depression, extraversion, age and RR were among the top determinants. The MASQ-D30 Anxious Arousal and 4DSQ Somatic scales were negatively correlated with 'increasing severity' and positively with 'partial recovery'. Minor depression, extraversion and RR were positively correlated and age was negatively correlated with 'full-recovery'. 4DSQ Distress and WHODAS Participation were positively correlated with 'partial-recovery'.

4. Discussion

This study aimed to train models that optimally predict the 9-year course of general psychological distress, pure depression and pure anxiety, and to identify and compare the main determinants of these outcomes. The used 9-year course outcomes for general psychological distress were previously-estimated LCGA-based classes with 'chronic', 'partial recovery' and 'full recovery' course trajectories. For pure depression, LCGAs showed similar classes. For pure anxiety, LCGA showed 'partial recovery', 'full recovery' and 'increasing severity' classes, aligning with previous observations that depression and anxiety-trajectories do not always run parallel (Olino et al., 2010; Wardenaar et al., 2015). For each outcome, optimized SLs were estimated with base-learner weights differing across outcomes, indicating that different learners were optimal for different outcomes and using a single learner would have been suboptimal. Prediction-correlations ranged from small (ρ_{pred}=0.41) to high (ρ_{pred}=0.91) with a moderate median of 0.73 and consistently better performance than OLS regression. Interestingly, the only outcome class, for which prediction performance was weak for the SL was the general psychological distress 'partial recovery' class. This could be due to this outcome's high within-class heterogeneity (many different symptoms can partially recover), making it a comparatively noisy outcome.

Inspection of variable importance in the SL showed that for the general psychological distress course, a mix of different types of important determinants emerged, age, low income, youngest age of onset, WHODAS participation score, 1-M minor depression, mastery, RR and somatic disease variables. For pure depression course, mostly the same determinants were found, but also unique determinants (visit occupational physician, physiotherapist, or MH institute). For pure anxiety, some top determinants overlapped with pure depression (age, WHODAS participation, minor depression and extraversion), and unique determinants included self-reported somatic symptoms and psychological distress. The identification of different types of determinants aligns with the view that psychopathology is influenced by factors, functioning at different levels (e.g., McNamara et al., 2021; Eronen, 2019). The observed overlap in determinants between outcome domains and lower number of domain-specific determinants aligns with the view of depression and anxiety as related domains with shared and

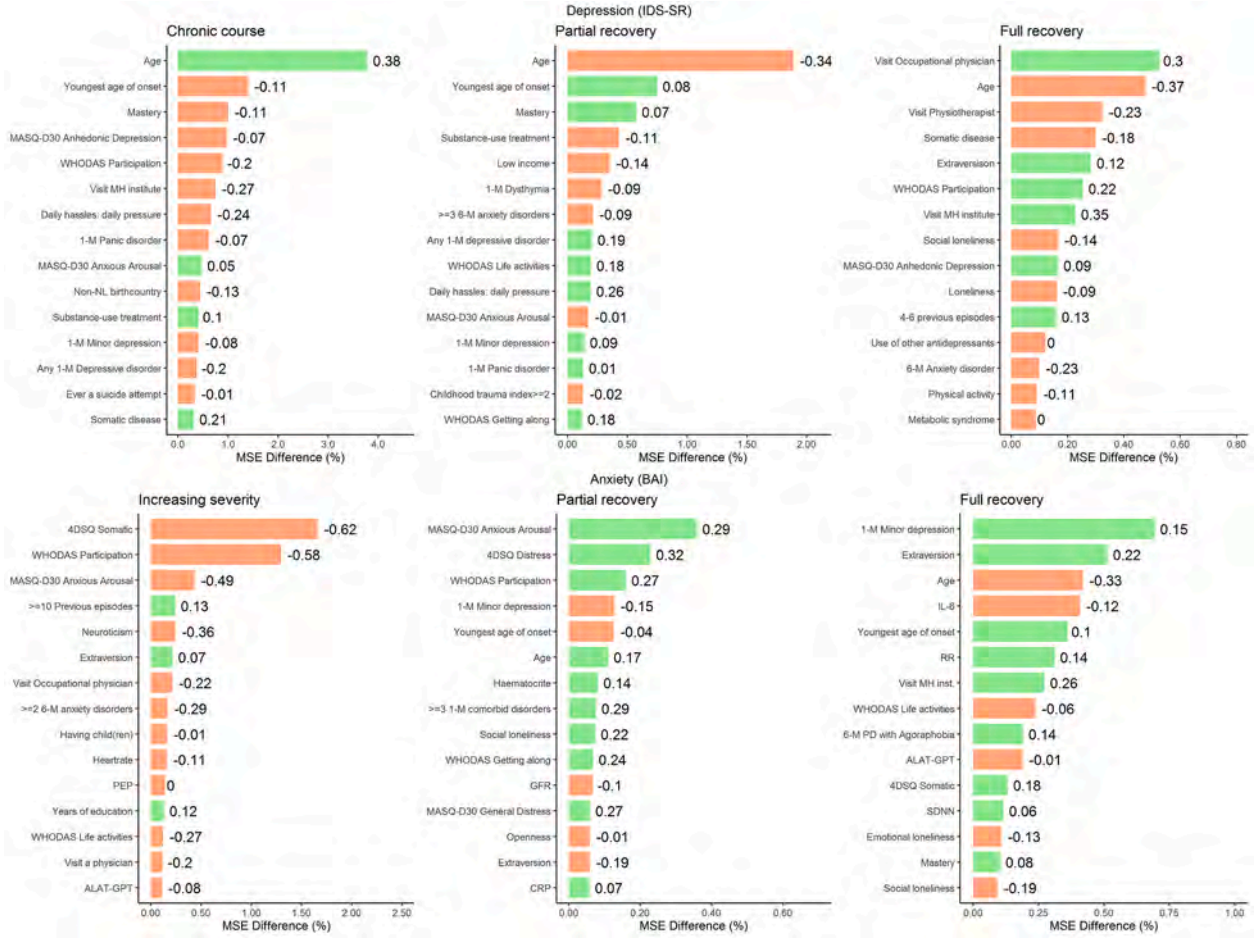

Figure 2. Variable importance for the course of individual depression (IDS-SR) and anxiety (BAI) severity, expressed as the percentage of change in the mean squared error if the given determinant is removed from the model ('MSE difference (%)' on x-axis). The Spearman correlations of the determinants with the predicted probabilities of the Super Learner (SL) are printed for each determinant. A green bar indicates a positive correlation and red indicates a negative correlation with the SL-predicted score.

domain-specific mechanisms and with the shared predictors overlapping with a general, higher-order psychological distress dimension (Clark & Watson, 1991; Goodwin, 2015; Kotov et al., 2020).

The roles of determinants in the algorithm were investigated by inspecting determinants' correlations with SL predicted probabilities. These should be interpreted carefully because they only capture linear relationships whereas variable importance also incorporates variables' roles in interactions and non-linear associations (Archer & Kimes, 2008; Hastie et al., 2009). Still, the correlations revealed some noteworthy patterns. Across outcomes, age was positively correlated with the chronicity and negatively with partial/full recovery. Indeed, previous work has found higher chronicity/recurrence with increasing age (e.g., Schaakxs et al., 2018). This may reflect that depressed patients that were older at baseline were more likely to already have had a history of persistent depression, making future persistence likely. Age of first onset was negatively correlated with an adverse course of psychological distress and pure depression, but not anxiety, indicating that it may be a depression-specific determinant. Others also showed that a young onset of depression is an important component of depression chronicity (Pettit et al., 2009) and related to higher illness burden (Zisook et al., 2007). Measures of extraversion and mastery were found be positively correlated with recovery and negatively with adverse course trajectories across outcomes, aligning with earlier work showing these domains to be positively associated with lower chronicity/recurrence (Steunenberg et al., 2007; Colman et al., 2007; Wardenaar et al., 2014; Wiersma et al., 2011; Hovenkamp-Hermelink et al., 2021), pointing toward a role as cross-diagnostic vulnerability markers (Ormel et al., 2013; Struijs et al., 2018) that likely predict over longer time periods given their temporal stability (Hovenkamp_Hermelink et al., 2019; (Mund et al., 2020). Somatic illness correlated positively with an unfavourable course, aligning with work showing poor somatic health to be associated with less favourable depression and anxiety course (Ferro et al., 2015; Ambresin et al., 2014). RR was the only biological determinant for both general psychological distress and pure anxiety, indicating a more anxiety-specific role. Indeed, respiratory deviations, such as a higher RR, are known to be related to anxiety symptom severity and worry (Papp et al., 1997; Blechert et al., 2007). However, here RR was positively correlated with more favourable course trajectories. It is possible that this reflects the role of RR in a more complex interactive/non-linear model, or it could reflect the fact that anxiety severity and related somatic arousal (including higher RR) were on average higher (data not shown) in those with a 'chronic' or 'increasing severity' course. The finding of a single biological determinant indicates that in algorithms for clinical use it could be preferable to predominantly include other measures that are easier and less invasive to measure.

Interestingly, previous ML prediction studies of the 2-year course of depression (Dinga et al., 2018) and anxiety (Bokma et al., in press) using the same data found baseline symptom severity to be the most important predictor. Another ML-study of 9-year diagnosis-based course prediction (van Eeden et al., 2021) used an automated algorithm-selection approach for prediction (auto-sklearn; Feurer et al., 2015), but found only moderate prediction accuracy. Differences between these and the

current findings could be explained by different methodological choices. First, the first two studies used only a 2-year follow-up interval. Second, the current study looked at dimensional rather than discrete diagnostic course outcomes. This meant a conceptually different approach, but also that baseline severity was used in outcome definition and could not be used as determinants. Interestingly though, other severity scales (e.g., MASQ-D30 General Distress) did not emerge as important either. Dinga et al., (2018) also used LCGA-based outcomes, but these were for 2-year course only. Third, two studies used a single learner (Elasticnet [Dinga et al., 2018]; Random Forests [(Bokma et al., in press)]), so although many baseline variables were included (up to 567 in (Bokma et al., in press)), the chosen learner may not have been suitable to identify more predictors. Vice versa, (van Eeden et al., 2021) did use a more flexible algorithm, but a relatively small set of 35 baseline predictors.

There are several study limitations. First, the findings were based on data-driven dimensional course outcomes, which do justice to the way course-variations naturally occur, but are harder to translate to DSM-oriented clinical practice. Second, the SL analyses were computationally demanding and to save computation time, single imputation was used to handle missing data, whereas multiple imputation would have been optimal. Third, the optimized SL-algorithm was based on cross-validated base-learners to prevent overfitting, but generalizability of the findings should still be independently evaluated. Also, the performance of the SL itself was not evaluated through cross-validation, adding to the necessity of external evaluation. Fourth, the use of class-probabilities rather than memberships as outcomes make results harder to interpret, but the low entropy indicated that participants could not be allocated to classes with acceptable certainty (Celeux & Soromenho, 1996). Fifth, LCGA model selection was strongly driven by the requirement of sufficiently large classes for the SL, whereas a range of fit indices is often primarily used to identify the optimal class-solution (e.g., Nylund et al., 2007). Sixth, to allow inclusion of the same variables in all analyses, only baseline variables measured irrespective of diagnosis were included; more diagnosis-specific course determinants may have been missed. Finally, the final SL algorithm can be seen as a 'black box' that is hard to interpret. For instance, the SL may include complex interactions, but provides no direct insight into their nature or importance. Importantly, model transparency is sacrificed here in favour of optimal predictions.

When implemented in clinical practice, ML-based algorithms could primarily be used to predict patients' general prognosis irrespective of treatment. A next step is to develop algorithms that predict course conditional on treatment type, which could be used to select a patient's most suitable treatment. To develop such algorithms, larger datasets with detailed treatment information are needed.

In conclusion, when optimal SL-based prediction models are applied, the most important determinants in the algorithms were mostly shared for the pure-depression and pure-anxiety outcomes and also showed sizable overlap with determinants of general psychological distress course. Domain-specific exceptions were healthcare use for pure depression and somatic arousal and distress for pure anxiety-severity course. This indicates that the both depression and anxiety course can be contemporaneously predicted based on mostly shared and some domain-specific of predictors.

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The funders of this study played no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; nor in the decision to submit the article for publication.

Author contributions

KJW, HR, EJG and BP came up with the study concept. KJW conducted the data analyses with input from EJG. KJW wrote the initial draft with feedback from HR. EJG, ME, AvH, BP, AJB, and RAS contributed further feedback on the manuscript. All authors approved the final version of the article.

Data availability statement

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

Declaration of Competing Interest

None

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.06.029.

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Research paper

Identifying mismatch and match between clinical needs and mental healthcare use trajectories in people with anxiety and depression: Results of a longitudinal study

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ABSTRACT

Background: Mismatch between need and mental healthcare (MHC) use (under-and overuse) has mainly been studied with cross-sectional designs, not accurately capturing patterns of persistence or change in clinical burden and MHC-use among persons with depressive and/or anxiety disorders.
Aims: Determining and describing [mis]match of longitudinal trajectories of clinical burden and MHC-use.
Methods: Six-year longitudinal burden and MHC-use data came from the Netherlands Study of Depression and Anxiety (n=2981). The sample was split into four subgroups: I) no clinical burden but constant MHC use, II) constant clinical burden but no MHC-use, III) changing clinical burden and MHC-use, and IV) healthy non-users. Within subgroups I)-III), specific clinical burden and MHC trajectories were identified (growth mixture modeling). The resulting classes' associations with predisposing, enabling, and need factors were investigated (regression analysis).
Results: Subgroups I-III revealed different trajectories. I) increasing MHC without burden (4.1%). II) slightly increasing (1.9%), strongly increasing (2.4%), and decreasing (9.5%) burden without MHC. III) increasing (41.4%) or decreasing (19.4%) burden and concurrently increasing MHC use (first underuse, then matched care), thus revealing delayed MHC-use. Only having suicidal ideation ($p<.001$, Cohen's $d= .6$-1.5) was a significant determinant of being in latter classes compared to underusers (strongly increasing burden without MHC-use).
Limitations: More explanatory factors are needed to explain [mis]match.
Conclusion: Mismatch occurred as constant underuse or as delayed MHC-use in a high-income country (Netherlands). Additionally, no meaningful class revealed constantly matched care on average. Presence of suicidal ideation could influence the probability of symptomatic individuals receiving matched MHC or not.

1. Introduction

Despite the availability of evidence-based treatments for different severity levels of anxiety and/or depressive disorders, the type and amount of received mental healthcare (MHC) have been shown to not necessarily match a person's clinical need (Jörg et al., 2016; Jureidini et al., 2006; Kooistra et al., 2018; Kronenfeld, 2008; Saxena et al., 2007; Verhaak et al., 2009; Demyttenaere, et al., 2004).

A cross-sectional study by the WHO showed that while about 33-50% of people with severe mental disorders, including depression and anxiety, show underuse, only 2.4-8.1% show overuse in high-income countries (HIC) (Demyttenaere, et al., 2004). In previous cross-sectional

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studies, mismatch has been defined in the following ways: on the one hand, mismatch relates to *underuse*, defined as having needs but not receiving the right type and amount of care (Verhaak et al., 2009). On the other hand, mismatch can relate to a seemingly unjustified provision of care given a low need, defined as *overuse* (Keyhani et al., 2008).

Both underuse and overuse may generate negative consequences on a personal, economic, and societal level, making it a public health concern (Armstrong et al., 2018; Mcdaid, 2011; Jörg et al., 2016; Jureidini et al., 2006; Kooistra et al., 2018; Kronenfeld, 2008; Saxena et al., 2007; Verhaak et al., 2009; Demyttenaere, et al., 2004). Underuse can lead to adverse clinical outcomes and may induce high economic burden due to, for example, the consequent loss of productivity (Mcdaid, 2011). Overuse of MHC can have negative consequences such as the deprivation of resources for those in need (Armstrong et al., 2018; Jureidini et al., 2006).

One limitation of the mismatch research that has been published so far is that results are mainly based on cross-sectional study designs (Bet et al., 2013; Verhaak et al., 2009; Demyttenaere, et al., 2004). Evaluations of the presence of mismatched MHC based on cross-sectional studies may provide only partial insight into the issue because such studies do not capture the way in which symptomatology changes over time and how treatments for anxiety and depressive disorders are carried out over longer periods of time (Blier et al., 2007; Penninx et al., 2008).

From the above-mentioned definitions of underuse and overuse that were based on cross-sectional studies, one can also derive patterns of [mis]match that could appear over time in prospective studies: (1) those without needs and no MHC-use (healthy non-users), (2) those without need but constant MHC-use (constant overusers), (3) those with constant needs but no MHC-use (constant underusers) and finally, (4) a varied group of persons with different trajectories of needs and MHC-use (changing [mis]match). It is important to note that the extent of the under- or overuse can vary, that is, MHC-use can increase or decrease among the overusers, or needs may increase or decrease among underusers. In the changing [mis]match group, the way in which the match or mismatch between needs and MHC-use changes over time can vary considerably. For instance, changes in MHC-use could largely correspond with changes in needs, but there could also be patterns where a matched situation transitions to a mismatched situation (diverging needs and MHC-use trajectories) or vice versa (converging trajectories). To prevent underuse and overuse, policymakers and clinicians can benefit from insights into the frequency and extent of different types of mismatches over time, and the underlying mechanisms.

To identify explanatory factors for [mis]match patterns, Andersen's Behavioural Model of Health Services Use (BMH; Andersen, 1968) can be used. According to the BMH, healthcare use depends on three main factors: enabling factors, predisposing factors, and need factors. Previous cross-sectional studies have investigated how these factors are associated with under-or overuse of MHC (Babitsch et al., 2012; Demyttenaere et al., 2004; Jörg et al., 2016; Verhaak et al., 2009). Enabling factors include the individual's financial resources or the structure of healthcare systems, which can make it more or less difficult to access care. Examples are the limited availability and financing of services (e.g., public or private), which have been shown to be associated with high MHC underuse, especially in middle- and low-income countries (Babitsch et al., 2012; Demyttenaere, et al., 2004). Predisposing factors include individual demographics and social influences on healthcare-seeking patterns (Babitsch et al., 2012). For example, male gender and negative attitudes towards MHC have previously been associated with MHC underuse (Mackenzie et al., 2007). Need factors can be divided into subjective and clinical needs. Subjective needs are defined as one's own perspective on having a psychological problem that warrants care. Verhaak et al. concluded that the presence of subjective needs determines whether a person received care or not (Verhaak et al., 2009). In contrast, clinical needs are defined as the objective need for (professional) treatment as determined by a clinician (Verhaak et al., 2009). The WHO study shows that when defining the clinical need as the presence of a diagnosis, overuse seems to be present (Demyttenaere et al., 2004). However, another study that included the severity in addition to the DSM-diagnosis concluded that there is no overuse (Jörg et al., 2016).

In countries with an equal-access healthcare system, such as the Netherlands, clinical needs are crucial for appropriate healthcare distribution (Kroneman et al., 2016). However, the different ways in which clinical needs were defined previously may have led to the contradictory results on the presence of overuse (Demyttenaere et al., 2004; Jörg et al., 2016). To accurately assess under-and overuse, developing a more realistic clinical need definition is important. We, therefore, intended to generate a composite clinical need measure (also called clinical burden), which includes information on the diagnosis, based on diagnostic criteria (i.e., the Diagnostic and Statistical Manual [DSM]), severity (also called symptom burden), and comorbidity. This selection is based on previous literature, showing that the symptom burden, in addition to the diagnosis, explains why people obtain care vs. no care (Jörg et al., 2016). Furthermore, because the symptom burden strongly depends on whether a person has only one or more anxiety and/or depressive disorders, we additionally considered information on the symptom burden of comorbid anxiety (two or more anxiety disorders), comorbid depression (two or more depressive disorders), and anxiety-depression disorders (one or more anxiety and depressive disorders) (Hofmeijer-sevink et al., 2012).

The aim of this study was, first, to extend the definition of under-and overuse derived from cross-sectional studies by investigating how mismatch between needs and MHC-use is presented over time. Second, we aimed to explain why people show certain mismatch patterns by describing these identified mismatch patterns with predisposing, enabling, and need factors from Andersen's BMH. We used 6-year prospective data from the Netherlands Study of Depression and Anxiety (NESDA) cohort to address these aims.

2. Methods

2.1. Sample and procedures

This study has an observational, longitudinal design, using the NESDA study data from baseline (wave one), two- (wave three), four- (wave four), and six-year follow-up (wave five). NESDA is an ongoing multisite, naturalistic cohort study examining long-term courses of people with depression and/or anxiety. In total, 2,981 participants were recruited from the general population (18.9%), primary MHC services (54%), and specialized MHC settings (27.1%). The cohort included participants with different stages of anxiety and depressive disorders: 1,701 participants with a current DSM-IV disorder of depression and/or anxiety, 907 with a life-time diagnosis or high risk for developing these disorders and 373 healthy controls. Participants not being fluent in Dutch and with a primary psychiatric diagnosis of a disorder that is not anxiety or depression were excluded. NESDA was approved by the medical ethical review boards of all participating centres. All participants signed informed consent. For a detailed description of the study rationale and methods of NESDA, see Penninx et al. (2008).

2.2. Measures

To be able to determine a [mis]match, the clinical burden and MHC-use trajectories over time were estimated and compared. To enable accurate comparison of the trajectories, we developed two standardized scales to be used in the trajectory estimations: clinical burden (Fig. 1) and MHC-use (Fig. 2).

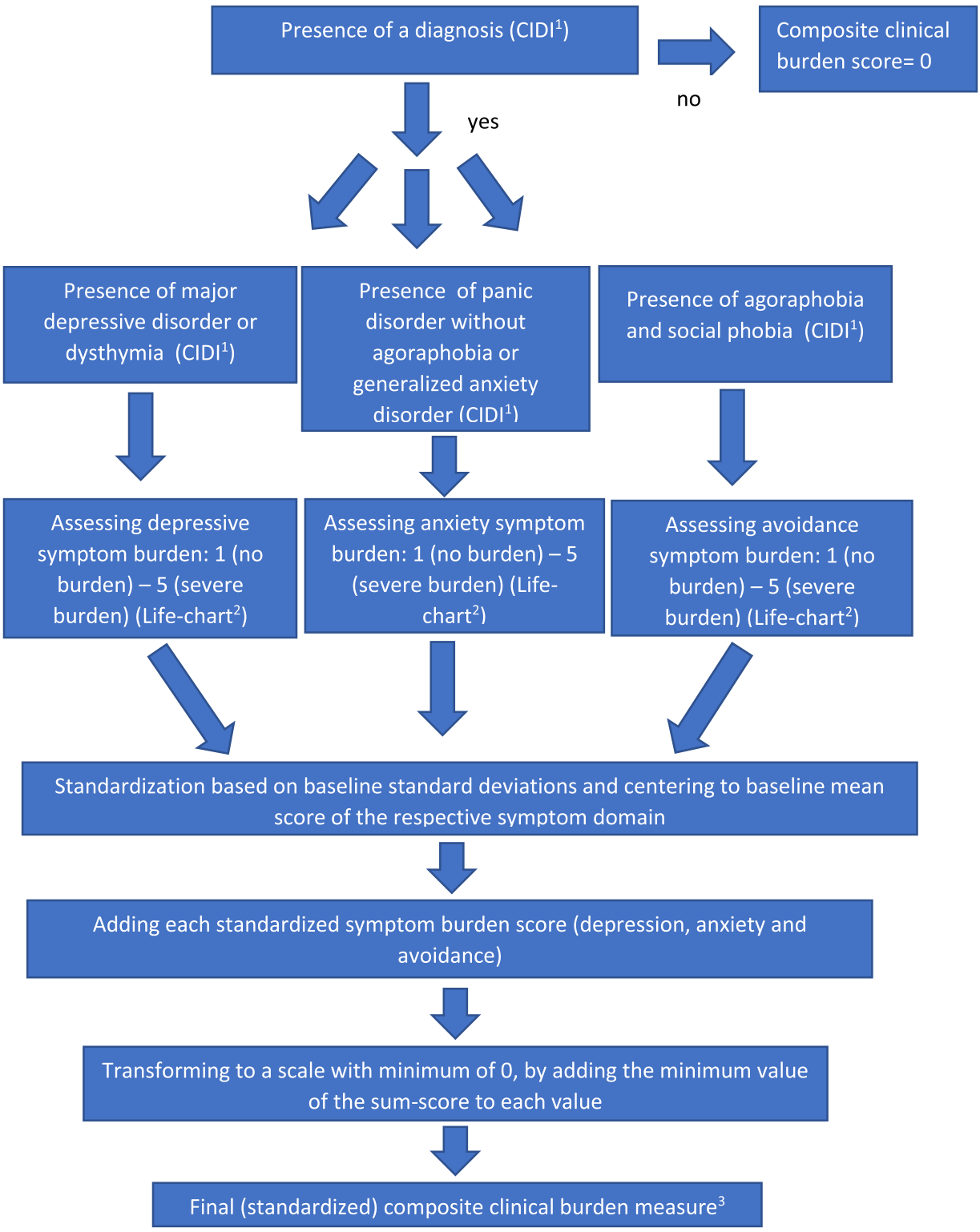

Fig. 1. Flow-chart on each process step in generating the clinical burden composite measure. 1: The CIDI (composite international diagnostic interview – lifetime version 2.1 assesses the presence of a diagnosis for the past 6 months at each wave. 2: The life-chart questionnaire retrospectively assesses symptom burden for the past 6 months at each wave. The only exception were the assessments for anxiety, depression and/or avoidance at baseline. Here a one-year burden was available, which was taken as a proxy for the 6-months burden. 3: The final composite measure of the clinical burden scale can be interpreted as follows: 0= no clinical burden and, >0 = higher scores reflect higher clinical burden of diagnosed (comorbid) disorders.

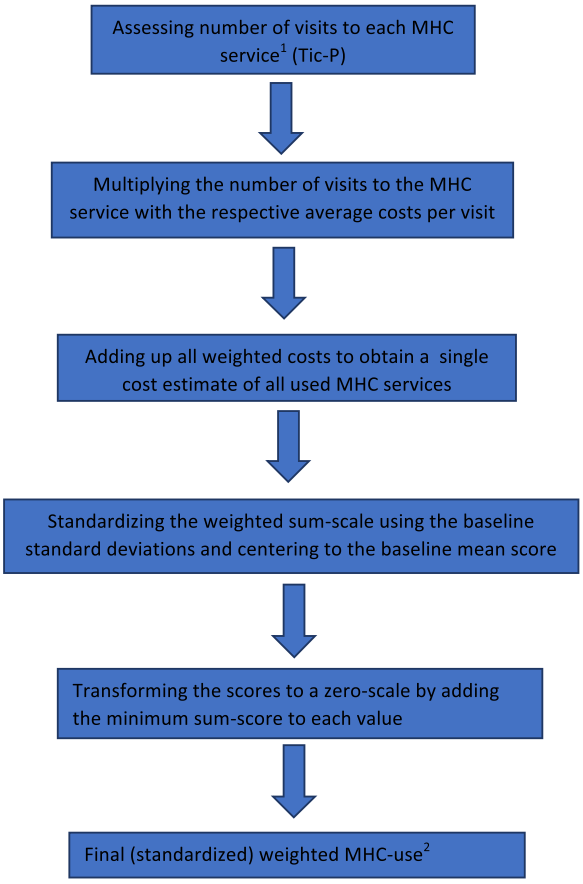

Fig. 2. Flow-chart on each process step in generating the weighted MHC use measure
1: MHC-use refers to the past 6-months of each interview. 2: The weighted MHC-use measure can be interpreted as follows= 0 (no MHC use), >0 = higher scores reflect higher levels of MHC use (frequency of visits and type of MHC service).

2.3. Clinical burden

We created a composite clinical burden measure that includes information on the presence of a current diagnosis (6-months prevalence), symptom burden (i.e., severity of symptoms), and comorbidity. In particular, we focus on the symptom burden of single diagnosed anxiety or depressive disorders, combinations of two or more anxiety/depression disorders, and combination of one or more anxiety and depressive disorders. At each wave, the composite international diagnostic interview (CIDI)-lifetime version (Robins et al., 1988; Wittchen, 1994). was used to determine the presence of seven DSM-IV-based disorders (i.e., major depressive disorder, dysthymia, social phobia, panic disorder with and without agoraphobia, agoraphobia, and generalized anxiety disorder), in the preceding six months. Symptom burden was assessed retrospectively with the Life-chart questionnaire (Lyketsos et al., 1994; Denicoff et al. 1997), which yields monthly scores ranging from 1 (no burden) to 5 (severe burden) for three main symptom domains: anxiety, depression, and avoidance. Similar to the time window of the CIDI, we used symptom burden scores of the preceding six months for waves 3, 4, and 5. For wave 1, only a one-year symptom burden assessment was available, which was therefore used as a proxy for the six months symptom burden. For each wave, information on all diagnoses and their associated symptom burden was combined into a single clinical burden score (see Appendix p.2 for a worked example of the calculations). On this composite continuous scale, a zero-score is interpreted as having no diagnosis (thus no clinical burden), and the higher the score, the higher the clinical burden of (comorbid) anxiety and depressive disorders.

2.4. MHC-use

We defined MHC-use as mental health-related visits to the general practitioner (GP), social worker, first-primary care psychologist, psychiatric nurse, psychotherapist, psychiatrist, MHC institutions, MHC specialists in hospitals, centers for alcohol and addiction, and mental health-related hospital admissions in the past six months at each wave, which was assessed with the Tic-P (Bouwmans et al., 2013). Furthermore, we created a weighted sum-score, using the average costs per visit, because costs are a good proxy for the level of care (see appendix p.4-7 for worked examples of this procedure). Medication use is included in visits to any (mental health) physician, including the GP, as in the Netherlands, medication needs to be prescribed and protocolled by such a professional (Kroneman et al., 2016; Magnée, 2017; Poll et al., 2020; Roijen et al., 2015). On the final weighted continuous MHC-use scale, a zero-score can be interpreted as no use, and increasing scores reflect increasing MHC-use.

2.5. Predictors

As predisposing factors, we included sex, age, and attitudes towards MHC, assessed at baseline. Attitudes towards MHC were measured with the Confidence in Help Scale, which has been previously validated and used by Verhaak et al. and consists of three domains. Two items measured the domain „confidence in professional help" (Cronbach's alpha= .46), two items measured the domain "confidence in lay help" (Cronbach's alpha=.78) and one item assessed the domain "confidence in self-help" (psychological problem are best kept to yourself). The response options on all items ranged from 1-5 (1=strongly disagree, 2=disagree, 3=no opinion, 4=agree, 5= strongly agree). For the domains, 'confidence in professional help' and 'confidence in lay help', the mean of the two items was taken. Afterward, the scores were rounded to obtain interpretable scores (Verhaak et al., 2009). Finally, for the purpose of our statistical analysis, we merged the first two and the last two options: 1=(strongly) disagree, 2=no opinion, 3= (strongly) disagree.

As enabling factors, we included socio-economic status (SES) in the form of educational level with three levels, that was assessed at baseline: 1=basic, 2=intermediate and, 3=high education.

As need factors, we included the following variables: suicidal ideation, disability, subjective need and presence of a somatic disease. The referral guidelines of the Dutch healthcare system suggest that in

addition to the presence of a diagnosis based on diagnostic criteria, the course of symptomatology, the severity of symptoms (symptom burden), and the complexity (comorbidity), also suicidality and disability play a role when deciding who will receive which type of care (Kroneman et al., 2016). The latter two could however not be included in the composite burden measure because they were not assessed on all time points and/or did not capture the same time frame (6 months prevalence). Hence, we included them as explanatory need measures. Furthermore, we used suicidal ideation as a proxy to assess suicidality. The presence of suicidal ideation was assessed for the past week of the interview (Beck et al., 1979). It is defined as having thoughts of suicide and was assessed with a shortened version of Beck's scale for suicidal ideation (SSI), which was previously found to have acceptable internal consistency ($\alpha > .74$) (Beck et al., 1979; Kivelä et al., 2019). Moreover, this variable was assessed at each wave. The four assessed suicidal ideation variables were then recoded into a single variable, that provided information on whether a person experienced suicidal ideation at least at one wave. Disability was measured using the World Health Organization Disability Assessment Schedule II, which was previously shown to have high reliability and validity (Buist-Bouwman 2008, Chwastiak, Von Korff, 2003). This interview focuses on past-month health-related disability in six different life-domains: cognition, mobility, self-care, interpersonal interactions, life activities, participation in society. The scale at each wave ranged from 1-100 (higher scores indicating higher disability) (Mckibbin et al, 2004). To obtain a variable reflecting the total experience of disability during the follow-up time, the scores from each of the four waves were summed for each participant (range: 0-400). Participants expressed their subjective needs in the first question of the perceived need for care interview (PNCQ) and expressed if they experienced any psychological problem in the past 6 months (yes/no) (Verhaak et al., 2009). Subjective needs were assessed at each wave. We recoded these variables into a single variable, to capture the time-varying component: 1. No subjective needs, 2. Subjective needs present at <50% of the waves, 3. Subjective needs present at >50% of the waves. Finally, we included information on whether a chronic, somatic disease was present or not (see Table 1 for an overview of the predictors).

2.6. Statistical analysis

The study protocol and analysis code were preregistered on the open science framework (Wijekoon et al., 2021). To deal with the missing values, we conducted a multiple imputation (10 imputed datasets) on the raw data using the predictive mean matching method (PMM). Furthermore, we inspected the observed characteristics of dropouts vs. completed cases with chi-square and independent t-tests.

Table 1
Description of the explanatory predictors based on Andersen's BMH.

BMH factor	Measurement instrument	Assessment time-point	Type of variable used in the analyses	Method	Citation
Predisposing factors					
Sex		Baseline	Dichotomous: female, male	SR[1]	
Age		Baseline	Continuous	SR[1]	
Attitudes towards MHC[3]	Nivel Consumer Panel Questionnaire: Confidence in professional, lay and self help	Baseline	Nominal: 1= (strongly) disagree 2=no opinion 3=(strongly) agree	Int[2]	Verhaak et al., 2009
Enabling factors					
Socio-economic status (SES)	SES was measured with the educational status	Baseline	Ordinal: 1=basic 2=intermediate 3=high	SR[1]	
Need factors					
Suicidal ideation	Shortened version of the Beck's scale for suicidal ideation	Waves 1,3,4,5	Dichotomous: Present or absent at any wave	Int[2]	Beck et al., 1979
Disability	World Health Organization Disability Assessment Schedule II	Waves 1,3,4,5	Continuous: 0-400 (higher scores indicating greater disability)	SR[1]	Mckibbin et al, 2004
Subjective need	In the first question of the perceived need for care interview (PNCQ)	Waves 1,3,4,5	Nominal: 1.Absent 2.Present at <50% of the waves 3.Present at >50% of the waves	Int[2]	Verhaak, 2009
Chronic somatic disease		Waves 1,3,4,5	Dichotomous: Present or absent at any wave	SR[1]	

[1] : SR=self-report.
[2] : Int=Interview.
[3] : The original scale of the confidence in help measurement was:1=strongly disagree, 2=disagree, 3=strongly agree, 4=no opinion. To facilitate interpretation of our statistical analysis, we first reversed the scale into 1= strongly disagree, 2= disagree, 3= no opinion, 4= agree, 5= strongly agree. Then, we combined the first two and the last two response options.

The handling of outliers and results of the missing value analysis can additionally be found in the appendix (p.9).

We first divided the NESDA sample into four groups, based on what we already know about under-and overuse from cross-sectional studies. These subgroups can then be used to extend the already established mismatch definitions by exploring how [mis]match is presented over time. Such a qualitative division of the sample, prior to the statistical analysis, helps to make sure that we build our analysis on existing definitions and concurrently avoids under-or overestimations of the presence of [mis]match. The sample was therefore split as follows: I) the overuse subgroup (n=121) with constantly no clinical burden (clinical burden at wave 1-4 = 0), but MHC-use present at least at one wave (MHC-use at wave x>0), II) the underuse subgroup (n=409) with constantly no MHC-use (MHC-use at wave 1-4 = 0) but clinical burden at least at one wave (clinical burden at wave x>0) and III) the changing [mis]match subgroup (n=1,807) with any MHC-use and clinical burden present at least at one wave (clinical burden at wave x>0; MHC-use at wave x>0), and finally, IV) the healthy non-user subgroup (n=631). Second, to further identify different patterns of [mis]match within subgroups I-III, we identified classes using a data-driven, growth mixture modeling approach (GMM) in Mplus (version 8.4) (Muthén and Muthén, 2012). The GMM helps to probabilistically classify individuals into latent classes based on their longitudinal response pattern on the clinical burden and/or MHC-use variables (Jung and Wickrama, 2008).

2.7. Trajectory analysis

Three GMM analyses were run. First, a GMM was used to identify classes with different MHC-use trajectories in the overuse subgroup. Second, GMM was used to identify classes with different clinical burden trajectories in the underuse subgroup. Third, a parallel trajectories/process GMM (pp-GMM) was used in the changing [mis]match subgroup to identify classes with different contemporaneous trajectories on both scales.

In all GMMs, models with increasing numbers of classes were fit to the data and their fit was compared based on the Akaike Information Criterion and (adjusted) Bayesian Information Criterion, with the lowest values indicating the optimal model. In addition, entropy, interpretability, and parsimony were considered as well in selecting the optimal model (Jung and Wickrama, 2008; Wright and Hallquist, 2014) . See appendix p.8-9 for more detailed model information.

2.8. Identifying mismatch and match trajectories

For each identified class in subgroups I-III, we plotted the mean trajectories over time on the clinical burden (overuse subgroup), MHC-use (underuse subgroup) or both (changing [mis]match subgroup). To identify the extent of underuse and overuse, we evaluated the growth of the single trajectories (strong vs. slight increase/decrease) of burden and MHC-use. To identify patterns of change in the changing [mis]match subgroup, we plotted the trajectories of mean burden and MHC-use scales and evaluated whether the trajectories ran parallel (match), converged (mismatch to match), or diverged (match to mismatch) over time. To determine the type of growth of each observed trajectory, the following criteria were used: a non-significant (alpha $\geq$ 05) slope equals a stable trajectory and significant positive and negative slopes indicate an increasing or decreasing trajectory, respectively.

2.9. Multivariate multinomial regression analysis

Regression analyses were used to investigate associations between the predictors and [mis]match class-membership. For the regression analysis, we used the pooled function in SPSS (version 27) based on the 10 imputed datasets. We first tested each predictor in a univariate analysis and then included the significant univariate predictors ($p<0.1$) into a multivariate model with class membership as outcome variable.

Multicollinearity of the predictors was examined using the variance inflation factor (cut-off>10), and the False Discovery Rate (FDR) was used to adjust for the effects of multiple testing (Benjamini and Hochberg, 1995). Furthermore, we converted the log odds ratio in the final model to the standardized mean difference Cohen's d (d) (Cohen, 1988).

In all analyses, an alpha of 0.05 was used.

3. Results

3.1. Baseline characteristics

Table 2 depicts the baseline charactersitics of the NESDA sample. Our total baseline sample consisted of 2,981 eligible participants (66.4% females, mean age of 41.9 years). Of these, 41.7% had no current disorder (6-months prevalence) and 58.3% suffered from a current comorbid anxiety and/or depressive disorder. Additionally, the raw mean burden for anxiety, depression, and avoidance symptoms (Life-chart) in the diagnosed group was low (results of the missing value analysis can be found in the appendix on p 9-10).

Table 2
Baseline characteristics[1] [N= 2981].

Sex, % female	66.4
Age, mean years (SD)	41.86 (13.08)
No current disorder[2], %	41.7
Comorbidity	
>1 current depressive and/or anxiety disorder, %	58.3
Symptom burden[3], mean (SD)	
Anxiety burden	1.8 (1.78)
Avoidance burden	1.29 (1.71)
Depression burden	1.9 (1.89)
Agoraphobia, %	6.3
GAD, %	15.6
Dysthymia, %	10.2
MDD, %	37.4
Mental healthcare users	50.59

[1] The baseline characteristics refer to the total baseline sample including outliers.
[2] CIDI: current disorder refers to a 6-month prevalence.
[3] The symptom burden was assessed by the Life-chart questionnaire.

3.2. Trajectory analysis

Based on the above-mentioned selection criteria, we selected the following class-solutions in each subgroup of the NESDA sample, excluding outliers, leaving n=2,968 (see appendix p.11-13 for more elaborated information on the selection process of the class-solution). Fig. 3 depicts the trajectories for each class. We additionally described each identified class with Andersen's BMH factors (Table 3).

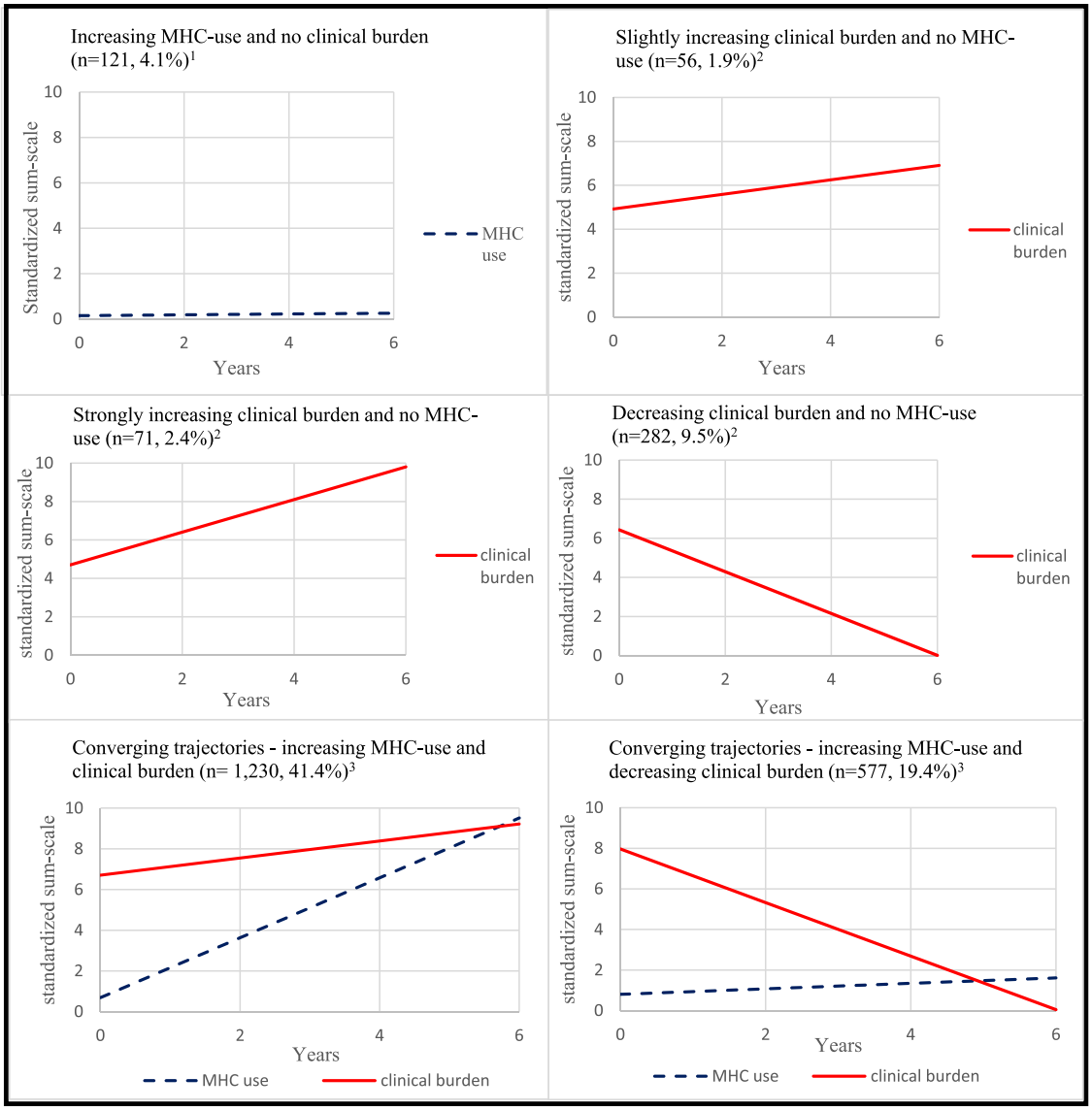

Fig. 3. MHC use and clinical burden trajectories based on single and parallel linear growth mixture models. 1. Variances for the MHC-use intercept (i_u) and slope (s_u) in the *increasing MHC-use and no clinical burden class*: intercept (i_u)=.32, slope (s_u)=.03. 2. Variances for the clinical burden intercept (i_b) and slope (s_b) in the *strongly increasing clinical burden, slightly increasing clinical burden, and decreasing clinical burden and no MHC use* were fixed to zero (i_b=0, s_b=0). 3. Variances for the MHC-use intercept (i_u) and slope (s_u) and clinical burden intercept (i_b) and slope (s_b) in the *Converging trajectories - increasing MHC-use and clinical burden* and *Converging trajectories - increasing MHC use and decreasing clinical burden:* i_u=1.16 s_u=.7, i_b= 5.45, s_b= 0.14. All the trajectories had significant ($p<.05$) positive or negative slopes, indicating statistically significant increasing or decreasing trajectories in each class.

Table 3
Descriptive of BMH factors in each identified [mis]match class in each subgroup of the NESDA sample (N=2968)[1].

NESDA subgroups	Healthy non-users (N= 631, 21.3%)	Overuse subgroup	Underuse subgroup			Changing [mis]match subgroup	
Classes within the subgroups		Increasing MHC use and no clinical burden (N= 121, 4.1%)	Slightly increasing clinical burden and no MHC use (N=56, 1.9%)	Decreasing clinical burden and no MHC use (N=282, 9.5%)	Strongly increasing clinical burden and no MHC use (N=71, 2.4%)	Converging trajectories: increasing MHC use and clinical burden (N=1,230, 41.4%)	Converging trajectories: decreasing MHC use and clinical burden (N=577, 19.4%)
Predisposing factors							
Age Mean (SD)	43.1 (14.25)	38.64 (12.47)	46.77 (12.02)	44.91 (13.12)	46.39 (14)	41.52 (12.51)	40.85 (12.48)
Sex (female), %	61.8	69.4	67.9	64.5	83.1	66.7	68.8
Confidence in professional help[2], %							
(Strongly) disagree	4.3	9.5	7.2	6.9	9.9	14.9	8.1
No opinion	11.2	12.6	21.6	16	25.9	15.9	12.7
(Strongly) agree	84.5	77.9	71.2	77.1	64.2	69.2	79.2
Confidence in lay help[2], %							
(Strongly) disagree	17.3	21.9	25.3	21.3	26.81	26.9	27.4
No opinion	34.3	19.7	37.8	35.3	34.4	36.9	42
(Strongly) agree	48.5	26.6	36.9	43.4	38.8	36.2	30.6
Confidence in self-help[2], %							
(Strongly) disagree	89.6	85.7	84	83.2	73.4	71.3	80.8
No opinion	4.8	4.5	1.8	5.7	5.2	6.4	5.6
(Strongly) agree	5.6	9.8	14.1	11.1	21.4	22.3	13.7
Enabling factors							
Level of education, %							
Basic	4	3.3	3.6	5.3	11.3	9.3	4.9
Intermediate	52.5	45.5	67.9	63.8	62	61.2	56.7
High	43.6	51.2	28.6	30.9	26.7	29.4	38.5
Need factors							
Subjective needs, %							
Not present	63.1	8.3	3.6	13.8	1.4	0	2.6
Present at <50% of the waves	30.9	59.5	33.9	50.7	36.6	19.4	30.5
Present at >50% of the waves	6	32.2	62.5	35.5	62	72.6	66.9
Presence of chronic disease (somatic), %	39.1	60.3	76.8	74.8	81.7	87.8	73.7
Suicidal ideation, %							
Present at any wave	1.7	8.3	17.5	16	20.21	79.7	37.3
Disability[3], mean (SD)	26 (23.67)	37.38 (29.76)	78.46 (43.87)	61.91 (42.69)	93.31 (52.32)	103 (55.44)	53.29

[1] These are pooled estimated based on 10 imputed datasets. The total sample in each sample, excluding outliers is N=2968.
[2] We merged the first two and the last two scores of the confidence in professional, lay-and self-help-scale (original reverse-scale: 1=strongly disagree, 2=disagree,3=no opinion, 4=agree 5= strongly agree).
[3] Disability: the maximum score of this time-varying sum-scale for disability is 400.

3.2.1. Overuse subgroup (n=121)

In the overuse subgroup, the 1-class solution was deemed the best option.

3.2.1.1. Increasing MHC-use and no clinical burden (n=121, 4.1%). This class showed on average a low baseline MHC-use level *(intercept$_{MHC\text{-}use}$ [i_u]=0.31, p<.001)* that slightly increased *(slope$_{MHC\text{-}use}$ [s_u]=0.1, p=.002).*

3.2.2. Underuse subgroup (n=409)

In the underuse subgroup, the 3-class solution was deemed the best option.

3.2.2.2. Slightly increasing clinical burden and no MHC-use (n=56, 1.9%). This group had a relatively medium clinical burden level at baseline *(intercept$_{clinical\ burden}$ [i_b]=4.78, p<.001)* that slightly increased *(slope$_{clinical\ burden}$ [s_b]=0.34, p<.001).*

3.2.2.3. Decreasing clinical burden and no MHC-use (n=282, 9.5%). In contrast, this group showed a higher baseline clinical burden level *(i_b=6.45, p<.001),* that decreased *(s_b=-1.07, <.001).*

3.2.2.4. Strongly increasing clinical burden and no MHC-use (n=71, 2.4%). This group revealed a relatively medium baseline clinical burden level *(i_b=4.9, p<.001)* that increased strongly *(s_b=0.81, p<.001),* in comparison to the *slightly increasing clinical burden and no care class.*

3.2.3. Changing [mis]match subgroup (n=1807)

In the mismatch and match subgroup, the 2-class solution was deemed the best option.

3.2.3.5. Converging trajectories- increasing MHC-use and clinical burden (n=1,230, 41.4%). This class had a high baseline clinical burden level *(i_b=6.81, p<.001)* that increased *(s_b=0.37, p<.001).* Simultaneously, these participants revealed a lower baseline MHC-use level *(i_u=0.69, p<.001)* that increased strongly *(s_u=1.55, p<.001).* Hence, both trajectories show a high discrepancy between the burden and MHC-use levels in the beginning of the study that decreased with time. In other words, the trajectories converged over time, indicating a mismatch to match transition. This class is comparably the largest.

3.2.3.6. Converging trajectories- increasing MHC-use and decreasing clinical burden (n= 577, 19.4%). Similarly, this class shows converging trajectories with increasing MHC-use *(i_u=0.81, <.001, s_u=0.21, p<.001).* However, in contrast to the first converging trajectory class, here the participants revealed a high baseline clinical burden *(i_b=8.01, p<.001)* that decreased *(s_b= -1.33, p<.001).*

3.3. Regression analysis

For the regression analysis, we chose as a reference the group with the least favourable mismatch situation: strongly increasing burden and no MHC-use (i.e., constant underuse) (Table 4). Moreover, we excluded gender from the multivariable analysis, as it was not significant (p=.01) in the univariable analysis, using the FDR-based cut-off (alpha=.002). In comparison to the reference class, the increasing MHC-use class (overuse) was significantly less likely to experience higher disability *(b=-.03, p<.001, d<0.2).* However, around 59.5% of this class experienced subjective needs for care (Table 3). Furthermore, both classes with converging trajectories were significantly more likely to experience suicidal ideation *(b=1.14-2.78=2.78, p<.001, d=0.63-1.5)* compared to the reference class (Table 4). There were no differences between the reference class and the other classes regarding enabling or predisposing factors (Table 4).

Table 4
Results of the multinomial logistic regression: BMH factors that predict membership in the identified [mis]match classes (dependent variable)[1].

Predictors: BMH factors[2]	b	P	E[b] (95%CI)	Cohens' d[3]	Predictors: BMH factors	b	P	E[b] (95%CI)	Cohens' d[3]
Dependent category: Healthy non-user class (n= 631, 21.3%) (Reference category: strongly increasing clinical burden and no MHC-use).									
Enabling factors					***Need factors***				
SES (educational level)	.42	.124	1.53 (.89-2.62)	.23	*Subjective needs*				
Predisposing factors					Present at <50% of the waves	-2.94	.001*	.05 (.01-.3)	1.6
Confidence in professional help[4]					Present at >50% of the waves	-4.69	<.001*	.01 (0-.05)	2.59
(strongly) disagree	.11	.884	1.12 (.26-4.87)	<.2	Suicidal ideation	-2.71	<.001*	.07 (.03-.18)	1.49
(strongly) agree	.45	.354	1.56 (.61-4.01)	.25	Chronic somatic disease	-.31	.502	.73 (.3-1.82)	
Confidence in self-help[4]					Disability	-.03	<.001*	.97 (.96-.08)	<.2
(strongly) disagree	.22	.801	1.25 (.22-7.22)	.12					
(strongly) agree	-.34	.735	.71 (.1-5.11)	.19					
Confidence in lay help[4]									
(strongly) disagree	-.37	.418	.69 (.29-1.69)	.2					
(strongly) agree	.02	.958	1.02 (.49-2.11)	<.2					
Age	-.01	.595	.99 (.97-1.02)	<.2					
Dependent category: Increasing MHC-use and no clinical burden class (n= 121, 4.1%) (Reference category: strongly increasing clinical burden and no MHC-use)									
Enabling factors					***Need factors***				
SES (educational level)	.71	.02	2.03 (1.12-3.66)	.39	*Subjective needs*				
Predisposing factors					Present at <50% of the waves	-.23	.806	.79 (.12-5.14)	.13
Confidence in professional help[4]					Present at >50% of the waves	-1.1	.251	.34 (.06-2.13)	.59
(strongly) disagree	.87	.313	2.4(.44-13.28)	.48	Suicidal ideation	-.49	.316	.61 (.24-1.59)	.27
(strongly) agree	.34	.524	1.41 (.49-4.01)	.19	Chronic somatic disease	-.27	.575	.76 (.29-1.98)	.15
Confidence in self-help[4]					Disability	-.03	<.001*	.97 (.96-.98)	<.2
(strongly) disagree	-.1	.909	.91 (.17-4.91)	<.2					
(strongly) agree	-.61	.53	.54 (.08-3.65)						

(continued on next page)

Table 4 (*continued*)

Predictors: BMH factors[2]	b	P	E^B (95%CI)	Cohens' d[3]	Predictors: BMH factors	b	P	E^b (95%CI)	Cohens' d[3]
Confidence in lay help[4]									
Strongly disagree	-.02	.969	.98 (.37-2.62)	<.2					
(strongly) agree	-.05	.896	.95 (.44-2.05)	<.2					
Age	-.03	.027	.97 (.94-.99)	<.2					
Dependent category: Slightly increasing clinical burden and no MHC-use class (n= 56, 1.9%) (Reference category: strongly increasing clinical burden and no MHC-use)									
Enabling factors					***Need factors***				
SES (educational level)	.1	.786	1.11 (.53-2.33)	<.2	*Subjective needs*				
Predisposing factors					Present at <50% of the waves	3.81	.604	4.95 (0-7.02)	2.1
Confidence in professional help[4]					Present at >50% of the waves	3.72	.616	4.15 (0-7.37)	2.05
(strongly) disagree	-.02	.987	.98 (.13-7.73)	<.2	Suicidal ideation	-.04	.944	.96 (.32-2.91)	<.2
(strongly) agree	.09	.901	1.09 (.26-4.6)	<.2	Chronic somatic disease	.28	.712	.76 (1.6-3.49)	.15
Confidence in self-help[4]					Disability	<-.01	.477	.1 (.1-1.01)	<.2
(strongly) disagree	7.4	.993	16 (0-18.29)	4.08					
(strongly) agree	6.92	.993	12.3 (0-19.29)	3.82					
Confidence in lay help[4]									
Strongly disagree	-.17	.791	.84 (.23-3.07)	<.2					
(strongly) agree	-.19	.699	.82(.31-2.21)	<.2					
Age	.02	.348	1.02 (.98-1.06)	<.2					
Dependent category: Decreasing clinical burden and no MHC-use class (n= 282, 9.5%) (Reference category: strongly increasing clinical burden and no MHC-use)									
Enabling factors					***Need factors***				
SES (educational level)	.13	.630	1.14 (.67-1.93)	.07	*Subjective needs*				
Predisposing factors					Present at <50% of the waves	-.99	.27	.37 (.06-2.16)	.54
Confidence in professional help[4]					Present at >50% of the waves	-1.86	.032	.16 (.03-.84)	1.02
(strongly) disagree	.34	.612	1.4 (.38-5.17)	.19	Suicidal ideation	-.16	.677	.85 (.4-1.8)	<.2
(strongly) agree	.5	.29	1.65 (.65-4.15)	.28	Chronic somatic disease	-.2	.664	.82 (.34-2.01)	<.2
Confidence in self-help[4]					Disability	-.01	.057	.99 (.99-1)	<.2
(strongly) disagree	-.2	.803	.82 (.18-3.85)	.11					
(strongly) agree	-.69	.407	.5 (.1-2.56)	.38					
Confidence in lay help[4]									
Strongly disagree	-.19	.662	.83 (.35-1.94)	<.2					
(strongly) agree	.01	.975	1.01 (.5-2.05)	<.2					
Age	<.01	.948	1 (.97-1.03)	<.2					
Dependent category: Converging trajectories - increasing MHC-use and clinical burden class (n= 1230, 41.4%) (Reference category: strongly increasing clinical burden and no MHC-use)									
Enabling factors					***Need factors***				
SES (educational level)	.25	.326	1.28 (.78-2.11)	<.2	*Subjective needs*				
Predisposing factors					Present at <50% of the waves	-1.2	.187	.3 (.05-1.77)	.6
Confidence in professional help[4]					Present at >50% of the waves	-.69	.417	.5 (.1-2.65)	.38
(strongly) disagree	.84	.219	2.31 (.61-8.79)	.46	Suicidal ideation	2.78	<.001*	16.04 (7.95-32.37)	1.5
(strongly) agree	.77	.112	2.17 (.84-5.56)	.42	Chronic somatic disease	.36	.479	1.44 (.42-4)	.2
Confidence in self-help[4]					Disability	<.01	.427	1 (.1-1.01)	<.2
(Strongly) disagree	-.19	.795	.83 (.2-3.41)	<.2					
(strongly) agree	-.39	.615	.68 (.15-3.11)	.2					
Confidence in lay help[4]									
Strongly disagree	-.02	.954	.98 (.43-2.21)	<.2					
(strongly) agree	-.01	.974	.99 (.5-1.97)	<.2					
Age	-.03	.012	.97 (.94-.99)	<.2					
Dependent category: Converging trajectories- increasing MHC-use and decreasing clinical class (n=577, 19.4%) (Reference category: strongly increasing clinical burden and no MHC-use)									
Enabling factors					***Need factors***				
SES (educational level)	.43	.092	1.54 (.93-2.54)	.24	*Subjective needs*				

(*continued on next page*)

Table 4 (*continued*)

Predictors: BMH factors[2]	b	P	E[b] (95%CI)	Cohens' d[3]	Predictors: BMH factors	b	P	E[b] (95%CI)	Cohens' d[3]
Predisposing factors					Present at <50% of the waves	.03	.969	1.04 (.18-5.91)	<.2
Confidence in professional help[4]					Present at >50% of the waves	.3	.73	1.34 (.25-7.17)	.2
(strongly) disagree	.56	.42	1.76 (.44-6.99)	.31	Suicidal ideation	1.14	.001*	3.14 (1.56-6.32)	.63
(strongly) agree	.81	.114	2.24 (.83-6)		Chronic somatic disease	-.03	.954	.98 (.41-2.35)	<.2
Confidence in self-help[4]					Disability	-.01	.055	.99 (.99-1)	<.2
(Strongly) disagree	-.32	.687	.73 (.15-3.46)	.2					
(strongly) agree	-.59	.467	.56 (.11-2.72)	.33					
Confidence in lay help[4]									
Strongly disagree	-.06	.888	.94 (.41-2.17)	<.2					
(strongly) agree	-.46	.174	.63 (.32-1.22)	.26					
Age	-.04	.004	.96 (.94-.99)	<.2					

[1] These results are based on pooled estimates of 10 imputed datasets. The *strongly increasing clinical burden and no MHC-use class (N=71, 2.4%)* was chosen as a reference category in this regression analysis.

[2] Following reference categories were chosen for each BMH variable: educational status = continuous variable; confidence in professional, self-and lay help= no opinion; age= continuous; subjective needs at <50% and >50% of the waves= no subjective needs; suicidal ideation= no suicidal ideation present; chronic somatic disease= no chronic somatic disease present; disability= continuous.

[3] Cohens' d can be interpreted as follows: >=.2 (small effect), >=.5 (medium effect) >=.8 (large effect) (Cohen, 1988).

[4] Confidence in help variable: We merged the first two and the last two scores of the confidence in professional, lay-and self-help-scale (original reversed scale: 1=strongly disagree, 2=disagree,3=no opinion, 4=agree 5= strongly agree).

* marks significant p-values based on an adjusted (FDR) cut-off of p=.002.

4. Discussion

This longitudinal study revealed four main groups having a specific (mis)match pattern: healthy non-users, overusers, constant underusers and a group showing a changing mismatch-to-match pattern, which was the largest group (60.9%). In the latter group, MHC use increases to match high clinical burden, that increases in one subclass and decreases in the other. The constant underusers could be divided in three subclasses, with decreasing, slightly and strongly increasing clinical burden, respectively. Constant underusers (reference) and those with delayed care (mismatch-to-match) differed from each other only in the presence of suicidal ideation among those receiving delayed care. Interestingly, we did not identify any meaningful class that continuously revealed matched care on average over the six years.

4.1. Overuse

We found that the overuse class was less likely to show disability than the reference group, which underused MHC. The associated effect size was, however, very small. Despite finding no other significant differences, we could detect a large proportion with subjective needs (59.5%) in the overuse class. This finding hints on an existing misfit between subjective and clinical needs, which previous researchers have already supported (Druss et al., 2008; Fretian et al., 2020) . This misfit can appear in two ways. First, there are those that have clinical needs but do not feel that they need help (Fretian et al., 2020). Second, similarly to our findings, there are those that do not have clinical needs (i.e., a diagnosis) but experience a need for help, potentially explained by other stressors (Druss et al., 2008; Jörg et al., 2016, Bloem 2012). Hence, it may be important to explore further the reasons for these types of misfits between clinical and subjective needs. Additionally, it could be that these were recovering individuals who still obtained some form of care to prevent relapse. However, because we do not have data on the actual type of received MHC (whether it is preventive or active treatment), we cannot surely say that this MHC-use was for recovering patients. Furthermore, it should be noted that the average care level in this class was quite low in comparison to those who obtained care (all underuse classes and the classes with converging trajectories). Hence, we should be cautious when labeling this class as actual overusers. We suggest that more need factors, such as subthreshold symptoms, should be included in future research to gain better insight into the mechanisms that explain this pattern. Only then could we fairly classify such patterns as signs of overuse or not.

4.2. Constant underuse

The fact that in this study only 13.8% of participants revealed constant underuse can be explained by the fact that around 80% of NESDA participants were recruited at MHC settings. When taking a closer look, the overall level of the clinical burden of the constant underuse class is not entirely different from the clinical burden of the converging classes. These findings suggest that even when the diagnosis, symptom burden and comorbidity are similar between different individuals, the presence of suicidal ideation appeared as a key determinant of who will receive care. Suicidal ideation is known to be linked to suicidality, which is mentioned as a criterion for receiving care in the Dutch guidelines for referral (Kroneman et al., 2016; Harmer et al. 2021). However, suicidal ideation is known to be very fluctuating and thus a heterogenous state, which can relate to other factors than just the presence of a diagnosis (Foster et al., 1999; Harmer et al., 2021). Thus, we recommend future researchers to explore the link between suicidal ideation, that occurs in addition to having clinical burden, and suicidality. Furthermore, future research is needed to explore how this link is related to different healthcare use patterns.

Moreover, based on previous research, we would have expected that also other BMH factors may have played a role in explaining the

different [mis]match patterns, such as gender. This is because men are known to be less likely to seek MHC compared to women (Sagar-Ouriaghli et al., 2019). However, in this study, we did not find any predisposing or enabling factors that could explain why these participants showed constant underuse compared to for example those who obtained care. A broader range of potential explanatory factors, such as mental health-related stigma, might be included and explored in future studies (Conner et al, 2010).

One class showed ameliorating clinical burden despite receiving no care. These results emphasize that underuse of common, evidence-based MHC services, does not necessarily always lead to exacerbation of clinical burden. A previous cross-sectional study showed that about 83% of recovery can be attributed to treatment-unrelated factors and spontaneous remission (Ormel et al., 2019), which could be an explanation of the presently observed pattern. Another explanation could be the usage of alternative self-help services. Hence, the question remains who will recover spontaneously and what factors facilitate recovery in the long term in these people.

4.3. Mismatch to match transition

Interestingly, two classes showed more dynamic patterns in form of converging trajectories. Both groups showed underuse in the first half of the study, which gradually changed to matched care. These mismatch to match transitions may indicate the presence of delayed access to appropriate MHC. Striking is the fact that one of the converging trajectory classes included almost half of the NESDA sample. Similarly, another study found that 80% of the participants with a lifetime disorder, did not obtain care in a timely manner (Wang et al., 2002). A consequence of delayed MHC-use is a potentially poor prognosis of the symptoms with time (Osso et al., 2012). One could argue that this may explain why especially this large group shows constantly increasing clinical burden, despite increasing care. However, as mentioned above, our study also showed that underuse does not always result in poorer outcomes. Hence, why underuse (constant or delayed MHC-use) leads to a poor clinical burden progression in some people, but not in others, remains unclear. Other factors explaining such delays may be waiting lists, which should therefore be included in future studies (Vallerand and Mclennan, 2013)

4.4. Correct users

We did not identify any class with a sufficient and meaningful sample size that revealed continuously matched care on average. There were few people that showed constantly matched care, but they did not make up a meaningful sample size. This is alarming and reveals the great extent of the mismatch problem even in a HIC, such as the Netherlands. Because most participants who eventually received matched care showed a delayed MHC-use on average, we need to develop and implement strategies that overcome such delay.

4.5. Limitations and strengths

The strengths of this study include the use of a large longitudinal dataset, that allowed for investigation of different types of underuse over time. Moreover, we used the Dutch guidelines for referral to include further explanatory clinical variables (disability and suicidality) in addition to the literature. Additionally, we used all types of regular MHC services. This approach provided a more accurate reflection on the real-world MHC needs and use, increasing our findings' generalisability.

However, some methodological limitations need to be considered. First, despite the many explanatory BMH factors, only limited associations were found with the observed mismatch patterns. Hence, other (time-varying) exploratory variables (such as stigmatization of MHC or waiting lists) should be investigated. Second, our analysis revealed that among all the explanatory factors that were included, only one need factor (suicidal ideation) was a significant determinant for receiving care between those with similar clinical burden. This raises the question if, given the close relationship between suicidal ideation and clinical burden, these entities can indeed be seen as factors with distinct roles in healthcare delivery. Future research could look more closely into the overlap and/or distinction between need factors and components of clinical burden. Third, the approach to capture comorbid severity, while avoiding overestimations of the symptom burden, may have caused people with symptom burden scores around the average on all three symptom burden domains (anxiety, depression, avoidance) and people with symptom burden scores above and below the average to be treated as having similar clinical burden. However, the symptom burden estimates on which the scale was standardized were relatively low, still enabling us to capture people with highly comorbid disorders in the high clinical burden trajectories and people with single (less severe) disorders in the low clinical burden trajectories. Fourth, the retrospective nature of the Life-chart questionnaire may have caused recall-bias. Fifth, the fact that most participants were recruited from MHC settings ensured that there was variation in obtained MHC services but may have caused a selection bias. A general population sample could circumvent that problem but may have caused difficulties in identifying trajectory classes with sufficient group sizes. This may be especially the case for identifying less commonly found groups such as overusers. Thus, when merely focusing on underuse, we recommend that future research should use a general population sample. Sixth, the GMM classes reflected homogeneous subgroups with different levels and types of mismatches between clinical burden and MHC-use, but these bottom-up classifications are almost certainly also influenced by other sources of population heterogeneity. Still, this data-driven approach to identify these subgroups was deemed the best option to achieve the research aims, given the lack of clear existing ideas of what kinds of match- or mismatch-patterns over time exist in the real world. Finally, we only captured medication use through the visits to the MHC setting, assuming that a specialist prescribes and supervises the medication use. This, however, may have caused some bias, because for instance some people visit the specialist more often while receiving the same amount of medication, which would consequently result in a higher MHC-use score. However, because previous literature has found that a combination of psychotherapy and pharmacotherapy is more effective than only medication, the impact of this limitation on the mismatch does not seem to be large (Cuijpers et al., 2009).

5. Conclusion

This paper reveals that in HIC such as the Netherlands, participants with different disease progressions show mismatch mainly in the form of constant underuse or delayed MHC-use, and no meaningful sample revealed constant matched care within six years. Interestingly, the clinical burden of people who did not use any care or had delayed care was either deteriorating or ameliorating, which emphasizes the importance to detect factors influencing the disease progression, with and without care. The presence of suicidal ideation could most prominently explain why symptomatic individuals received (delayed) care compared to those who did not receive care (underusers). Furthermore, we cautiously conclude that there was generally no mismatch in the form of overuse, given the high proportion of people with subjective needs and the relatively low average MHC-use levels obtained in this group. Therefore, in contrast to overuse, mismatch in the form of underuse still seems to be a problem, even in HIC. The additional absence of a meaningful class with constantly matched care on average is alarming. Hence, to decrease the mismatch in HIC, such as in the Netherlands, the focus should lie on identifying and targeting factors that can explain the treatment gap, especially those leading to delayed MHC.

Author contribution

KWWM, JAB and FJ came up with the study concept. KWWM conducted the data analysis with input from RS and KJW. KWWM wrote the initial draft with feedback from JAB, KJW, BWJHP, RAS, AMVH and FJ. All authors approved the final version of the article.

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Data availability statement

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

Declaration of Competing Interest

BWJHP received (non-related) research grants from Boehringer Ingelheim and Jansen Research.

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Research paper

An integrated approach to understand biological stress system dysregulation across depressive and anxiety disorders

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ABSTRACT

Background: Affective disorders involve dysregulation of major biological stress systems (hypothalamic-pituitary-adrenal (HPA)-axis, immune system, autonomic nervous system (ANS)). Suchdysregulationshave rarely beensimultaneously examined across different stress systems.

Methods: In the Netherlands Study of Depression and Anxiety (n=2789), we investigated whether current or remitted depressive and/or anxiety disorders (based on the CIDI semi-structured interview), including specific symptom profiles, were associated with separate markers and cumulative indexes of the HPA-axis (cortisol awakening response, evening cortisol, dexamethasone suppression test cortisol), immune system (C-reactive protein, interleukin-6, tumor necrosis factor-α), and ANS (heart rate, respiratory sinus arrhythmia, pre-ejection period).

Results: Depressive andanxiety disorderswere significantlyassociated with changes in three biological stress systemsincluding HPA-axis hyperactivity, increased inflammatory activity, and a higher ANS tone, particularly for integrative and cumulative indexes of these stress systems (pFDR <.05) vs. controls. The strongest associations were seen with current disorders andcumulative indexes of the HPA-axis (β=.124, pFDR=.001), the immune system (β =.057, pFDR=.032), and total cumulative index across stress systems (β=.102, pFDR=.004). Atypical, energy-related depression severity was linked to immune system markers (pFDR<0.001), melancholic depression severity to HPA-axis markers (pFDR=.032), and anxiety arousal severity to both HPA-axis and immune system markers (pFDR<0.05). Findings were partially explained by poorer lifestyle, more chronic diseases, or (especially for ANS-function) antidepressant use.

Limitations: Cross-sectional analyses limit examination of temporal associations.

Conclusion: Patients withdepressive and anxiety disorders showed consistent dysregulation across biological stress systems, particularly for current episodes.To understand stress system functionality in affective disorders, an integrated approach capturing cumulative stress indices within and across biological stress systems is important.

1. Introduction

In order to survive in a challenging environment, continuous adaptation to such an environment is essential. Three biological stress systems play a major role in these adaptations and responses to stress: the hypothalamic-pituitary-adrenal (HPA)-axis, the immune system, and the autonomic nervous system (ANS).Patients with an affective disorder respond differently to stress (Zorn et al., 2017). The functionality of biological stress systems is pivotal in the context of stress, and stress, particularly traumatic stress, is a significant risk factor for both depressive and anxiety disorders (Vinkers et al., 2014).Consequently, most research on these stress systems related to affective disorders has been carried out in the context of acute or chronic stress (e.g. life events, disasters, or childhood trauma) (Liu and Alloy, 2010; Stroud et al.,

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2008). However, dysregulation of stress systems may also occur in the absence of stressors such as daily hassles, life events, or childhood trauma. In this context, the well-known concept of allostatic load is important, which refers to the wear and tear due to repeated and chronic exposure to biological stressors (McEwen, 1998). Allostatic overload may result in inefficient functionality and, eventually, failure of the biological stress systems to mount an adequate stress response. Such allostatic load may not only result from stressors, but mood and anxiety disorders themselves may exert harmful effects on our biological stress systems (McEwen, 2003). Importantly, mediators of these stress systems (e.g. cortisol and (nor)adrenaline) play a major role in the etiology of affective disorders, and stress system dysregulation could also contribute to disease onset. Moreover, developing and recovering from an affective disorder may take its toll on the functionality of stress systems. Consequently, independent of stress, patients with a current or remitted mood or anxiety disorder may have problems to dynamically switch on and off the appropriate biological stress system (Hermans et al., 2014; van Leeuwen et al., 2018), and display long-term dysregulation of biological stress systems.

All three major biological stress systems have been linked to the onset and course of affective disorders. First, the HPA-axis has been implicated in the pathophysiology of anxiety and depression for over several decades (Keller et al., 2017), with a substantial proportion of depressed patients displaying elevated HPA-axis activity or altered circadian rhythmicity (e.g. cortisol awakening response (CAR), diurnal cortisol slope) (Menke, 2019; Vinkers et al., 2015; Vreeburg et al., 2009a), which seems especially present in those with melancholic depression (Lamers et al., 2013; Stetler and Miller, 2011). Second, next to the HPA-axis, immune system functionality and low-grade inflammation (e.g. signalled by high C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α) have been implicated in the pathophysiology of depressive and anxiety disorders (Beurel et al., 2020; Mac Giollabhui et al., 2020; Osimo et al., 2020), and especially of symptoms overlapping with sickness behaviour (van Eeden et al., 2020). Recently, immunometabolic dysregulation was found to map to atypical depressive symptoms reflecting altered energy and fatigue, and that this immunometabolic depression subtype could be used to reduce depression heterogeneity and as a tool in developing personalized medicine strategies (Milaneschi et al., 2020).Third, altered ANS functionality (such as reduced heart rate variability)has been found in affective disorders (Hu et al., 2016; Mac Giollabhui et al., 2020), and ANS dysregulation has been hypothesized to explain the increased prevalence of coronary heart disease in patients with depression and anxiety (Kemp et al., 2010), even though antidepressant useis an important confounding factor in these studies (Kemp and Quintana, 2013; Licht et al., 2012).

In the current literature on stress system dysregulation related to depression and anxiety, the three major biological stress systems are often studied in isolation. However, stress does not only affect multiple biological systems, but these systems are often correlated and interact with each other to adequately respond and recover from a challenging environment (McEwen and Akil, 2020). An integrated approach may shed more light on how dysregulation occurs in patients with depressive or anxiety disorders and various symptom indexes (i.e. immunometabolic and melancholic depression), steering away from simple models to more nuanced and integrated dysregulation where stress systems are not operating independently (Hu et al., 2018; Rotenberg and McGrath, 2016). The usefulness of such an integrated approach has recently been shown in the context of childhood trauma,where cumulative indexes across stress systems were found to be altered following childhood trauma (Kuzminskaite et al., 2020). The present study,therefore,aimed to comprehensively investigate possible dysregulation across the three major biological stress systems (including cumulative indexes per stress system and across stress systems) related to depression and anxiety disorders in a large adult cohort – the Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2008), adjusting for multiple covariates to understand the contributing role of poorer lifestyle and somatic disease status.

2. Materials and methods

2.1. Sample

Data came from an ongoing longitudinal cohort (NESDA; $n = 2981$) (Penninx et al., 2008). Participants were Dutchadults (18-65 years) with or without depressive and/or anxiety disorder (current or remitted; Composite International Diagnostic Interview, CIDI version 2.1) (Robins et al., 1988) recruited from community, primary health care, and specialized mental health care. Patients with a primary diagnosis other than depressive or anxiety disorder (e.g., post-traumatic stress disorder, bipolar disorder, psychotic disorder, obsessive-compulsive disorder) and persons not fluent in Dutch were excluded. For the current study, we excluded participants based on pregnancy/breastfeeding ($n = 27$, 0.9%) andcorticosteroid use ($n = 165$, 5.5%), leading to a sample size of 2789 participants (1592 individuals with a current depressive and/or anxiety disorder; 585 individuals with a remitted depressive and/or anxiety disorder, and 612 healthy controls, for details see Table 1). For individual stress systems, data was missing for the cortisol area under the curve with respect to the ground (AUCg; $n = 950$, 34.1%), cortisol AUC with respect to the increase (AUCi; $n = 950$, 34.1%), evening cortisol ($n = 789$, 28.3%), dexamethasone suppression test (DST) cortisol ($n = 898$, 32.2%), plasma CRP ($n = 39$, 1.4%), plasma IL-6 ($n = 39$, 1.4%), plasma TNF-α ($n = 58$, 2.1%), heart rate (HR) ($n = 111$, 4.0%), respiratory sinus arrhythmia (RSA) ($n = 111$, 4.0%), and pre-ejection period (PEP) ($n = 133$, 4.8%). NESDA's protocol was approved by the ethical review board of each participating research center in Amsterdam, Leiden, and Groningen. All participants provided written informed consent. For this study, we used data from the baseline wave, collected between 2004-2007.

2.2. Measures

2.2.1. Psychopathology

Current (past six months) and remitted (lifetime, but not past six months) depression and anxiety diagnoses were assessed by the CIDI version 2.1(Robins et al., 1988) as based on the criteria of DSM-IV (American Psychiatric Association (APA), 2001). Depressive disorders included major depressive disorder and dysthymia, while anxiety disorders included social anxiety disorder, agoraphobia, generalized anxiety disorder, and panic disorder. Six depression and anxiety symptom profiles were created based on the Inventory of Depressive Symptomatology (IDS) (Rush et al., 1996), Beck Anxiety Inventory (BAI) (Beck et al., 1988), Fear Questionnaire (FQ) (Marks and Mathews, 1979), and Penn State Worry Questionnaire (PSWQ) (Meyer et al., 1990). Depression symptom profiles included: overall depression severity (total IDS score; range 0-84), atypical, energy-related severity (IDS-atypical; range 0-15), and melancholic severity (IDS-melancholic; range 0-24), while anxiety symptom profiles included: anxiety arousal severity (total BAI score; range 0-63), fear severity (total FQ score; range 0-120), and worry severity (total PSWQ score; range 11-55). The atypical, energy-related depression profile represented a sum of 5 immuno-metabolic IDS items: increased appetite, increased weight, hypersomnia, leaden paralysis, and low energy (Lamers et al., 2020). The melancholic depression profile represented a sum of 8 melancholic IDS items: diurnal variation (mood worse in the morning), early morning awakening, distinct quality of mood, excessive guilt, decreased appetite, decreased weight, psychomotor agitation, and retardation (Khan et al., 2006).

2.2.2. HPA-axis, immune system, and ANS

The activity of stress systems was assessed by markers of the HPA-axis, immune system, and ANS. For the HPA-axis, three salivary cortisol patterns were measured (Vreeburg et al., 2009b): (1) CAR,

Table 1
Sample characteristics.

Characteristics	N	Mean (SD) / Median (IQR) / n (%)
Sociodemographics		
Age in years, mean (SD)	2789	41.68 (13.11)
Sex, female, n (%)	2789	1829 (65.60)
Years of education, mean (SD)	2789	12.18 (3.27)
Lifestyle and health		
Current smoker, yes, n (%)	2789	1084 (38.90)
Alcohol consumption (drinks per week), mean (SD)	2750	7.15 (10.03)
Physical activity (1000 MET-min/wk), mean (SD)	2789	3.69 (3.02)
BMI (kg/m^2), mean (SD)	2787	25.50 (4.94)
Number of chronic diseases, mean (SD)	2789	.84 (1.02)
Psychopathology		
Clinical status		
Current depressive and/or anxiety disorder (CIDI), yes, n (%)	2789	1592 (57.10)
Current 'pure' depressive disorder, yes, n (%)		366 (13.10)
Current 'pure' anxiety disorder, yes, n (%)		511 (18.30)
Current comorbid depressive and anxiety disorder, yes, n (%)		715 (25.70)
Remitted depressive and/or anxiety disorder (CIDI), yes, n (%)	2789	585 (21.00)
Healthy controls (CIDI), yes, n (%)	2789	612 (21.90)
Depression and anxiety symptom profiles		
Total depression severity (IDS), mean (SD)	2753	21.40 (14.14)
Atypical, energy-related depression severity (IDS-atypical), mean (SD)	2754	3.27 (2.73)
Melancholic depression severity (IDS-melancholic), mean (SD)	2728	4.44 (3.82)
Anxiety arousal severity (BAI), mean (SD)	2756	12.04 (10.61)
Fear severity (FQ), mean (SD)	2756	24.83 (19.88)
Worry severity (PSWQ), mean (SD)	2442	30.79 (11.91)
Antidepressant use		
Tricyclic antidepressants (TCAs), yes, n (%)	2789	72 (2.60)
Selective serotonin reuptake inhibitors (SSRIs), yes, n (%)	2789	467 (16.70)
Other, yes, n (%)	2789	145 (5.20)
Hypothalamic-Pituitary-Adrenal-Axis		
Cortisol awakening response, mean (SD)	1839	
AUCg (nmol/L/hr)		18.90 (6.95)
AUCi (nmol/L/hr)		2.15 (6.23)
Evening cortisol (nmol/L), median (IQR)	2000	4.81 (3.22)
DST cortisol, median (IQR)	1891	2.39 (1.50)
Immune system		
C-reactive protein (mg/L), median (IQR)	2750	1.19 (2.38)
Interleukin-6 (pg/mL), median (IQR)	2750	.74 (.74)
Tumor necrosis factor-α (pg/mL), median (IQR)	2731	.80 (.50)
Autonomic Nervous System		
Heart rate (bpm), mean (SD)	2678	71.77 (9.59)
Respiratory sinus arrhythmia (ms), mean (SD)	2678	44.67 (25.84)
Pre-ejection period (ms), mean (SD)	2656	120.27 (17.81)
Stress-system-specific covariates		
Awakening time (00:00-23:59), mean (SD)	1873	7.46 (1.24)
Working on the sampling day, yes, n (%)	1877	1104 (58.80)
Season on the sampling day, n (%)	2789	
October-February (less daylight)		1210 (43.40)
March-September (more daylight)		1579 (56.60)
Anti-inflammatory medication use, yes, n (%)	2789	109 (3.90)
Cardiac medication use, yes, n (%)	2789	334 (12.00)
Respiratory rate, mean (SD)	2678	17.08 (1.20)
Mean arterial pressure, mean mmHg (SD)	2784	99.60 (13.40)

Note. Not-normally distributed outcome variables are presented as medians with interquartile ranges.

SD, standard deviation; IQR, interquartile range; 1000 MET-min/wk, 1000 metabolic equivalent minutes in the past week; BMI, body mass index; CIDI, Composite International Diagnostic Interview; IDS, Inventory of Depressive Symptomatology; BAI, Beck Anxiety Inventory; FQ, Fear Questionnaire; PSWQ, Penn State Worry Questionnaire; AUCg, the area under the curve with respect to the ground; AUCi, the area under the curve with respect to the increase; Nmol/L/hr, nanomoles per liter per hour; Nmol/L, nanomoles per liter; Mg/L, milligrams per liter; Pg/mL, picograms per liter; Bpm, beats per minute; Ms, milliseconds.

reflecting 1-hour cortisol secretion after awakening (AUCg) and changes over 1 hour (AUCi) (Pruessner et al., 2003), (2) evening cortisol, reflecting basal cortisol secretion (Kirschbaum and Hellhammer, 1989), and (3) DST cortisol, reflecting the negative feedback of the HPA-axis (Carroll et al., 1981). For the immune system, three inflammation markers in blood plasma were assessed: (1) CRP, (2) TNF-α, and (3) IL-6 (Vogelzangs et al., 2012). For the ANS, three physiological measures were measured: (1) HR, reflecting the combined effect of sympathetic and parasympathetic activity, (2) RSA, reflecting cardiac parasympathetic activity, and (3) PEP, reflecting cardiac sympathetic activity (Licht et al., 2010b). For more detailed information on assessments and previous findings on psychopathology with individual stress system findings, see (Licht et al., 2010b; Vogelzangs et al., 2012; Vreeburg et al., 2009b).

2.2.3. *Cumulative indexes of stress systems*

To assess the cumulative activity of stress systems, cumulative marker scores (indexes) were created, reflecting the activity within each system and across all systems in line with previous paper (Kuzminskaite et al., 2020). For the cumulative score, markers of DST cortisol, RSA, and PEP were reversed, as lower values represent higher disease risk. To standardize values across each marker, values were transformed into Z-scores. The score for each system was calculated as the average standardized score of the three markers within the system. Similarly, the score across systems was calculated as the average standardized score of all markers within all systems. These scores were estimated only for participants with complete data on all markers within each system or across all systems.

2.2.4. *Covariates*

Standard covariates for all analyses included age in years, sex, smoking, alcohol consumption, physical activity(International Physical Activity Questionnaire (IPAQ) (Hagströmer et al., 2007)), body mass index (BMI), number of chronic diseases, and antidepressant use (tricyclic antidepressants (TCAs), anatomical therapeutic chemical (ATC) code N06AA; selective serotonin reuptake inhibitors (SSRIs), ATC code N06AB; othertypes, ATC code: N06AX, not N06AA, not N06AB)) no/yes frequent use). Stress-system-specific covariates were based on previous studies utilizing the same data. Awakening time, working status on the day of the sampling, and season on the day of the sampling were included for HPA-axis-focused analyses (Vreeburg et al., 2009b). Anti-inflammatory medication use (ATC codes M01A, M01B, A07EB, A07EC; no/yes frequent use) was included for inflammation-focused analyses (Vogelzangs et al., 2012), while cardiac medication use (ATC codes C01, C02, C03, C04, C05, C07, C080; no/yes frequent use), respiratory rate (for RSA), and mean arterial pressure (for PEP) was included for ANS-focused analyses (Houtveen et al., 2005; Licht et al., 2012). Analyses on cumulative dysregulations included all relevant covariates.

2.3. *Data-analyses*

Sample characteristics were explored descriptively and presented as means with standard deviations, medians with interquartile ranges (for skewed outcome distributions), or numbers with percentages. Spearman's correlation (ρ) was used to determineassociations between psychopathology and markers of stress systems. Markers with skewed distributions (evening cortisol, DST cortisol, CRP, IL-6, and TNF-α) were further log-transformed (ln).

In the following multiple linear regression analyses, psychopathology was included as a predictor variable and markers of stress systems as outcome variables, including cumulative markers in the group of individuals with complete data. First, associations with current and remitted depressive and/or anxiety disorder (two dummy-coded variables referenced to the healthy control group) were examined. Afterward, we zoomed in on the current disorder sample and looked at

associations of current "pure" depressive disorder and current comorbid disorder (two dummy-coded variables referenced to current "pure" anxiety disorder) with stress systems' markers to examine possible significant differences.Three models were created: Model 1,controlling for age, sex, and stress-system-specific covariates (see covariates section); Model 2, additionally controlling for lifestyle and health-related factors; Model 3, additionally controlling for antidepressant use as a putative confounder as antidepressants themselves can influence stress system markers, particularly within the ANS (Licht et al. 2008; 2010).Cohen's *d* (the difference in estimated means divided by their pooled standard deviation) was calculated as a measure of effect size. To examine which types of antidepressant medication (TCAs, SSRIs, other) should be included in Model 3, we a priori determined associations between antidepressant types and stress systems' markers.

Further analyses focused on depression and anxiety symptom profiles in the full sample. Depression profiles included overall depression severity (total IDS score), atypical, energy-related severity (IDS-atypical), and melancholic severity (IDS-melancholic). Anxiety profiles focused onanxiety arousal severity (BAI), fear severity (FQ), and worry severity (PSWQ). To avoid high multicollinearity, all symptom profiles were included in separate analyses. These analyses were performed using Model 1 covariates only.

For all analyses, the statistical significance was based on a p-value < .05. Benjamini-Hochberg False Discovery Rate (FDR p-value < .05) corrected for multiple analyses (14 tests per model) (Benjamini and Hochberg, 1995). Data were interpreted with IBM SPSS-25 and R Studio 1.3.959 software (IBM Corp., 2017; RStudio Team, 2020).

Table 2
Multiple regression results on stress systems' markers associated with current and remitted depressive and/or anxiety disorder.

	Current Depressive and/or Anxiety Disorder vs. Healthy Controls										
	Model 1 Basic adjustment				Model 2 +Lifestyle/health adjustment				Model 3 +Antidepressant adjustment		
	N	Beta†	P	FDR‡	N	Beta†	p	FDR‡	Beta†	P	FDR‡
HPA-axis markers											
CAR – AUCg	1609	.100	.001	.004	1602	.079	.009	.042	.066	.035	.263
CAR – AUCi	1609	.078	.010	.023	1602	.056	.070	.194	.049	.126	.353
Evening cortisol	1739	.065	.026	.046	1731	.016	.557	.751	-.002	.944	.969
DST cortisol	1645	-.036	.239	.304	1638	-.017	.590	.751	.001	.969	.969
Cumulative HPA-axis markers	1542	.124	<.001	.001	1535	.080	.007	.042	.058	.059	.263
Immune system markers											
C-reactive protein	2750	.064	.007	.020	2711	.021	.345	.549	.008	.702	.969
Interleukin-6	2750	.034	.145	.203	2711	-.003	.901	.901	-.013	.571	.969
Tumor necrosis factor-α	2731	.013	.594	.594	2692	-.007	.765	.824	-.010	.675	.969
Cumulative inflammation markers	2723	.057	.016	.032	2684	.007	.738	.824	-.005	.834	.969
ANS markers											
Heart rate	2678	-.014	.539	.581	2639	-.022	.353	.549	-.044	.075	.263
Respiratory sinus arrhythmia	2678	-.095	<.001	<.001	2639	-.103	<.001	<.001	-.039	.067	.263
Pre-ejection period	2653	.050	.036	.056	2614	.042	.083	.194	.010	.682	.969
Cumulative ANS markers	2653	.022	.331	.386	2614	.028	.220	.440	.002	.917	.969
Cumulative stress markers	1422	.102	.001	.004	1415	.062	.040	.140	.034	.285	.665
	Remitted Depressive and/or Anxiety Disorder vs. Healthy Controls										
HPA-axis markers											
CAR – AUCg	1609	.045	.140	.178	1602	.038	.202	.257	.034	.257	.327
CAR – AUCi	1609	.054	.078	.137	1602	.043	.154	.216	.041	.177	.275
Evening cortisol	1739	.048	.103	.160	1731	.022	.428	.461	.016	.564	.607
DST cortisol	1645	-.059	.051	.137	1638	-.047	.123	.191	-.041	.177	.275
Cumulative HPA-axis markers	1542	.091	.004	.047	1535	.069	.020	.091	.062	.037	.130
Immune system markers											
C-reactive protein	2750	.003	.895	.895	2711	-.020	.345	.403	-.022	.307	.358
Interleukin-6	2750	-.036	.127	.178	2711	-.053	.023	.091	-.053	.021	.098
Tumor necrosis factor-α	2731	.005	.829	.893	2692	-.004	.877	.877	-.005	.844	.844
Cumulative inflammation markers	2723	-.012	.609	.711	2684	-.037	.099	.191	-.038	.083	.232
ANS markers											
Heart rate	2678	-.045	.056	.137	2639	-.053	.026	.091	-.055	.018	.098
Respiratory sinus arrhythmia	2678	-.035	.077	.137	2639	-.038	.059	.165	-.023	.248	.327
Pre-ejection period	2653	-.061	.010	.047	2614	-.059	.014	.091	-.070	.003	.042
Cumulative ANS markers	2653	.041	.069	.137	2614	.039	.089	.191	.035	.113	.264
Cumulative stress markers	1422	.084	.007	.047	1415	.048	.110	.191	.043	.151	.275

Note. Model 1: adjustment for age, sex, awakening time (for HPA-axis), working status on the day of the sampling (for HPA-axis), season on the day of the sampling (for HPA-axis), anti-inflammatory medication use (for inflammation), cardiac medication use (for ANS), respiratory rate (for RSA), and mean arterial pressure (for PEP). Model 2: additional adjustment for smoking, alcohol consumption, physical activity, BMI, and number of chronic diseases. Model 3: additional adjustment for antidepressant use: TCAs (for inflammation and ANS), SSRIs (for HPA-axis and ANS), other (for inflammation and ANS).
Abbreviations: TCA, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors; HPA-axis, hypothalamic-pituitary-adrenal-axis; CAR, cortisol awakening response; AUCg, the area under the curve with respect to the ground; AUCi, the area under the curve with respect to the increase; DST, dexamethasone suppression test; ANS, autonomic nervous system; RSA, respiratory sinus arrhythmia; PEP, pre-ejection period.
Current disorder (max $n = 1573$), remitted disorder (max $n = 572$), healthy controls (max $n = 605$).
Boldface indicates statistical significance ($p < .05$)
† Standardized beta
‡ FDR adjustment for 14 tests per model.

3. Results

3.1. Sample characteristics

Participants (n = 2789) had a mean age of 41.68 (SD = 13.11), majority was female (65.6%), and had 12.18 years of education (SD = 3.27; Table 1). More than half of the sample had a current depressive and/or anxiety disorder (57.1%), while around one fifth had a remitted disorder (21.0%). Confirming the necessity of an integrative stress system approach, all markers within each stress system were significantly intercorrelated (ρ = -.282 to .440, all $p < .01$). Significant correlations were also observed between almost all immune markers and ANS markers (ρ = -.194 to .180, all$p < .01$), some of the HPA-axis markers (AUCg, evening cortisol) and ANS markers (RSA, PEP; ρ = -.099 to .048, all $p < .05$), and some of the immune system markers (CRP, IL-6) and HPA-axis markers (evening cortisol, DST cortisol; ρ = -.079 to .046, all $p < .05$ (Table S1)).

3.2. Psychopathology and stress system activity

Current depressive and/or anxiety disorder (compared to controls) was significantly associated with a number of stress systems' markers including CAR (AUCg, β = .100, p_{FDR} = .004;d = .198, 95% CI = .078–.318; AUCi, β = .078, p_{FDR} = .023;d = .187, 95% CI = .067–.307), evening cortisol (β = .065, p_{FDR} = .046; d = .129, 95% CI = .014–.244), CRP (β = .064, p_{FDR} = .020;d = .128, 95% CI = .034–.222), cumulative inflammation index (β = .057, p_{FDR} = .032;d = .113, 95% CI = .019–.207), RSA (β = -.095, p_{FDR}< .001;d = -.189, 95% CI =-0.284–-0.093) in Model 1controlling for age, sex, and stress-system-specific covariates (Table 2). The strongest associations were seen with cumulative index of HPA-axis (β = .124, p_{FDR} = .001; d = .248, 95% CI = .124–.371)and the total cumulative index across stress systems (β = .102, p_{FDR} = .004;d = .207, 95% CI = .079–.335). Significant associations with AUCi, evening cortisol, CRP, cumulative inflammation index, and cumulative stress index across all systems were reduced after adjustment for lifestyle and health-related covariates in Model 2 (p_{FDR}> .05). Significant Model 1 associations with AUCg, cumulative HPA-axis index, and RSA were reduced by additional antidepressant medication adjustment in Model 3 (p_{FDR}> .05; more than 10% drop of the standardized regression coefficient of current disorder on AUCg, cumulative HPA-axis index, and RSA).No significant differences were also found between current "pure" depressive disorder (referenced to current "pure" anxiety disorder) and current comorbid disorder (referenced to current "pure" anxiety disorder) in any of the stress systems markers (p_{FDR}> .05; Table S2).

Remitted depressive and/or anxiety disorder (referenced to healthy controls) was significantly associated with cumulative HPA-axis index (β = .091, p_{FDR} = .047;d = .231, 95% CI = .082–.380), PEP (β = -.061, p_{FDR} = .047;d = -.149, 95% CI = -.266–-.032), and cumulative stress index across all systems (β = .084, p_{FDR} = .047;d = .20, 95% CI = .045–.355) in Model 1. Overall, standardized beta coefficients were smaller for remitted disorders than for current disorders, indicating that stress system dysfunctions were overall in between those of current patients and healthy controls and less often significantly present. After adjustment for lifestyle and health-related covariates in Model 2, no significant effects remained (p_{FDR}> .05).Significant associations in Model 1 were reduced by higher levels of smoking (more than 10% reduction of the standardized regression estimate of remitted disorder on cumulative HPA-axis index and cumulative stress index) and BMI (more than 10% reduction of the standardized regression coefficient of remitted disorder on PEP and cumulative stress index) in those with remitted disorder.

For antidepressant medication, both TCAs and other antidepressant medication were most strongly associated with immune system markers and ANS markers (p_{FDR}< .05), while SSRIs were most strongly linked to HPA-axis markers and ANS markers (p_{FDR}< .05; Table S3). Based on these findings, HPA-axis-focused analyses were controlled for SSRIs, immune system-focused analyses for TCAs and other antidepressant medication, whereas ANS-focused analyses for all types of antidepressant medication (Model 3).

3.3. Symptom profiles and stress systems

Associations between symptom profiles and stress systems controlling for age, sex, and stress-system-specific covariates (Model 1) are shown in Fig. 1 (Table S4). Total depression severity was significantly associated with all immune system markers (CRP, β = .091, p_{FDR}<.001; IL-6, β = .076, p_{FDR}<.001; TNF-α, β = .056, p_{FDR} = .009; cumulative inflammation index, β = .110, p_{FDR}<.001), RSA (β = -.074, p_{FDR}<.001), PEP (β = .054, p_{FDR} = .010), and cumulative stress index across all stress systems (β = .078, p_{FDR} = .006).Of depressive symptom profile scores, atypical, energy-related depression severity was linkedtotheimmune system markers(CRP, β = .137, p_{FDR}<.001; IL-6, β = .068, p_{FDR}<.001; TNF-α, β = .059, p_{FDR} = .005; cumulative inflammation index, β = .131, p_{FDR}<.001), RSA(β = -.063, p_{FDR}<.001), and cumulative index across the systems (β = .115, p_{FDR}< .001), while melancholic depression severity was linked to HPA-axis markers (cumulative HPA-axis index, β = .067, p_{FDR} = .032), immune system markers (CRP, β = .046, p_{FDR}= .045; IL-6, β = .056, p_{FDR}= .014; cumulative inflammation index, β = .068, p_{FDR}= .003), and RSA (β = -.062, p_{FDR} =.002).

With regard to anxiety, themajority of the significant associations with stress systems' markers were found foranxiety arousal severity (cumulative HPA-axis index, β = .074, p_{FDR} = .008; CRP, β = .091, p_{FDR}< .001; IL-6, β = .061, p_{FDR} = .003; TNF-α, β = .061, p_{FDR} = .003; cumulative inflammation index, β = .106, p_{FDR}< .001; HR, β = .045, p_{FDR} = .033; RSA, β = -.051, p_{FDR} = .003; PEP, β = .057, p_{FDR} = .007).Fear severity was significantly associated with CRP (β = .060, p_{FDR} = .009), cumulative inflammation index (β = .064, p_{FDR} = .007), and RSA (β = -.065, p_{FDR} = .001), while worry severity was significantly associated only with RSA (β = -.062, p_{FDR} = .004).

3.4. Sensitivity analysis

As a sensitivity analysis, we repeated stress system associations related to current and remitted depressive and anxiety disorders in the group of individuals with complete data on all stress system markers (n=1422). This yielded comparable results to previous analyses in the total sample (Tables S5 and S6).

4. Discussion

To deepen our understanding of the stress system dysregulation in depressive and anxiety disorders, the current study employed a comprehensive and integrated approach to map stress system functionality. Using combined and cumulative measures within and across the three major biological stress systems (HPA-axis, immune system, and ANS), we found HPA-axis hyperactivity, increased inflammatory activity, and a higher ANS tone, particularly for integrative and cumulative indexes of these stress systems. Stress system dysregulation was stronger in patients with current depressive and/or anxiety disorders. This was the case for measures of the HPA-axis (CAR, evening cortisol, and cumulative HPA-axis index), the ANS (RSA), the immune system (CRP and cumulative immune system index), and cumulative indexes across all systems. Of the depression symptom domains, atypical, energy-related depression severity showed the strongest links to immune system markers which is in line with current literature (Milaneschi et al., 2020), while melancholic depression severity showed strongest links to HPA-axis markers (Belvederi Murri et al., 2014; Lamers et al., 2013; Nelson and Davis, 1997).With regard to anxiety, the majority of significant associations were found for anxiety arousal severity, whereas fear and worry severity were much less related to changes across biological stress systems.

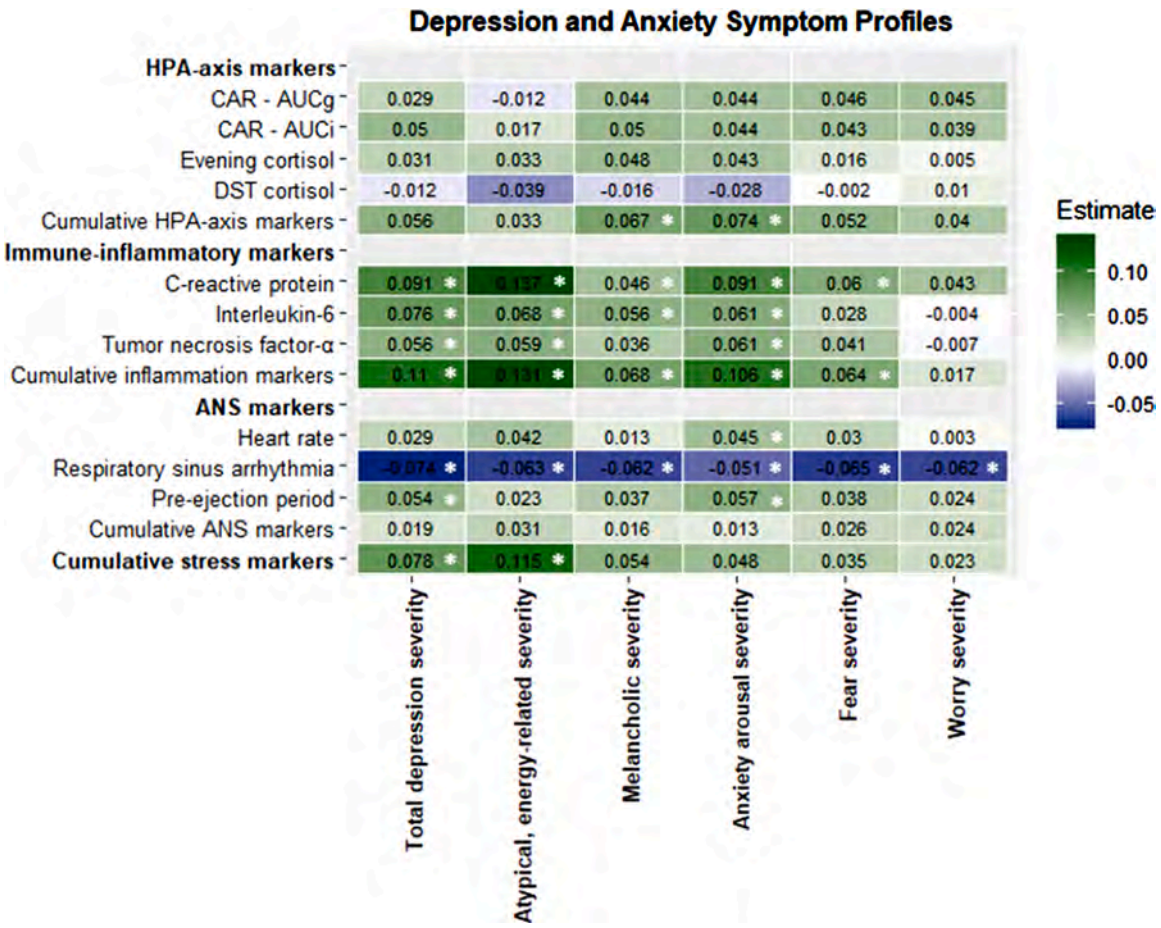

Fig. 1. Heatmap of adjusted standardized regression estimates of stress systems' markers associated with depression and anxiety symptom profiles in the full sample (max n = 2719). Note. Model 1: adjustment for age, sex, awakening time (for HPA-axis), working status on the day of the sampling (for HPA-axis), season on the day of the sampling (for HPA-axis), anti-inflammatory medication use (for inflammation), cardiac medication use (for ANS), respiratory rate (for RSA), and mean arterial pressure (for PEP). Abbreviations: HPA-axis, hypothalamic-pituitary-adrenal-axis; CAR, cortisol awakening response; AUCg, the area under the curve with respect to the ground; AUCi, the area under the curve with respect to the increase; DST, dexamethasone suppression test; ANS, autonomic nervous system; RSA, respiratory sinus arrhythmia; PEP, pre-ejection period. *FDR p-values < .05; FDR adjustment for 14 tests per model.

Findings were partially driven by poorer lifestyle, more chronic diseases, and antidepressant use. Obviously, the association between stress systems and affective disorders may be indirect and explained by other factors such as an unhealthy lifestyle. Our findings indicate that higher rates of smoking, BMI, and chronic diseases explain stress system dysregulation, and thus, stress system dysregulation may occur via specific behavioral processes. Consequently, lifestyle is an important theme to understand and target for stress system dysregulation in affective disorders (Sarris et al., 2014). Moreover, antidepressant use strongly influenced stress system markers, with TCAs altering immune system and ANS markers, and SSRIs being related to altered HPA-axis and ANS markers. Our findings confirm and extend earlier findings that antidepressants are an important confounding factor in the relation between affective disorders and biological stress systems (Hu et al., 2019). ANS function changes appears to be largely driven by pharmacological impact of antidepressant use itself, as was evidenced in longitudinal analyses in which we also confirmed that starting and stopping of antidepressants – but not changes in psychopathology – were paralleled with ANS changes (Hu et al., 2019; Licht et al., 2010a). In contrast, antidepressant effects on the HPA-axis and immune system were quite heterogeneous and could reflect not just an effect of antidepressants themselves but rather constitute a proxy for disorder severity. There may be confounding-by-indication as we know that the most severe/-chronic patients are more likely to be using antidepressants.

The current study has several strengths. First, we analysed a large sample with and without current affective psychopathology, with adequate power to determine associations between stress systemsand psychopathology. Second, this is the first study with an integrative approach to understand stress system dysregulation by not only analyzing separate stress system markers, but also cumulative indexes within and across stress systems. Across analyses, we employed a transparent approach by correcting for multiple known confounders having an impact on the accuracy of the results. Finally, depressive and anxiety disorders are by nature quite heterogeneous, hence, we analysed known disorder subtypes to examine stress system dysregulation in subtypes of both depression and anxiety disorders.

The limitations of the current study are the cross-sectional design, the use of static stress systems markers outside of (a stressful) daily life context and analyzing possible genetic vulnerability for affective disorders. First, due to the cross-sectional design, no temporality between affective disorders and the major biological stress systems can be explored. Second, due to the static nature of stress system markers used, sensitivity to detect functional dysregulation might have been limited. The contribution of stress system dysregulation may not be robust when measured with static biological stress system markers. In this context, stress system dysregulation may appear in response to stress or measured with repeated dynamic measures of stress systems (van Leeuwen et al., 2018; van Oort et al., 2017; Zorn et al., 2017).Indeed, effect sizes related to the effects of stress systems markers and indexes were generally small and the explained variance limited. Our results

cannot and should not be considered as individual predictors for psychopathology, but rather be evaluated at group-level. Third, alterations in stress systems may only emerge in individuals with a genetic vulnerability for depressive or anxiety disorders, and direct effect in a large sample may be diluted. For instance, vagal heart rhythm regulation and heart rate variability are heritable (Nolte et al., 2017). Moreover, variations in stress-related genes (e.g. mineralocorticoid receptor and glucocorticoid receptor) moderate the link between childhood trauma and the HPA-axis (Gerritsen et al., 2017; Vinkers et al., 2015). If stress system dysregulation is particularly present in genetically vulnerable individuals, it is to be expected that direct associations between stress system markers and affective disorders are rather limited. Fifth, some of the stress system findings have been previously published, even though these were hitherto never integrated into cumulative indexes within and across stress systems.

In conclusion, employing a comprehensive approach using measures of the major stress systems, we found that patients with current depressive and/or anxiety disorders show dysregulation across biological stress systems, both for current and remitted episodes, and disease subtypes. It is clear that HPA-axis hyperactivity, increased inflammatory activity, and a higher ANS tone occur. The fact that integrative markers of these stress systems show the most consistent effects emphasizes that cumulative stress indices with combined markers within and across biological stress systems have clear added value. Such an approach is rational as it builds upon the notion that altered stress system functionality in affective disorders does not limit itself to a single marker or a single system. Further fine-grained and dynamic approaches to quantify and understand stress systems are needed, but integrative and cumulative indexes of stress systems show promise to better understand when and how stress systems become dysregulated in the context of depression and anxiety.

Declaration of Competing Interest

BP has received (non-related) research grants from Boehringer Ingelheim and Jansen Research.

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Research paper

The day-to-day bidirectional longitudinal association between objective and self-reported sleep and affect: An ambulatory assessment study

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ABSTRACT

Background: Ambulatory assessments offer opportunities to evaluate daily dynamics of sleep and momentary affect using mobile technologies. This study examines day-to-day bidirectional associations between sleep and affect using mobile monitoring, and evaluates whether these associations differ between people without and with current or remitted depression/anxiety.

Methods: Two-week ecological momentary assessment (EMA) and actigraphy data of 359 participants with current (n = 93), remitted (n = 176) or no (n = 90) CIDI depression/anxiety diagnoses were obtained from the Netherlands Study of Depression and Anxiety. Objective sleep duration (SD) and efficiency were obtained from actigraphy data. Self-reported SD, sleep quality (SQ), positive affect (PA) and negative affect (NA) were assessed by electronic diaries through EMA.

Results: A bidirectional longitudinal association was found between self-reported SQ and affect, while no association was found for self-reported SD and objective SD and efficiency. Better SQ predicted affect the same day (higher PA: b = 0.035, p < 0.001; lower NA: b = -0.022, p < 0.001), while lower NA on the preceding day predicted better SQ (b = -0.102, p = 0.001). The presence of current depression/anxiety disorders moderated the association between better SQ and subsequent lower NA; it was stronger for patients compared to controls (p = 0.003).

Limitations: Observational study design can only point to areas of interest for interventions.

Conclusions: This 2-week ambulatory monitoring study shows that, especially among depression/anxiety patients, better self-reported SQ predicts higher PA and lower NA the same day, while lower NA predicts better self-reported SQ. The value of mobile technologies to monitor and potentially intervene in patients to improve their affect should be explored.

1. Introduction

Depressive and anxiety disorders are highly prevalent psychiatric disorders (Zorn et al., 2017), associated with high disability (Vos et al., 2016), with at least a third of patients experiencing poor treatment outcomes (Gaynes et al., 2009). Disturbances in mood and sleep are core symptoms of affective disorders and are therefore intricately linked to each other (Kahn et al., 2013) .

Persons with affective disorders typically report low levels of positive affect (i.e., anhedonia) and high levels of negative affect (i.e., sad mood, guilt) on questionnaire and interview measures (American Psychiatric Association, 2013; Peeters et al., 2006). Sleep disturbances in affective disorders can entail difficulty initiating or maintaining sleep, or early morning awakening (insomnia), but also sleeping too much (hypersomnia), or both (Staner et al., 2006). As affect and sleep can fluctuate on a daily basis (Fung et al., 2014; Peeters et al., 2006), ambulatory assessments using mobile technologies (i.e., actigraphy devices and smartphones) may offer new opportunities to study the longitudinal

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day-to-day bidirectional associations between sleep and momentary affective states (i.e., positive and negative affect). With repeated measures throughout the day or even continuous data collection, high resolution data can be obtained that allows us to study associations within much smaller time-scales (within day or across days). Determining the extent to which sleep and affect interact on a daily level will provide additional insight and can inform on the usefulness of daily monitoring using mobile technologies and on target areas for (and timing of) user-feedback & micro-interventions.

Ecological Momentary Assessment (EMA) can provide detailed and frequent information on self-reported sleep quality and quantity, and on variations in mood and affect (Ebner-Priemer and Trull, 2009) assessed via a smartphone. This allows the examination of day-to-day bidirectional associations between self-reported sleep quality and affect. Better sleep quality has been found to predict improved affect in healthy controls as well as persons with depressive (Bouwmans et al., 2017; Bower et al., 2010; Triantafillou et al., 2019) and anxiety disorders (Triantafillou et al., 2019). Better affect has been found to be predictive of better self-reported sleep quality in both healthy controls as well as persons with depressive and anxiety disorders (Triantafillou et al., 2019).

Besides EMA, another ambulatory assessment, actigraphy, provides objective and daily measurements of a person's sleep quality and quantity in their living environments (Martin and Hakim, 2011). To date, less studies have examined the relationship between objectively assessed sleep and affect. Two studies found no bidirectional association between actigraphy-assessed sleep quality and mood in elderly (Parsey and Schmitter-Edgecombe, 2019) and between sleep duration and mood in a sample of persons with lifetime diagnosis of unipolar and bipolar depression and healthy controls (Merikangas et al., 2019). As in our previous study using the current sample we found that self-reported sleep and actigraphy-based sleep are often poorly correlated (Difrancesco et al., 2019), passive monitoring of sleep with wrist-worn actigraphy may provide new opportunities for sleep monitoring in patients with depression and anxiety.

The aim of this study was to investigate the (1) day-to-day bidirectional longitudinal association between sleep measures and positive and negative momentary affect from ambulatory assessments using mobile technologies, and (2) whether these associations differ in persons with and without current or remitted depression and/or anxiety disorders.

2. Method

2.1. Sample

Participants from the Netherlands Study of Depression and Anxiety (NESDA) were selected to participate in the Ecological Momentary Assessment (EMA) & Actigraphy sub-study (NESDA-EMAA). Details about NESDA have been provided extensively before (Penninx et al., 2008). NESDA was designed to investigate the course of depressive and anxiety disorders over a period of several years and the factors that influence the development and prognosis of such disorders. NESDA participants were initially included at the baseline assessment in 2004-2007 (n = 2981), and seen for the fifth time at the nine-year follow-up assessment wave (2014-2017, n = 1776) for a follow-up interview. At that time, also 367 siblings of NESDA participants were added, bringing the 9-year follow-up sample to 2143 subjects. At this wave, 384 participants enrolled for the EMAA sub-study. The NESDA study, including NESDA -EMAA, was approved by the VUmc ethical committee (reference number 2003/183) and all respondents gave informed consent for both the regular interview and the EMAA sub-study. See for a flowchart and details of the NESDA-EMAA in our previous work (Difrancesco et al., 2019; Schoevers et al., 2020).

Participants of the NESDA-EMAA study were asked to fill out the EMA assessments, an electronic diary on their smartphone, and to wear a wrist-worn actigraphy device (GENEActiv, Activinsights Ltd, Kimbolton, UK) for 14 days. In case participants did not possess a smartphone, or their phone was not suitable for participation (e.g. no internet bundle), a smartphone was provided for the duration of the study (n = 107, 27.9%). Participants of the EMA assessment completed a set of items 5 times a day (i.e. every 3 hours; fixed design). Of all sent EMA assessment invites to 384 participants, only 8.72% were missing. EMA data of 19 participants were excluded due to various reasons such as low response rate (response rate below 50%; in line with Servaas et al. (2017)) or technical failure, resulting in 365 participants with available data. Participants wore the wrist-worn GENEActiv actigraphy device on their non-dominant wrist, day and night. Of the 384 participants included in the NESDA-EMAA study, 14 had no available actigraphy data for several reasons, such as technical failure, resulting in 370 (96.4%) participants with available data. According to previously published criteria (da Silva et al., 2014), participant's actigraphy data were included in analyses if at least one week day and one weekend day of usable data was available, with at least 16 hours recorded per day and per night. The final sample was composed of 359 (93.5%) participants with on average 13.68 ± SE 1.26 valid days, of whom 90% of participants had complete 24-h actigraphy data for 14 days.

2.2. Assessment of depressive and/or anxiety disorders

As in the previous waves, at the 9-year follow-up, DSM-IV based diagnoses of depressive disorders (dysthymia and major depressive disorder) and anxiety (social anxiety disorder, panic disorder with and without agoraphobia, agoraphobia and generalized anxiety disorder) were established with the Composite International Diagnostic Interview (CIDI, version 2.1) (Wittchen, 1994). The interviews were conducted by specially trained clinical research staff. Participants were divided into three groups: 1) a group with no lifetime depressive and/or anxiety disorders, 2) a group with remitted depressive and/or anxiety disorders (having a lifetime, but not current (6-month) diagnosis), and 3) a group with current depressive or anxiety disorder in the past 6 months.

2.3. Ambulatory assessment variables

2.3.1. Positive and negative momentary affect states

EMA questionnaires were assessed five times a day and had up to 31 items per time point. They contained both momentary affect state items and other items on activities, context and lifestyle. To assess momentary affect states, items covering high and low arousal, positive and negative momentary affect states were used from the Uncovering the Positive Potential of Emotional Reactivity study (Bennik, 2015). Included items were: I feel satisfied, relaxed, upset, cheerful, irritated, listless, down, energetic, enthusiastic, nervous, bored, calm, and anxious. All items were rated on a 7-point Likert scale ranging from '1 = not at all' to '7 = very much'. As used previously (Schoevers et al., 2020), a positive affect (PA) subscale was calculated by taking the average of PA items (at this moment I feel satisfied, relaxed, cheerful, energetic, enthusiastic, and calm). Similarly, a negative affect (NA) subscale was calculated by averaging all NA items (at this moment I feel upset, irritated, listless/apathic, down, nervous, bored, anxious) (Schoevers et al., 2020).

2.3.2. Sleep variables

2.3.2.1. Actigraphy-assessed sleep. In this study, the accelerometer was set to sample at 30 Hz and raw actigraphy data was analyzed using an open source R package, GGIR (van Hees, 2017). As described before (Difrancesco et al., 2019), we used objective indicators of sleep: sleep efficiency per night [in %] and total sleep duration per night [in hh:mm]. The daily estimates were used in the current study. In short, objective sleep estimates were obtained using the GGIR package (van Hees, 2017) that uses an algorithm described extensively before (van Hees et al., 2018). This algorithm can distinguish whether inactivity

periods are sleep periods without the use of sleep diaries; the algorithm has been validated on a sample of the UK Biobank.

2.3.2.2. EMA-based sleep. Besides objectively assessed sleep duration, we also considered sleep variables collected in the EMA assessments, to get a full picture on how objective and self-reported measures relate. Self-reported sleep was assessed in each EMA questionnaire but for the purpose of this study were based on the first assessment of the day only. Included items were sleep duration ("How long did you sleep?" [in hh:mm]) and sleep quality. Sleep quality ("Did you sleep well?") was rated on a 7-point Likert scale ranging from '1 = not good' to '7 = very good'.

2.4. Covariates: age, sex and work/school days

Covariates were age, sex and work/school days at the time of the NESDA EMAA substudy. These covariates were selected as they have an established theoretical association with psychopathology and with sleep, circadian rhythm and physical activity levels, and have been regularly used in similar studies (Droomers et al., 2001; Stamatakis et al., 2007). Work/school days were identified with information from daily EMA assessment as participants were asked to document their location; if they reported their location to be at school/work at least once during a day it was counted as a work/school day.

2.5. Statistical analyses

For descriptive purpose, correlations between sleep variables were tested with Pearson's correlation.

Generalized estimating equation models (GEE) were used to test the bidirectional longitudinal association between momentary affect states assessed every three hours and EMA-based/actigraphy assessed sleep adjusting for age, sex and work days (a summary of the performed analyses is given in Fig. 1). Therefore, separate analyses were performed by first using momentary affect states (i.e., PA or NA) as outcome (Model 1) and then by using sleep variables (i.e., EMA-based sleep quality or EMA-based sleep duration or actigraphy-assessed sleep duration or actigraphy-assessed sleep efficiency) as outcome (Model 2). Although both short and long sleep duration (defined as ≤6 h and ≥10 h, respectively, (Levine et al., 2003)) are often reported in persons with depression/anxiety (Nutt et al., 2008; Zhai et al., 2015), a potential relationship between short and long sleep versus normal sleep (7 ≤ hours ≤ 9) and affect was not tested. This was not done as less than 10% of our participants slept ≥10 h in our sample (Difrancesco et al., 2019), making it impossible to have enough power to detect such effect. We therefore only used sleep duration as continuous variable in our analyses.

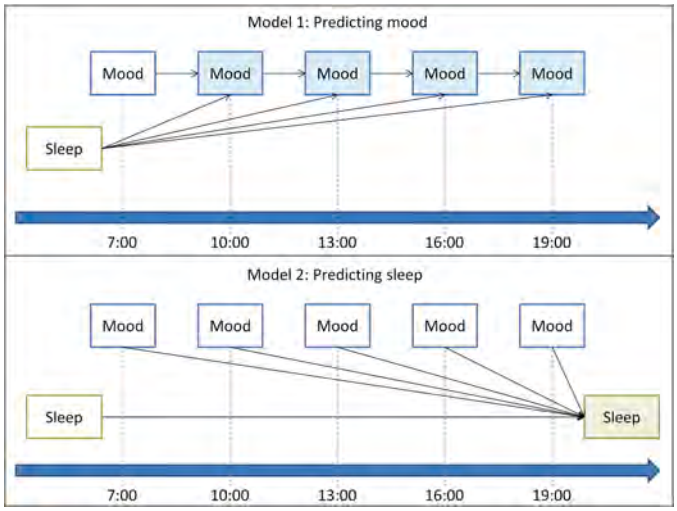

Fig. 1. Summary of the bidirectional longitudinal association between momentary affect states assessed every three hours and (actigraphy actigraphy assessed and EMA-based) sleep. The filled boxes indicate the outcomes. Note Model 1: as we included the previous affect affect state of the same day in the model, this variable is not present for the first assessment of the day and therefore not depicted as an arrow.

Data centring of momentary affect states and sleep variables was performed by within-person mean; therefore, estimates in the models indicate the effect of deviations of affect and sleep from the diurnal person-specific mean. The first-order autoregressive working correlation structure was chosen to take into account the within-person correlation over the 2-week observation period.

The same analyses were repeated to test for the moderating effect of current or remitted depressive and/or anxiety disorders. When moderation terms were significant, stratified analyses by diagnostic group were conducted to interpret and visualize the group effect.

Post-hoc analyses were performed to test the main effect and moderating effect of time of the day on the associations.

All analyses were performed with the statistical software R Studio (R Studio version 1.2.5033, R version 3.5) and the 'gee' library. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Demographics, ambulatory assessment variables and psychopathology

Table 1 and Fig. 2 show demographics, ambulatory assessment variables and psychopathology in the NESDA EMAA subsample. The average age was 49.5 ± 12.6 years, and 63.7% were females. Of the 16920 total EMA assessments, 32.7% were on work/school days. The median momentary affect states were 5 (IQR 1.5) and 1.3 (IQR 0.9) for positive and negative affect respectively. The median sleep quality was 5 (IQR 2), while the median sleep duration was 7.5 h (IQR 1.5 h) when assessed with EMA and 7.04 h (IQR 1.7 h) when assessed with actigraphy. The median actigraphy-assessed sleep efficiency was 90% (IQR 10%). Moderate significant correlations were found between EMA-based sleep quality and EMA-based sleep duration ($r = 0.41$, $p < 0.001$), and between EMA-based sleep duration and actigraphy-assessed sleep duration ($r = 0.50$, $p < 0.001$). Weak correlation was found between EMA-based sleep quality and actigraphy-assessed sleep duration ($r = 0.09$, $p < 0.001$).

Most of the persons included had a lifetime diagnosis of depressive and/or anxiety disorders: 93 (26.0%) persons had current depressive and/or anxiety disorders, 176 (49.0%) persons had remitted depressive and/or anxiety disorders and only 90 (25.0%) persons had no lifetime depressive and/or anxiety disorders.

3.2. Day-to-day longitudinal association between sleep and subsequent momentary affect states

Better sleep quality was predictive of subsequent higher positive

Table 1
Demographics and psychopathology in the NESDA sample.

	Sample
N	359
Demographic variables	
Age, mean (SD)	49.5 (12.6)
Female, n (%)	228 (63.7 %)
Psychopathology	
Depressive and/or anxiety disorders	
No, n (%)	90 (25.0 %)
Remitted, n (%)	176 (49.0 %)
Current, n (%)	93 (25.1 %)
Antidepressant use, n (%)	71 (19.7%)

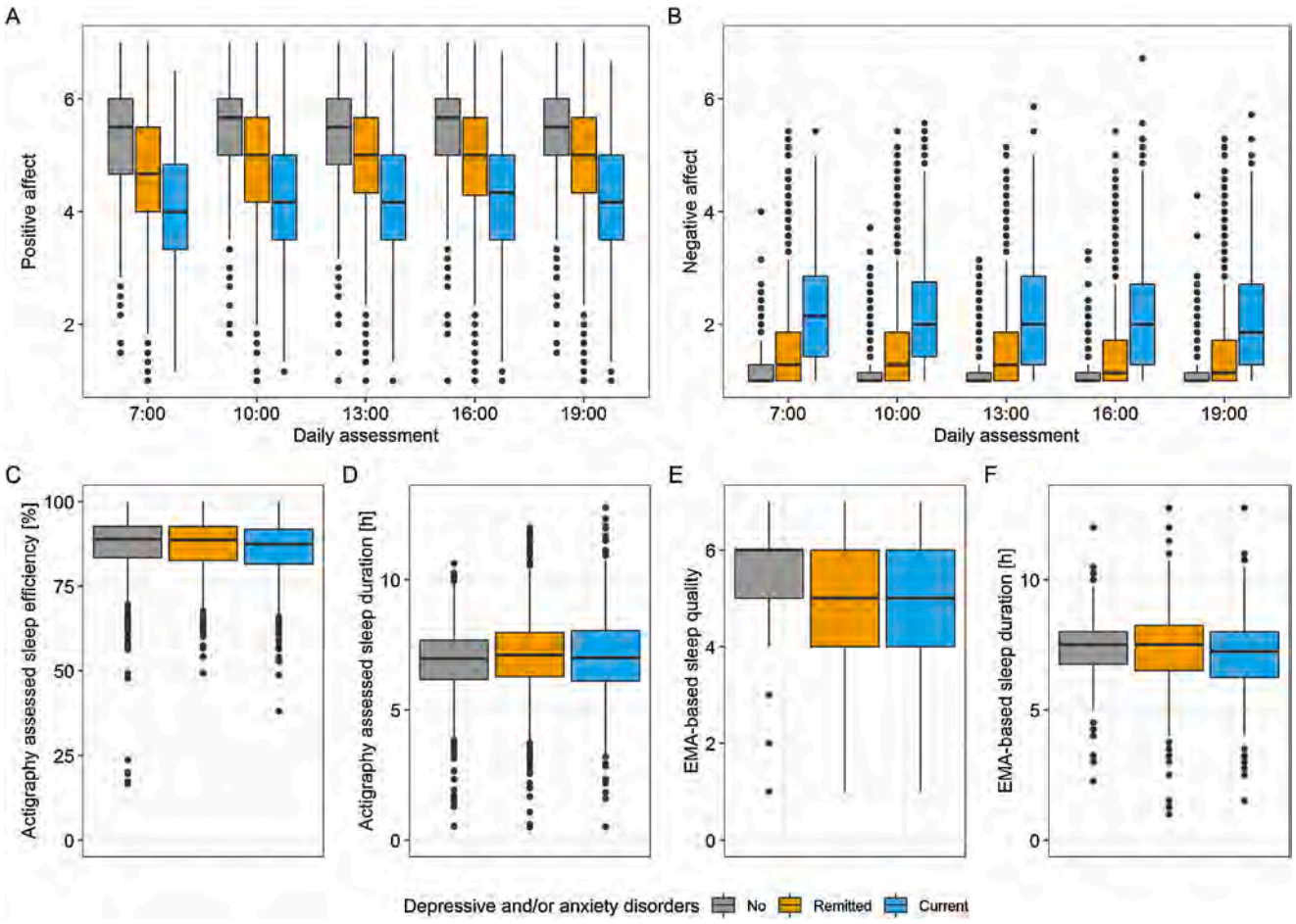

Fig. 2. Distribution of m momentary affect states and sleep variables in the NESDA sample (n = 359): positive (A) and negative (B) affect by daily assessment and by diagnosis, actigraphy assessed sleep variables by diagnosis (C = sleep efficiency, D = sleep duration), EMA E EMA-based sleep variables by diagnosis (E = sleep quality, F = sleep duration).

affect scores and lower negative affect scores the same day (Table 2, both $p < 0.001$). When testing the moderating effect of current or remitted depressive and/or anxiety disorders: having a current depressive and/or anxiety disorder moderated the relationship between better sleep quality and lower negative affect score, as the interaction term was statistically significant ($p = 0.003$, Supplemental Material, Table S1). As the interaction term was significant, we visualize group effects (Fig. 3): a more pronounced negative association was observed between better sleep quality and subsequent negative affect for the groups with current and remitted depressive and/or anxiety disorders. Self-reported and objective sleep duration were not predictive of subsequent affect the same day (Table 2), nor did current/remitted depressive and/or anxiety disorders have a moderating effect (Supplemental Material, Table S1 and Table S2). When adjusting for time of the day, results did not change. Time of the day did not moderate the associations (results not shown).

Table 2
Association between sleep and momentary affect states of the following day (n = 359).

	Positive affect			Negative affect		
	b	se	p	b	se	p
Predictor = EMA assessed sleep quality						
Sleep quality (t-1)	0.035	0.006	<0.001	-0.022	0.005	<0.001
Mood (t-1)						
Positive affect (t-1)	0.327	0.014	<0.001			
Negative affect (t-1)				0.350	0.020	<0.001
Predictor = EMA assessed sleep duration						
Sleep duration (t-1)	0.011	0.008	0.147	-0.008	0.005	0.161
Mood (t-1)						
Positive affect (t-1)	0.334	0.014	<0.001			
Negative affect (t-1)				0.356	0.020	<0.001
Predictor = Actigraphy assessed sleep efficiency						
Sleep efficiency (t-1)	0.198	0.120	0.099	-0.078	0.071	0.273
Mood (t-1)						
Positive affect (t-1)	0.335	0.014	<0.001			
Negative affect (t-1)				0.357	0.021	<0.001
Predictor = Actigraphy assessed sleep duration						
Sleep duration (t-1)	-0.002	0.006	0.785	0.004	0.004	0.256
Mood (t-1)						
Positive affect (t-1)	0.335	0.014	<0.001			
Negative affect (t-1)				0.357	0.021	<0.001

3.3. *Day-to-day longitudinal association between momentary affect states and subsequent sleep*

Higher score on positive affect and lower score in negative affect predicted better sleep quality the next day (Table 3, both $p < 0.01$). No interaction with current/remitted depressive and/or anxiety disorders was observed, suggesting that such associations do not depend on diagnostic group (Supplemental Material, Table S3). Affect states neither predicted self-reported and actigraphy assessed sleep duration (Table 3), nor did current/remitted depressive and/or anxiety disorders have a moderating effect (Supplemental Material, Table S3 and Table S4). When adjusting for time of the day, results did not change. Time of the day did not moderate the associations (results not shown).

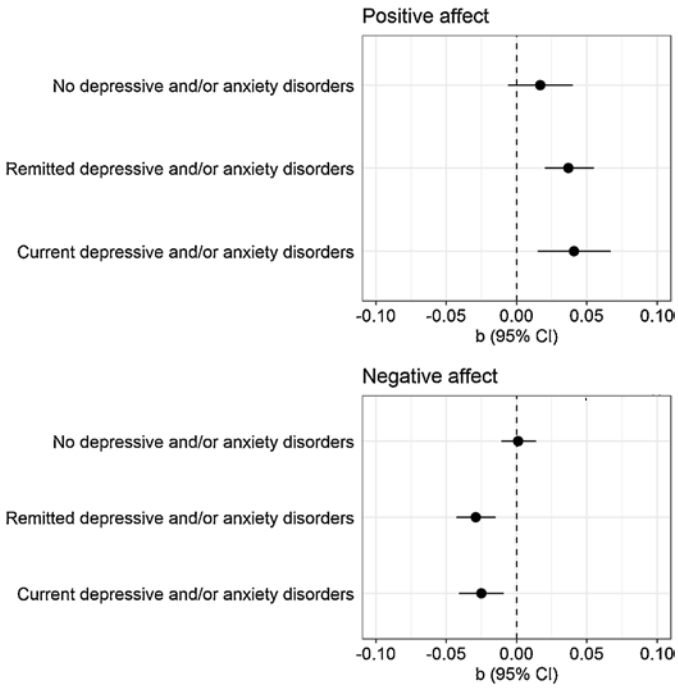

Fig. 3. Longitudinal association between EMA-based sleep quality and subsequent momentary assessment states stratified by diagnostic group.

Table 3
Association between momentary affect states and sleep of the following night (n = 359).

	Sleep			Sleep		
	b	se	p	b	se	p
Outcome = EMA assessed sleep quality						
Mood (t-1)						
Positive affect (t-1)	0.031	0.02	0.128			
Negative affect (t-1)				-0.102	0.031	0.001
Sleep quality (day-1)	-0.063	0.024	0.010	-0.066	0.024	0.006
Outcome = EMA assessed sleep duration						
Mood (t-1)						
Positive affect (t-1)	-0.003	0.019	0.870			
Negative affect (t-1)				-0.047	0.026	0.078
Sleep duration (day-1)	-0.085	0.021	<0.001	-0.086	0.021	<0.001
Outcome = Actigraphy assessed sleep efficiency						
Mood (t-1)						
Positive affect (t-1)	0.001	0.001	0.434	-0.001	0.002	0.523
Negative affect (t-1)						
Sleep efficiency (day-1)	-0.106	0.029	<0.001	-0.106	0.029	<0.001
Outcome = Actigraphy assessed sleep duration						
Mood (t-1)						
Positive affect (t-1)	-0.015	0.016	0.348			
Negative affect (t-1)				0.005	0.025	0.833
Sleep duration (day-1)	-0.111	0.028	<0.001	-0.111	0.028	<0.001

4. Discussion

This study examined the day-to-day bidirectional longitudinal association between self-reported and actigraphy-based sleep measures and momentary affect in a population with and without remitted or current depressive and/or anxiety disorders. Better self-reported sleep quality was predictive of improved affect the same day especially in persons with current depressive and/or anxiety disorders. On the other hand, better affect on the preceding day was predictive of higher self-reported sleep quality. No bidirectional longitudinal association was found between self-reported and actigraphy-based sleep duration and affect. Thus, the bidirectional associations between sleep quality and affect may highlight the potential of improving sleep quality as a target for affect improvement and regulation in patients with depression and anxiety by breaking the vicious circle.

This study supports previous findings on the bidirectional longitudinal relationship between sleep quality and affect. Similarly to our results, better self-reported sleep quality has been linked to subsequent increased positive affect and decreased negative affect (Bouwmans et al., 2017; Triantafillou et al., 2019), and better affect has been linked to improved sleep quality (Triantafillou et al., 2019) in individuals without and with depressive and anxiety disorders when using daily (electronic) diaries and EMA. Both cognitive and biological mechanisms may explain the relationship between poor sleep quality and affect. Sleep deprivation may impact on emotions with alterations in especially the limbic system. Rapid eye movement (REM) sleep has been suggested as a modulator of affective brain processes, offering a regulatory function which restructures experiences in an emotionally adaptive manner (Kahn et al., 2013). Emotional information and memory processing may also be relevant, as a negative remembering bias has been shown, by which individuals tend to remember negative but not positive experiences following loss of sleep (Kahn et al., 2013). Finally, the cognitive-energy model (Zohar et al., 2005) suggests that sleep loss depletes energy levels, thus disrupting adaptive affective responses to stress. On the other hand, there is also data to suggest that an individual's coping style and emotion regulation strategy (e.g., avoidant emotion regulation, rumination) may moderate the relationship between low mood and sleep loss (Kahn et al., 2013)

Interestingly, in our study better sleep quality was found to improve subsequent affect especially in persons with current depression and/or anxiety. Although some studies have found that history of depression and anxiety did not mediate the relationship (Bouwmans et al., 2017; Triantafillou et al., 2019), a possible explanation of our results is that individuals with an already vulnerable emotion-regulation system may experience even more adverse effects from poor sleep quality or more pronounced beneficial effects from better sleep quality (Harvey, 2011).

In contrast, no association was found between self-reported or actigraphy-based sleep duration and affect. These results seem to be consistent with other research which found no bidirectional association between affect and actigraphy-based sleep quality in an elderly population (Parsey and Schmitter-Edgecombe, 2019) and actigraphy-based sleep duration in a population with lifetime diagnosis of unipolar and bipolar depression (Merikangas et al., 2019). In line with our previous findings (Difrancesco et al., 2019), this study showed that the correlation between objective sleep duration and self-reported sleep quality was low and therefore objective and self-reported measures capture different aspects, enhancing the assessment of sleep.

While the current study looking at day-to-day associations did not observe associations between sleep duration and affect, sleep duration may nevertheless impact on affect. Results from meta-analyses on prospective longitudinal studies have shown that insomnia (Baglioni et al., 2011) and, both short and long vs normal sleep duration (Zhai et al., 2015), assessed with self-reported retrospective ratings, are longitudinally associated with increased risk of depression 6 months later. Therefore, self-reported sleep disturbances may have important long-term effects resulting in depression and worsening of depressive symptoms. More research is needed to understand the underlying biological mechanisms.

We observed bidirectional day-to-day effects between sleep quality and affect, possibly pointing to a vicious circle. A question for future studies is whether improving sleep quality may have positive outcomes on daily affect, especially in patients with depression and anxiety. As online psychological interventions have been shown to be effective for psychiatric disorders (Carlbring et al., 2018) and EMA can provide day-to-day assessments, EMA may be an add-on monitoring tool to (online) psychotherapy and Ecological Momentary Interventions (EMI). Specifically for insomnia, digital cognitive behavioral therapy (CBT-I)

can be administered to patients with depression and anxiety; self-reported sleep quality may be an indicator of treatment response. Mobile technologies may also be used to monitor patients more broadly. Similarly to the biofeedback-based treatments for insomnia, integrating mobile technologies with apps summarizing affect and sleep may provide feedback to patients. This may help raise patients' awareness, and may help them to gain control.

This study has limitations. First, the observational study design can only point to areas of interest for monitoring and interventions, but does not allow us to make definitive recommendations on such interventions. Future clinical trials may further investigate the application of mobile technologies to monitor and measure treatment response. While actigraphy is feasible, it only detects sleep based on wrist movement and therefore may not be optimal to measure sleep. As restless REM sleep has been identified as a potential target for treatment of mental disorders (Wassing et al., 2019), REM sleep may be a better indicator of objective sleep disruptions. Although antidepressant use can be seen as a confounder, it is also closely associated with severity of depression and anxiety (the most severe cases use it), therefore, using it as a covariate may be seen as an overcorrection. In addition, as we have previously shown, antidepressant use is not associated with sleep duration (Difrancesco et al., 2019). Important strength of the study is the use of mobile technology to study the bidirectional day-to-day relationships between objective and self-reported indicators of sleep and affect on a relatively large sample with CIDI-based depression and anxiety diagnoses. Another strength of this study is that it strongly supports previous research on the longitudinal association between sleep quality and affect.

To conclude, this 2-week intensive ambulatory assessment study using mobile technology has shown a bidirectional association between better self-reported sleep quality and better affect, while no bidirectional association was found between self-reported and actigraphy-based sleep duration and affect. Mobile technologies may be insightful tools to provide feedback to patients about their sleep and affect. Improving sleep quality may be an important target of treatment to enhance affect in patients with depression and anxiety. Future studies may investigate whether EMA technology measuring sleep quality can be used to monitor treatment outcomes in depression and anxiety.

5. Author Statement Contributors

S. Difrancesco, F Lamers, B. W. J. H. Penninx and H. Riese formulated the research questions. S. Difrancesco performed the data cleaning and the statistical analyses, interpreted the results, wrote the manuscript, and incorporated feedback from all co-authors. B. W. J. H. Penninx, F. Lamers reviewed and provided feedback in all drafts of the manuscript, and critically interpreted the results. H. Riese, A. M. van Hemert, N. Antypa contributed to the interpretation of results and revised the manuscript critically for important intellectual content. All authors approved of the final version of the paper.

Declaration of Competing Interest

None.

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Data Availability Statement

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

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.01.052.

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Familial resemblance in mental health symptoms, social and cognitive vulnerability, and personality: A study of patients with depressive and anxiety disorders and their siblings

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ABSTRACT

Background: Investigating siblings of probands with affective disorders enables the identification of psychopathology-related risk features. Leveraging data from an older adult sample, as compared to most previous sibling studies, enabled us to study more definitive clinical profiling across the lifespan. We examined prevalence of depressive/anxiety disorders in siblings, proband-sibling resemblance in psychopathology-related features, and whether unaffected siblings showed higher levels of these features than healthy controls.

Methods: The sample (N=929; M_{age}=50.6) consisted of 256 probands with lifetime depressive and/or anxiety disorders, their 380 siblings, and 293 healthy controls without affected relatives. Fifteen psychopathology-related features were investigated across four domains: mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality.

Results: Lifetime disorders were present in 50.3% of siblings. Prevalence was 2-3 times higher than Dutch population frequencies. We found small to medium probandsibling resemblance across psychopathology-related features (ρ=0.10-0.32). Unaffected siblings reported poorer interpersonal functioning and more negative life events, childhood trauma, and rumination than healthy controls.

Limitations: Due to the cross-sectional study design, the directionality of effects cannot be determined. No inferences can be made about potential differences in familial resemblance in psychopathology-related features between high- and low-risk families.

Conclusions: Siblings of probands with affective disorders are at higher risk for depressive/anxiety disorders. Even when unaffected, still show higher psychosocial vulnerability than healthy controls. Nevertheless, the only modest proband-sibling resemblance across psychopathology-related features suggests that individual mechanisms differentiate clinical trajectories across the lifespan. Identification of these mechanisms is crucial to improve resilience in subjects with familial risk.

1. Introduction

Depressive and anxiety disorders are highly prevalent disorders with a substantial impact on public health (Vos et al., 2012). One of the strongest risk factors for the onset of depressive and anxiety disorders is a family history of these disorders (Lawrence et al., 2019; Maciejewski

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et al., 2018; Rasic et al., 2014; Van Sprang et al., 2020). A two- to three-fold increased risk of these disorders is found in siblings of depressed and/or anxious probands as compared to persons without affected relatives (Li et al., 2011, 2008; Steinhausen et al., 2009). Due to shared genes and upbringing, at-risk siblings may also have elevated levels of features commonly associated with the development and onset of depressive and anxiety disorders (Goldstein and Klein, 2014), such as (subclinical) mental health symptoms (Holma et al., 2011; Tozzi et al., 2008), social vulnerabilities (e.g. poor interpersonal functioning, adverse events; Jansen et al., 2016; Watters et al., 2013; Zimmermann et al., 2008), cognitive vulnerabilities (e.g. cognitive reactivity, anxiety sensitivity; Aldao et al., 2010; Dong et al., 2018), and certain personality traits (e.g. neuroticism; Kotov et al., 2010). As such, these features may be important targets in preventative strategies in a high-risk population of unaffected siblings of affected probands.

There is little scientific insight into the degree of resemblance among probands with depressive and/or anxiety disorders and their siblings (i.e. proband-sibling resemblance) in (subclinical) mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality. Within at-risk families, higher proband-sibling resemblance in these features may increase the risk for depressive and anxiety disorders for all siblings in the family as probands' siblings may (have) experience(d) similar adversities. However, findings from previous studies in young adult samples investigating differences in these features between unaffected siblings and healthy controls have been inconsistent. While some studies found elevated vulnerability in unaffected relatives (i.e. depressive/anxiety symptoms, poor interpersonal functioning, childhood trauma, negative cognitive bias, neuroticism) as compared to healthy controls (Lauer et al., 1997; Modell et al., 2003; Van Oostrom et al., 2013; Watters et al., 2013), others found no differences between groups (i.e. depressive symptoms, state/trait anxiety, hopelessness, neuroticism, introversion; Farmer et al., 2002; Lauer et al., 1997; Modell et al., 2003; Ouimette et al., 1996). So, it remains unclear whether unaffected siblings have elevated (subclinical) mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality as compared to healthy controls.

The majority of previous sibling studies has been performed in children or young adult samples, when siblings still largely share their rearing environment. As compared to older adult samples, these studies have for example reported generally high estimates of proband-sibling resemblance in different subtypes of childhood trauma (Hines et al., 2006; MacMillan et al., 2013). However, it is unknown to what extent findings extend to older populations, in which long-term individual developmental trajectories and environmental factors may have impacted proband-sibling resemblance measured at younger age. Examining proband-sibling resemblance at relatively older age allows for an examination of more definite clinical profiles (e.g. psychiatric disorder status in siblings is more clear given the relatively long exposure time-frame) and individual differences that emerged across the lifespan. So far, the few studies in adult samples reported low to medium proband-sibling resemblance in depressive/anxiety symptoms, worry, hopelessness (Moskvina et al., 2008), introversion, and neuroticism (Farmer et al., 2002), and low to high proband-sibling resemblance in different subtypes of childhood trauma (Kullberg et al., 2020).

The present study aimed to assess familial resemblance in features commonly associated with the development and onset of depressive and anxiety disorders in a relatively older adult sample (mean age 51 years) including probands with lifetime depressive and/or anxiety disorders, their siblings, and healthy controls without affected relatives. First, we examined the prevalence of depressive and anxiety disorders in siblings. Second, we investigated the degree of proband-sibling resemblance in (subclinical) mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality within families with affected probands. Third, we examined whether unaffected siblings have elevated levels of these features as compared to healthy controls.

2. Methods

The present study is a substudy of the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study (2004-present) investigating the long-term course and consequences of depressive (i.e. major depressive disorder and dysthymia) and anxiety disorders (i.e. generalized anxiety disorder, panic disorder with and without agoraphobia, social phobia, and agoraphobia only). The NESDA baseline sample consisted of 2,981 participants, including 2,319 persons with a lifetime depression/anxiety diagnosis and 652 healthy controls. Participants were assessed in face-to-face interviews at baseline, and 2-, 4-, 6-, and 9-year follow-up. A detailed description of the NESDA study design and sampling procedure has been reported elsewhere (Penninx et al., 2008). The NESDA study protocol was approved by Medical Ethics Review Board of Amsterdam University Medical Centre, location Vrije Universiteit and by local review boards of each participating center - approval: 2003/183. All participants provided written informed consent. During the 9-year follow-up (2014-2017), siblings of lifetime affected participants were additionally recruited for the NESDA family study (NESDA-FS) to investigate the development of psychopathology, psychosocial functioning, and health (behavior) within the family context.

2.1. Sample and procedure

The sample used in this study included 929 participants, of whom 256 probands with lifetime depressive and/or anxiety disorders, their 380 siblings, with and without a lifetime depressive and/or anxiety disorders (hereafter referred to as 'affected siblings' and 'unaffected siblings', respectively), and 293 unrelated healthy controls. In siblings, lifetime depressive and/or anxiety disorders were assessed with the Composite Interview Diagnostic Instrument (CIDI, see below; WHO) at 9-year follow-up and indicated the presence of current disorder(s) or disorder(s) earlier in life.

See *Figure S1* of the supplementary materials for an inclusion flowchart of probands, siblings, and healthy controls into NESDA-FS. Inclusion criteria for probands of which siblings were invited were: (i) a depressive and/or anxiety disorder diagnosis (i.e. current, in between two waves, or earlier in life before baseline) assessed with the CIDI on at least two NESDA waves; (ii) 100% the same biological parents as their siblings; (iii) participated in at least three out of four NESDA face-to-face interviews prior to the 9-year follow-up (i.e., from baseline to 6-year follow-up); (iv) availability of genetic data; (v) provided approval of contacting siblings for research purposes; and (vi) participated at the 9-year follow-up face-to-face interview. The requirement of a diagnosis at two or more waves was chosen in order to ensure that there was at least some psychiatric burden in the patient. For instance, we wanted to prevent including targets and their siblings, where the target only suffered from a mild depressive episode 20 years ago. Moreover, our data showed that a vast majority of our lifetime affected targets fulfilled the criteria of having a diagnosis during at least two waves (61.83%), which is in line with the finding that that depressive and anxiety disorders are usually quite chronic conditions with frequent recurrences over an extended time (Verduijn et al., 2017).

Siblings of probands were included if they were: (i) currently living in the Netherlands; (ii) aged between 18 and 78 years; and (iii) consented to participate in a face-to-face interview. Most siblings were recruited at 9-year follow-up (N=367), but were enriched with 13 siblings of 10 probands that already participated in the original NESDA cohort based on genetic data. Unrelated (from each other and from siblings/probands) healthy controls from the original NESDA cohort were selected as a comparison group if they had: (i) no lifetime depressive and/or anxiety disorder diagnosis at any of the NESDA waves; and (ii) no parent and/or sibling with a lifetime depressive and/or anxiety disorder based on the Family Tree Inventory (Fyer and Weissman, 1999) or pedigree data.

Based on the inclusion criteria, 540 probands were excluded due to drop-out at the 9-year follow-up face-to-face interview, a further 622 were excluded because they did not give permission to contact their siblings, 3 were excluded because they did not participate in two of the first four NESDA face-to-face assessment, 25 were excluded because they did not have 100% the same biological parents, and 361 were excluded because they had a diagnosis at fewer than two NESDA waves. Of these 768 targets, siblings were approached (N=2027). Of those, 367 were eligible and agreed to participate. We compared included and excluded lifetime-affected targets on sex, age, and years of education. Results showed that included targets were significantly more often female (73% versus 67%; $p = .05$), younger (39.45 years versus 42.05 years; $p = .003$), and had more years of education (12.89 versus 11.91; $p < .001$). In our analyses, we controlled for these covariates. Healthy controls were mainly derived from the 9-year follow-up (N=219) but were enriched with unrelated controls of whom we had baseline data (N=74) to match the proband, sibling, and healthy control groups on age.

2.2. Measures

An overview of time points of assessment of the instruments can be found in *Table S1* in the supplementary materials. The present study used data mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality from the 9-year follow-up for most participants, that is, probands, their siblings, and healthy controls identified for NESDA-FS at 9-year follow-up; healthy controls identified at baseline were included with baseline data. However, for probands and healthy controls identified for NESDA-FS at 9-year follow-up, baseline or 6-year follow-up data were used for measures that were not administered at the 9-year follow-up in these participants. A detailed description of scale- and variable characteristics, including information on missing data, can be found in *Table S2* and *Table S3* of the supplementary materials. In the present sample, the internal consistency of (subscale) sum-scores was adequate to excellent (range α=.71-.96), except for neuroticism (α=.64).

2.2.1. Psychopathology

The presence of lifetime and current DSM-IV-TR (Association American Psychiatric, 2000) diagnoses of depressive and anxiety disorders was determined using the CIDI (lifetime version 2.1; WHO). The CIDI is a comprehensive diagnostic instrument developed for use in epidemiological studies with high validity for depressive and anxiety disorders (Wittchen, 1994). For the affected targets, the CIDI that was conducted at baseline assessed lifetime depressive and/or anxiety. The CIDI at the following waves assessed depressive and/or anxiety disorders since the previous assessment. A lifetime disorder was defined as either a lifetime disorder at baseline and/or a disorder since the previous assessment at the subsequent waves (based on all available waves from baseline to 9-year follow-up). For siblings, a lifetime diagnosis was based on a one-time lifetime CIDI interview. A lifetime diagnosis was operationalized as any depression or anxiety disorder that met DSM criteria and that took place earlier in life.

2.2.2. Mental health symptoms

The Inventory of Depressive Symptomatology-Self Report (IDS-SR; Rush et al., 1996) was used to assess past week severity and number of depressive symptoms. The IDS-SR contains all symptoms of depressive disorder as defined by the DSM-IV-TR (Association American Psychiatric, 2000) and symptoms commonly associated with depression. Past week severity of panic symptoms was measured using the Beck Anxiety Inventory (BAI; Beck et al., 1988). The Fear Questionnaire (FQ; Marks and Mathews, 1979) was used to assess the level of external avoidance behavior, reflecting the severity of phobia symptoms.

2.2.3. Social vulnerabilities

Poor interpersonal functioning was measured with the short version of the Inventory of Interpersonal Problems (IIP-32; Barkham et al., 1996), which assesses a person's most salient interpersonal problems on eight different domains: hard to be assertive, hard to be sociable, hard to be supportive, too caring, too dependent, too aggressive, hard to be involved, too open (Barkham et al., 1994). The List of Threatening Experiences (LTE) was used to assess the total number of past-year exposures to two different types of negative life events: (i) independent events, which are independent of a person's symptoms and unlikely to be influenced by the person as they are usually outside of a person's control (e.g. death of a loved one) and (ii) dependent events, which are likely, but do not have to be, influenced by a person and are therefore more controllable (e.g. job loss; Brugha et al., 1985; Liu, 2013; Maciejewski et al., 2021). The Childhood Trauma Questionnaire-Short Form (CTQ-SF; Bernstein et al., 2003) was used to assess childhood trauma before the age of 16 on five domains of trauma: sexual abuse, physical abuse, emotional abuse, physical neglect, and emotional neglect.

2.2.4. Cognitive vulnerabilities

The extent to which persons worry frequently and extensively was assessed with a shortened version of the Penn State Worry Questionnaire (PSWQ; Meyer et al., 1990), which included positively scored items of worry engagement only. Hopelessness and rumination were measured using subscales of the Leiden Index of Depression Sensitivity-Revised (LEIDS-R questionnaire; Van Der Does, 2002), which assessed cognitive reactivity to sad mood. The Anxiety Sensitivity Index (ASI; Peterson and Reiss, 1992) was used to assess anxiety sensitivity, reflecting the extent to which persons fear potentially negative consequences of anxiety-related somatic sensations. Consistent with previous NESDA studies (Drost et al., 2012; Struijs et al., 2018), two subscales of the ASI were used: physical concerns and social-cognitive concerns.

2.2.5. Personality

The Dutch NEO-FFI (Hoekstra et al., 1996) was used to assess two personality domains: neuroticism, the propensity to experience negative emotions, and introversion, the tendency to behave in a reserved and solitary fashion. The Mastery Scale (Pearlin and Schooler, 1978) was used to assess external locus of control, which represents the degree to which persons believe that outcomes in their lives are mainly due to chance or fate.

2.3. Statistical analyses

First, psychopathology risk in siblings of probands (research aim 1) were reported as current (past 12-month) and lifetime prevalence (%) of depressive and anxiety disorders and, as a 'bench-mark', compared to population-based estimates as assessed by the national representative and large-scale (N=6,646) Netherlands Mental Health Survey and Incidence Study (NEMESIS; De Graaf et al., 2012). For this, no formal statistical testing was used. The assessment of psychopathology was similar between NEMESIS and NESDA. Both used information on only one CIDI assessment that measured both lifetime as well as current recency of diagnoses. The NESDA sibling sample had a mean age of 50.5 years (SD = 13.25; range = 20-78), 62% were female, and the sample had on average 13.2 years of education (SD = 3.2; range = 6-18). The NEMESIS-2 sample (De Graaf et al., 2012) had a mean age of 44.3 years (SD = 12.5; range = 18-64) and 55% were female. The study did not provide data on years of education. However, similar with NESDA, the level of education was quite high, with 35.3% of participants having completed higher professional education (i.e., university).

For subsequent analyses (research aims 2 and 3), multilevel regression analyses were conducted using clustered bootstrapping (5000 bootstrap samples) and with 'family-ID' as random intercept to account for within-family clustering. To investigate the degree of resemblance among probands and their siblings in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality (research aim 2), intraclass correlations (ICC) were calculated, which have previously

been used as indicators of familial/proband-sibling resemblance in (genetic) epidemiology (see e.g. Farmer et al., 2002; Ferentinos et al., 2015; Kullberg et al., 2020; Moskvina et al., 2008). A total of 15 ICCs, one for each outcome measure, was calculated by dividing the between-family variance by the total family variance of a measure. Family variance components were obtained from unconditional means models. Based on previous research, ICC values <0.15 were considered as 'small', values ≥0.15 and <0.3 as 'medium', and values ≥0.3 as 'large' resemblance among probands and siblings of the same family (Bliese, 2000; James, 1982). If ICC values were significantly different from zero, this indicated the presence of proband-sibling resemblance. We controlled ICCs for covariates age, gender, and years of education to reduce residual error (Shoukri et al., 2013). Then, to test whether unaffected siblings showed elevated mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality as compared to healthy controls (research aim 3), 15 multilevel regression models were assessed: one for each outcome measure, with a group identifier (healthy controls '0' vs. unaffected siblings '1') added as predictor, and age, gender, and years of education as covariates. All *p*-values were derived from bootstrapped 95% confidence intervals (CI) according to a method described by Altman and Bland (Altman and Bland, 2011). The Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) was applied to the 15 outcome measures tested within the two research aims to correct for multiple testing. False discovery rate (FDR)-corrected *p*-values <.05 were considered to be statistically significant. Participants with missing values for an outcome measure were removed from the analyses for that measure (see *Table S2* of the supplementary materials for detailed information on missing data).

Data cleaning, preparation, and subsequent analyses were performed in R version 3.6.1 (Team, 2018). This paper, including the R code for the analyses, was pre-registered on the Open Science Framework (https://osf.io/9vn68/?view_only=fc54de1af6d94e6eb8bd50244fdaa291).

3. Results

3.1. Descriptive statistics

Family characteristics are reported in *Table 1*. The total of 256 proband-sibling families consisted of 2 (*N*=168 families), 3 (*N*=61 families), 4 (*N*=20 families), 5 (*N*=5 families), and 6 (*N*=2 families) family members. The sibling constellation was mixed-sex for 53.1%, female-only for 35.9%, and male-only for 10.9% of the families. For 90.6% of families, the maximum absolute age difference between probands and siblings from the same family ranged from 0 to 10 years. In the remaining families (9.3%), this difference ranged from 11 to 19 years.

Table 1
Family characteristics of proband-sibling families (*N*=256).

Family characteristics	*N*	%
Number of participating siblings[a] per family		
2	168	65.6
3	61	23.8
4	20	7.8
5	5	1.9
6	2	0.8
Total number of siblings[a,b] per family		
2	82	32.0
3	73	28.5
4	43	16.4
5	23	9.0
6	21	8.2
≥7	15	5.9
Gender constellation of siblings[a] per family		
Same sex – male	28	10.9
Same sex – female	92	35.9
Mixed sex	136	53.1
Maximum age difference between siblings[a] per family		
0-5 years	147	57.4
6-10 years	85	33.2
11-15 years	18	7.0
16-19 years	6	2.3

[a] Including probands.
[b] Based on Family Tree Inventory (Fyer and Weissman, 1999) data from the 9-year follow-up of NESDA.

The mean age of the sample (*N*=929) was 50.6 years (*SD*=13.4, range 20-78), mean years of education was 13.2, and 61.9% was female. Sample characteristics of the healthy control, sibling, and proband groups can be found in *Table 2*. Unaffected siblings were more often male as compared to healthy controls (*p*=.001), but did not differ in age (*p*=.100) and years of education (*p*=.366). At 9-year follow-up, 37.5% (96/265) of probands had a current (12-month) depressive and/or anxiety disorders, while 62.5% (160/256) was remitted.

3.2. Prevalence of depressive and anxiety disorders in siblings

Table 3 displays current (12-month) and lifetime prevalence of depressive and anxiety disorders in (i) siblings of lifetime depressed and/or anxious probands in the present sample and (ii) the Dutch population as found in the NEMESIS study (De Graaf et al., 2012). Of the 380 siblings included, 50.3% had a lifetime depressive and/or anxiety disorder (i.e. 'affected siblings'), while 49.7% had not (i.e. 'unaffected siblings'). As compared to what would be expected based on Dutch population frequencies, siblings of lifetime depressed and/or anxious probands showed a higher prevalence of current (26.8% vs. 10.0%; ~2.7 times higher) and lifetime (50.3% vs. 26.9%; ~1.9 times higher) depressive and/or anxiety disorders. Prevalence was higher quite similarly for all diagnoses. Specifically, current disorders were present in 13.2% of siblings for any depressive disorder (vs. 5.3% of the Dutch population; ~2.5 times higher) and in 19.5% of siblings for any anxiety disorder (vs. 6.3% of the Dutch population; ~3.1 times higher). Lifetime disorders were present in 38.9% of siblings for any depressive disorder (vs. 18.9% of the Dutch population; ~2.1 times higher) and in 31.1% of siblings for any anxiety disorder (vs. 15.1% of the Dutch population; ~2.1 times higher). The risk for specific diagnoses was between ~1.6 (15.3% vs. 9.3% of the Dutch population; lifetime social phobia) and ~3.3 times higher (12.6% vs. 3.8% of the Dutch population; lifetime panic disorder); the risk of current panic disorder, current and lifetime agoraphobia, and lifetime dysthymia appeared to be substantially higher (6.6% vs. 1.2% to 3.7% vs. 0.4%; ~5.7 to ~9.3 times higher) but was based on relatively low numbers of cases (*N*=14 to *N*=34). Affected siblings were more often diagnosed with current social phobia as compared to probands (*p*=.005), but did not differ in prevalence of other current anxiety or depressive disorders (all *p*>.06; results not shown). Overall, as indicated in the Methods section, the NEMESIS sample slightly differs from NESDA, which has slightly older participants and more females. We know from previous research that females have a higher rate of depression and anxiety and that the chance of a lifetime depression increases with age, which might have resulted in slightly more diagnoses in the sibling sample.

When comparing the affected targets with the affected siblings on diagnoses, results showed that 59% of targets had a lifetime comorbid diagnosis (versus 30% of affected siblings), 16% of targets had a lifetime pure anxiety disorder (versus 23% of affected siblings), and 24% of targets had a lifetime pure depressive disorder (versus 38% of affected siblings). These results indicate that siblings more often suffered from lifetime pure diagnoses, whereas the targets suffer more from comorbid diagnoses

3.3. Proband-sibling resemblance in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality

Fig. 1 shows the standardized covariate-adjusted ICCs of the 15 mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality traits, reflecting the degree of proband-sibling

Table 2
Socio-demographics, mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality for healthy control, sibling, and proband groups.

	Healthy controls N=293		Unaffected siblings N=189		Affected siblings N=191		Probands N=256	
	M	SD	M	SD	M	SD	M	SD
Socio demographics								
Female (N; %)	178	60.8	85	45.0	124	64.9	188	73.4
Age	52.60	13.68	50.66	13.57	50.27	12.96	48.52	13.10
Years of education	13.07	3.28	13.30	3.36	13.04	3.08	13.42	2.99
Mental health symptoms								
Depressive symptoms	7.33	6.63	8.36	6.44	18.05	10.55	16.49	10.61
Panic symptoms	0.88	1.71	0.80	1.37	3.13	3.61	3.00	3.31
Phobia symptoms	7.99	10.46	8.67	9.26	18.53	15.26	17.81	15.23
Social vulnerabilities								
Poor interpersonal functioning	17.34	14.30	22.06	13.12	35.79	17.99	33.91	18.05
Past-year negative life events – Independent	0.30	0.55	0.49	0.71	0.41	0.63	0.30	0.60
Past-year negative life events – Dependent	0.13	0.39	0.27	0.60	0.28	0.57	0.21	0.54
Childhood trauma	32.61	8.82	34.14	7.54	40.46	11.08	38.75	11.36
Cognitive vulnerabilities								
Worry	18.12	8.02	19.81	7.31	29.19	10.61	28.12	11.10
Hopelessness	1.12	2.05	1.42	1.90	3.58	4.06	3.70	3.56
Rumination	3.04	3.70	4.42	3.47	8.17	4.63	7.84	4.53
Anxiety sensitivity – Physical concerns	2.72	3.64	3.21	3.76	5.95	5.42	5.91	6.04
Anxiety sensitivity – Social-cognitive concerns	3.38	2.63	4.04	2.68	5.78	3.87	5.76	3.71
Personality								
Neuroticism	25.74	7.24	25.98	7.24	34.45	8.38	38.18	8.02
Introversion	29.85	6.43	30.93	6.72	34.38	7.06	35.37	6.99
External locus of control	8.19	3.57	8.89	3.59	12.07	4.37	11.20	4.26

Note. Sample sizes vary slightly due to marginally missing data on mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality (see *Table S1* in the supplementary materials). *M* = mean; *SD* = standard deviation.

Table 3
Current (12-month) and lifetime prevalence of depressive and anxiety disorders in siblings of lifetime depressed and/or anxious probands as compared to population-based estimates as assessed by the national representative and large-scale Netherlands Mental Health Survey and Incidence Study (NEMESIS; De Graaf et al., 2012).

	Current (12-month) prevalence		Lifetime prevalence	
	At-risk siblings *N*=380	General population[a] *N*=6,646	At-risk siblings *N*=380	General population[a] *N*=6,646
Diagnosis	%	%	%	%
Any depressive disorder	13.2	5.3	38.9	18.9
Major depressive disorder	12.4	5.2	38.2	18.7
Dysthymia	2.4	0.9	8.9	1.3
Any anxiety disorder	19.5	6.3	31.1	15.1
Generalized anxiety disorder	4.5	1.7	9.2	4.5
Panic disorder with or without agoraphobia	6.8	1.2	12.6	3.8
Social phobia	9.7	3.8	15.3	9.3
Agoraphobia only	3.7	0.4	7.1	0.9
Any depressive and/or anxiety disorder	26.8	10.0	50.3	26.9

Note. Permission to replicate (part of) the original table from the NEMESIS study has been given to the authors by M. Ten Have on April 22, 2020. No statistical testing was used for this comparison.
[a] Weighted figures. NEMESIS participants were aged 18-64 years.

resemblance in these features. Higher values indicate stronger resemblance among probands and siblings from the same family. The majority of features consistently showed some degree of proband-sibling resemblance (all *ps*<.05), with comparable ranges of small to medium ICCs (mental health symptoms: range 0.10-0.19; social vulnerabilities: range 0.10-0.32; cognitive vulnerabilities: range 0.06-0.21; personality: range 0.06-0.19). Thus, 6-32% of the variance in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality was explained by the family. The highest proband-sibling resemblance was found for childhood trauma (ρ=0.32, p<.001). ICCs of anxiety sensitivity – social-cognitive concerns (ρ=0.06, p=.116) and neuroticism (ρ=0.06, p=.116) were small and not significantly different from zero, indicating that probands and siblings from the same family do not resemble each other more in their reports of these vulnerabilities as compared to randomly chosen other persons in the analytic sample.

3.4. Group differences in mental health symptoms, social vulnerabilities cognitive vulnerabilities, and personality

Table 4 displays the standardized effects sizes of multilevel regression analyses that were computed to test for differences in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality between unaffected siblings of lifetime depressed and/or anxious probands and healthy controls. Unaffected siblings reported poorer interpersonal functioning (γ=0.41, p<.001), more independent (γ=0.29, p=.027) and dependent past-year negative life events (γ=0.27, p=.031), childhood trauma (γ=0.28, p=.030), and rumination (γ=0.37, p<.001), as compared to healthy controls. No significant differences were found between unaffected siblings and healthy controls on other measures of cognitive vulnerability, nor on any measures of the mental health symptom or personality domains. As expected, unaffected siblings reported significantly lower levels on most measures (all *ps*<.001, except for reporting more independent past-year negative life events [p=.018] and no difference in dependent past-year negative life events [p=.396]), as compared to their affected siblings (including probands; see *Table 5*).

4. Discussion

The present study showed that siblings of probands with depressive and/or anxiety disorders are at higher risk for the same psychopathology: lifetime disorders were present in 50.3% of siblings, which is higher than the lifetime population prevalence of 26.9% in the Netherlands (De Graaf et al., 2012). We consistently found small to medium proband-sibling resemblance across the majority of mental health

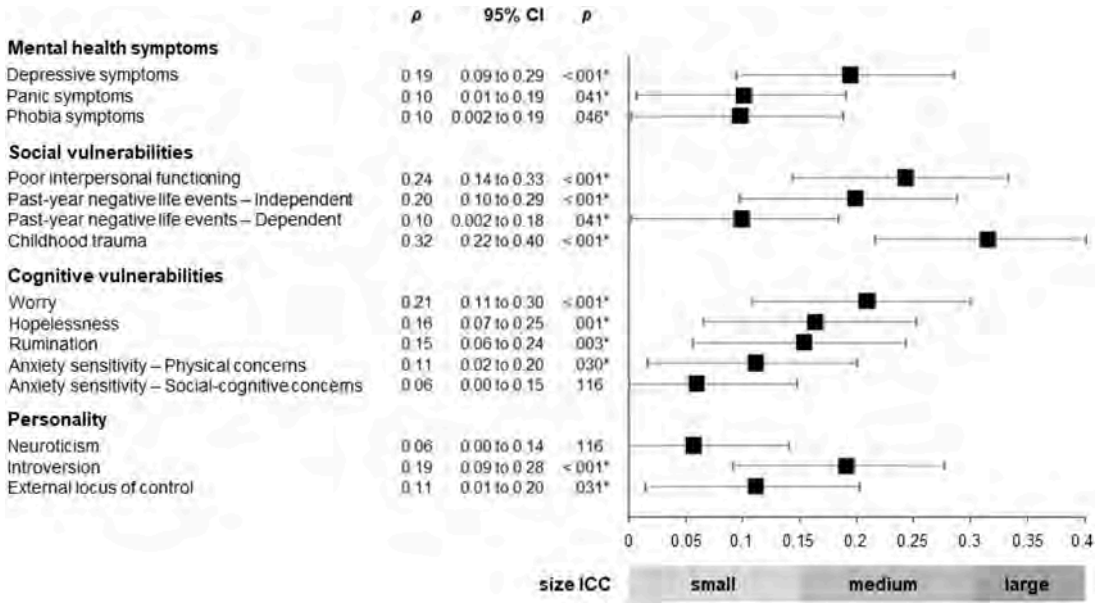

Fig. 1. Estimates (ρ) of standardized covariate adjusted intraclass correlations (ICC), reflecting the degree of proband-sibling resemblance for measures of mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality, with higher values indicating a higher degree of resemblance among probands and siblings from the same family ('small': $\rho<0.15$, 'medium': $0.15\leq\rho<0.3$, and 'large': $\rho\geq0.3$; Bliese, 2000; James, 1982). ICCs were calculated by dividing the between-family variance of an outcome measure by the total family variance of that measure. Family variance components were obtained from unconditional means models, controlled for covariates age, gender, and years of education to reduce residual error (Shoukri et al., 2013). 95% confidence intervals (CI) were obtained with bootstrapping for mixed models using 5000 bootstrap samples. *p*-values were derived from the bootstrapped 95%CIs according to a method described by Altman and Bland (Altman and Bland, 2011). The Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) was applied to the 15 outcome measures tested within this research aim to correct for multiple testing. False discovery rate (FDR)-corrected *p*-values are reported. Sample sizes vary slightly due to marginally missing data on the 15 outcome measures (see *Table S1* in the supplementary materials).
Note that these analyses included all siblings, irrespective of their diagnosis ($N = 256$ targets, $N = 380$ siblings).
* Significantly different from zero after correction for multiple testing with FDR<.05.

symptoms, social vulnerabilities, cognitive vulnerabilities, and personality traits, with highest resemblance in childhood trauma. Unaffected siblings showed poorer interpersonal functioning, more past-year negative life events, and higher levels of childhood trauma and rumination, as compared to healthy controls, but did not significantly differ in mental health symptoms, (most) cognitive vulnerabilities, and personality traits. Our findings implicate that siblings of lifetime depressed and/or anxious probands may (have) experience(d) similar adversities, but that substantial individual differences exist between siblings from the same family. Despite their familial disposition and enhanced social and cognitive vulnerability, half of the siblings were unaffected, which can teach us important insights into resilience.

4.1. *Prevalence of depressive and anxiety disorders in siblings*

The prevalence of current (26.8%) and lifetime (50.3%) depressive and/or anxiety disorders in siblings of lifetime depressed and/or anxious probands was substantial, and higher as compared to population frequencies in the Netherlands (10.0%, ~2.7 times higher and 26.9%, ~1.9 times higher respectively; NEMESIS; De Graaf et al., 2012). Our findings are comparable to the two- to three-fold increased risk found in previous sibling (Li et al., 2011, 2008) and family studies (Steinhausen et al., 2009). Furthermore, in line with previous studies (Li et al., 2011, 2008; Steinhausen et al., 2009), prevalence in siblings was higher to a similar extent for any depressive (current ~ 2.5 times higher; lifetime ~2.1 times higher) and any anxiety disorder (current: ~ 3.1 times higher; lifetime: ~2.1 times higher). Overall, given that our study is one of the few relatively large studies that thoroughly investigated multiple affected and unaffected siblings per family, our findings are important as they provide detailed insight into the risk for (specific) depressive and/or anxiety disorders in an at-risk group of siblings of lifetime depressed and/or anxious probands.

4.2. *Proband-sibling resemblance in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality*

Our findings show that, to a certain extent, mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality traits pose a family-wide problem. The consistent small to medium proband-sibling resemblance across features indicates that siblings of lifetime depressed and/or anxious probands may (have) experience(d) similar adversities, without a clear distinction in the degree of resemblance between domains, but that substantial individual differences exist between siblings from the same family.

The overall modest resemblance among probands and siblings is consistent with evidence from behavioral-genetic research suggesting an increased role across the lifespan for individual environments and unique risk and protective factors (Plomin, 2011; Plomin et al., 2001; Plomin and Daniels, 2011, 1987) in shaping behavioral, psychological, and personality features. This is corroborated by longitudinal twin studies that found increases in phenotypic variance in personality (Kandler et al., 2010; Laceulle et al., 2013; Viken et al., 1994) and depressive/anxiety symptoms (Kendler et al., 2011; Nivard et al., 2015) as a result of increasing nonshared environmental effects across the lifespan. It is therefore conceivable that the magnitude of proband-sibling resemblance in the features measured in the present study, in which participants were aged on the upper end of the age-range in which most first onsets appear (De Graaf et al., 2012), may vary over the course of the lifetime, with a higher degree of resemblance when estimated at younger age. Indeed, previous studies in younger samples have reported generally higher estimates of proband-sibling resemblance for depressive/panic/phobia symptoms, worry, hopelessness (Moskvina et al., 2008), subtypes of childhood trauma (Hines et al., 2006; MacMillan et al., 2013), neuroticism, and introversion (Farmer et al., 2002).

Table 4
Differences in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality between unaffected siblings and healthy controls.

	Unaffected siblings (*N*=189) vs. Healthy controls (*N*=293)		
	Estimate	95% CI	*p*
Mental health symptoms			
Depressive symptoms	0.20	0.003 to 0.40	.072
Panic symptoms	-0.02	-0.21 to 0.16	1.000
Phobia symptoms	0.14	-0.04 to 0.33	.155
Social vulnerabilities			
Poor interpersonal functioning	0.41	0.20 to 0.61	<.001*
Past-year negative life events – Independent	0.29	0.09 to 0.50	.027*
Past-year negative life events – Dependent	0.27	0.06 to 0.48	.031*
Childhood trauma	0.28	0.07 to 0.49	.030*
Cognitive vulnerabilities			
Worry	0.22	0.03 to 0.40	.051
Hopelessness	0.21	0.02 to 0.39	.052
Rumination	0.37	0.18 to 0.55	<.001*
Anxiety sensitivity – Physical concerns	0.14	-0.06 to 0.35	.184
Anxiety sensitivity – Social-cognitive concerns	0.22	0.03 to 0.42	.051
Personality			
Neuroticism	0.07	-0.12 to 0.26	.517
Introversion	0.19	-0.003 to 0.38	.072
External locus of control	0.20	0.01 to 0.39	.062

Note. Sample sizes vary slightly due to marginally missing data on mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality (see *Table S1* in the supplementary materials). Standardized estimates and 95% confidence intervals (CI) were retrieved from multilevel regression models fitted with clustered bootstrapping using 5000 bootstrap samples, with a random intercept of family ID and age, gender, and years of education added as covariates. *p*-values were derived from bootstrapped 95%CIs according to a method described by Altman and Bland (Altman and Bland, 2011). The Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) was applied to the 15 outcome measures tested within this research aim to correct for multiple testing. False discovery rate (FDR)-corrected *p*-values are reported. CI=confidence interval.
* Significant after correction for multiple testing with FDR<.05.

Table 5
Differences in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality between unaffected siblings and affected siblings (i.e., including probands).

	Unaffected siblings (*N*=189) vs. Affected siblings (including probands; *N*=447)		
	Estimate	95%CI	*p*
Mental health symptoms			
Depressive symptoms	-0.85	-0.99 to -0.72	<.001*
Panic symptoms	-0.73	-0.85 to -0.61	<.001*
Phobia symptoms	-0.62	-0.77 to -0.48	<.001*
Social vulnerabilities			
Poor interpersonal functioning	-0.77	-0.92 to -0.61	<.001*
Past-year negative life events – Independent	0.22	0.04 to 0.39	.018*
Past-year negative life events – Dependent	0.08	-0.10 to 0.27	.396
Childhood trauma	-0.50	-0.64 to -0.37	<.001*
Cognitive vulnerabilities			
Worry	-0.82	-0.96 to -0.68	<.001*
Hopelessness	-0.62	-0.75 to -0.47	<.001*
Rumination	-0.76	-0.90 to -0.61	<.001*
Anxiety sensitivity – Physical concerns	-0.49	-0.64 to -0.33	<.001*
Anxiety sensitivity – Social-cognitive concerns	-0.50	-0.66 to -0.34	<.001*
Personality			
Neuroticism	-1.08	-1.22 to -0.93	<.001*
Introversion	-0.64	-0.81 to -0.46	<.001*
External locus of control	-0.61	-0.77 to -0.45	<.001*

Note. Sample sizes vary slightly due to marginally missing data on mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality (see *Table S1* in the supplementary materials). Standardized estimates and 95% confidence intervals (CI) were retrieved from multilevel regression models fitted with clustered bootstrapping using 5000 bootstrap samples, with a random intercept of family ID and age, gender, and years of education added as covariates. *p*-values were derived from bootstrapped 95%CIs according to a method described by Altman and Bland (Altman and Bland, 2011). The Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) was applied to the 15 outcome measures tested within this research aim to correct for multiple testing. False discovery rate (FDR)-corrected *p*-values are reported. CI=confidence interval.
* Significant after correction for multiple testing with FDR<.05.

Nonetheless, even though estimates were small to medium in size, we add to the existing literature by showing proband-sibling resemblance in poor interpersonal functioning, past-year negative life events, rumination, anxiety sensitivity – physical concerns, and external locus of control. Particularly in the case of childhood trauma, probands and siblings likely experienced similar adversity as reflected by a large ICC ($\rho \geq 0.3$; Bliese, 2000; James, 1982). This is in line with earlier findings from our (Kullberg et al., 2020) and other studies (Hines et al., 2006; MacMillan et al., 2013), finding medium to high proband-sibling resemblance in the most prevalent subtypes of childhood trauma, emotional maltreatment and physical abuse. Childhood trauma, which does not change beyond childhood/adolescence, has strong long-term effects (Cloitre and Beck, 2017) and often occurs within a family context (i.e. parents account for 80% of the identified perpetrators in case of emotional maltreatment and physical abuse; Hovens et al., 2010), thereby increasing risk of childhood trauma for all siblings within the family (Hamilton-Giachritsis and Browne, 2005; Witte et al., 2018). This may explain the larger proband-sibling resemblance in childhood trauma as compared to the other tested features.

4.3. Group differences in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality

On top of poor interpersonal functioning and childhood trauma, already identified in a previous family study (Watters et al., 2013), we identified two additional features that were elevated in unaffected siblings as compared to healthy controls – (independent and dependent) past-year negative life events and rumination. These features may represent important vulnerabilities determining the increased risk of developing depressive and/or anxiety disorders in siblings of affected probands. It is interesting that the difference between unaffected siblings and healthy controls were so large for rumination, indicating that rumination might be one factor that is highly shared between siblings, even if they are not both affected. It has been shown that rumination is moderately heritable (Johnson et al., 2014). It might be that due to this genetic influence, siblings might also report higher rumination, but these might not lead to increased depressive symptoms due to other protective factors (e.g., the use of other more adaptive emotion regulation strategies).

On the other hand, in contrast to some previous family and sibling studies in younger samples (Lauer et al., 1997; Modell et al., 2003; Watters et al., 2013; although see Farmer et al., 2002; Lauer et al., 1997; Modell et al., 2003; Ouimette et al., 1996).,the majority of mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality traits were, in fact, not elevated in unaffected siblings as compared to healthy controls and were lower in unaffected siblings as compared to affected siblings (including probands). This suggests a potential degree

of individual resilience against the risk of developing depressive and anxiety disorders. The found differences suggest potential protective candidate factors that should be tested in future interventions studies aimed at preventing the onset of psychiatric disorders in siblings of affected patients. For instance, preventive interventions for children of parents with mood and/or anxiety disorders, which also have a higher chance to develop a mood/anxiety disorder, focus on, amongst other things, cognitive restructuring, likely improving rumination, and strengthening social support, likely improving interpersonal functioning. These programs have been shown to be effective in preventing the onset of anxiety/depressive disorders and reducing subthreshold symptoms (Havinga et al., 2021). While multiple observational studies stress the need for targeting siblings of affected individuals for preventive interventions (for a review see Ma et al., 2020), we are not aware of any randomized controlled trial that has studied the effect of an intervention or prevention targeting the identified vulnerabilities in our studies in this particular population. The fact that, in our study, we did not find that unaffected siblings differed from healthy controls on mental health symptoms, (most) cognitive vulnerabilities, and personality, suggests that these may be a direct result of the disorders, rather than prodromal indicators.

4.4. Strengths and limitations

Strengths of this study include the relatively large sample, consisting of lifetime depressed and/or anxious probands, their affected and unaffected siblings, and healthy controls, which contributes to the understanding of how mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality traits manifest themselves within at-risk families; the sibling structure of the data, which has the advantage that sibling relationships contain a higher shared proportion of (early) environmental factors as compared to parent-offspring relationships; the relatively older age of the sample, which allows for the examination of more definite clinical profiles in siblings and individual differences that emerged across the lifespan; the wide variety of assessed mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality traits; and the adequate correction for multiple testing.

Some limitations should be noted as well when interpreting the results. First, the present study only used cross-sectional data. Prospective longitudinal studies are needed to confirm the suggested psychopathology-related features potentially associated with the familial transmission of depressive and anxiety disorders. Second, no information was collected on siblings of healthy controls. We were therefore unable to investigate whether the proband-sibling resemblance in mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality traits is different (and potentially higher) in at-risk families as compared to families without affected persons (Wickramaratne, 1995). Third, the proband group exclusively consisted of persons that received a depressive and/or anxiety disorder diagnosis on at least two NESDA waves, which limits generalizability to at-risk families of lifetime affected persons with more severe problems.

One explanation for the null-findings of neuroticism is that the reliability of the neuroticism measure was relatively low in our subsample. However, previous NESDA papers have shown that neuroticism has a good predictive validity in the overall sample (e.g., Lamers et al., 2011; Renner et al., 2013). Moreover, while some research indicates that there are mean level changes in personality across the life-span with increases in neuroticism and decreases in extraversion (Graham et al., 2020), a paper using NESDA data showed the temporal stability of neuroticism and extraversion is moderate to strong and diminishes only slightly over time, suggesting that these indicators are rather traits than states (Struijs et al., 2020). Thus, we do not think that the latter might have influenced the results.

Additionally, there were some differences between the included and excluded group, which might limit the representativeness of the sample of included affected targets compared to the whole NESDA sample of affected targets. However, the differences were not large and we controlled for those demographic factors in all our analyses.

Lastly, an analytical choice that could have influence our results is controlling for years of education in our analyses, although this could potentially also be an outcome of psychopathology and not only an indicator and might thus remove variance that should be attributed to depression. However, when re-running the models without education as a covariate results were virtually the same.

4.5. Implications, conclusions, and future research

Siblings of probands with depressive and/or anxiety disorders are at higher risk to also be diagnosed with a depressive and/or anxiety disorder: about 50% of all siblings of affected probands in our study had a lifetime depressive and/or anxiety disorder themselves. However, our study did not examine concordance within siblings pairs, thus we can only draw conclusions about general prevalence rates of probands and siblings.. Despite this, resemblance among probands and siblings in features commonly associated with the development of the disorders such as mental health symptoms, social vulnerabilities, cognitive vulnerabilities, and personality traits was only mild to moderate. While our findings illustrate that the majority of these features, in part, pose a family-wide problem as probands' siblings may (have) experience(d) similar adversities, they also suggest substantial individual differences between siblings from the same family. Moreover, although probands' unaffected siblings showed some enhanced vulnerability as compared to healthy controls without affected relatives, they did not differ in mental health symptoms, (most) cognitive vulnerabilities, and personality traits which may indicate their underlying resilience. This underscores the importance for future studies to identify in siblings from at-risk families the exact mechanisms that determine divergent clinical trajectories across the lifespan. Such identification may give important clues about strategies to improve resilience in subjects with familial risk.

Moreover, while the current paper gives a better indication of familial resemblance of mental health symptoms and a large variety of vulnerabilities, we did not study the concordance of these factors within sibling pairs. Future studies should examine the overlap of diagnoses in sibling pairs to determine homotypic and heterotypic con- and discordance (e.g., do sibs of adults with depression have increased rates of anxiety disorders?). Moreover, studying whether certain factors (e.g., sociodemographic, social-environmental, lifestyle factors) can explain proband-sibling (dis)similarity in lifetime diagnosis and current symptoms of depression and anxiety would help to identify mechanisms that determine convergent/divergent clinical trajectories in probands and siblings from the same families.

5. Contributors

B.W.J.H.P. developed the NESDA study concept and design. Together with B.W.J.H.P., B.M.E. and A.M.v.H. were closely involved in the design of the family study of NESDA. E.D.v.S. and M.K. prepared the data for the analyses. E.D.v.S. performed the data analysis and interpretation under the supervision of D.F.M., Y.M., M.X.H., and B.W.J.H.P. E.D.v.S. drafted the manuscript, and B.W.J.H.P., D.F.M., Y.M., M.K., M. X.H., C.A.H., B.M.E., and A.M.v.H. provided critical revisions. All authors approved the final version of the paper for submission.

Declaration of Competing Interests

None.

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Data statement

The data that support the findings of this study are available via the website of NESDA (https://www.nesda.nl/pro-index/), which will be provided after handing in a data request. This paper and the R code for the analyses were pre-registered on the Open Science Framework (https://osf.io/9vn68/?view_only=fc54de1af6d94e6eb8bd50244fdaa291).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.06.072.

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