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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

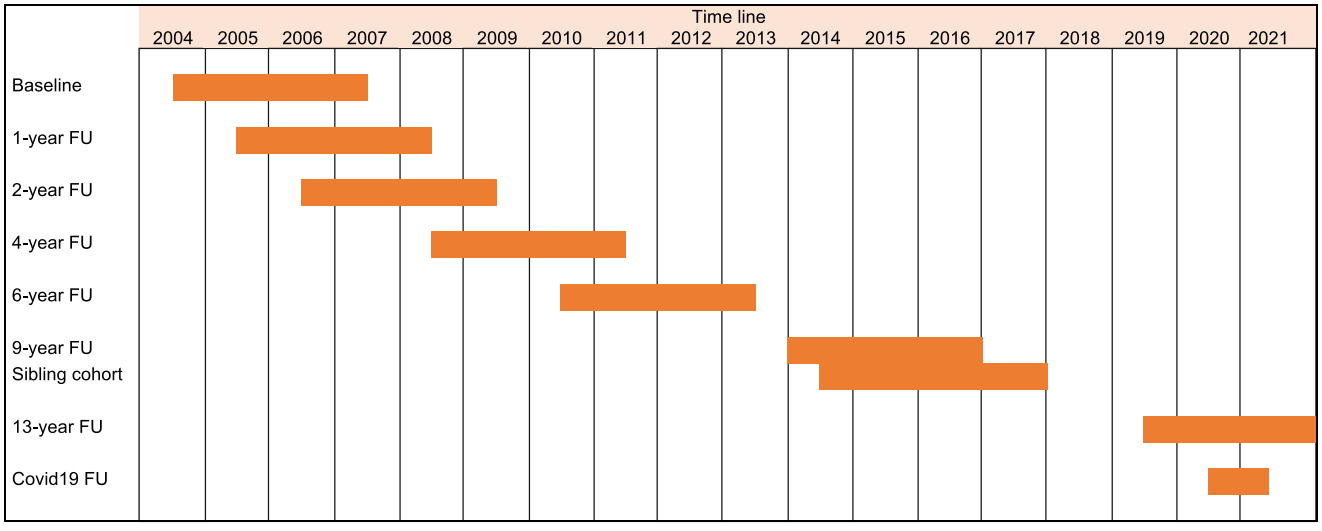

Fig. 1. Timeline with NESDA assessment schedule.

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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