The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods

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ABSTRACT

The Netherlands Study of Depression and Anxiety (NESDA) is a multi-site naturalistic cohort study to: (1) describe the long-term course and consequences of depressive and anxiety disorders, and (2) to integrate biological and psychosocial research paradigms within an epidemiological approach in order to examine (interaction between) predictors of the longterm course and consequences.

Its design is an eight-year longitudinal cohort study among 2981 participants aged 18 through 65 years. The sample consists of 1701 persons with a current (six-month recency) diagnosis of depression and/or anxiety disorder, 907 persons with life-time diagnoses or at risk because of a family history or

subthreshold depressive or anxiety symptoms, and 373 healthy controls. Recruitment took place in the general population, in general practices (through a three-stage screening procedure), and in mental health organizations in order to recruit persons reflecting various settings and developmental stages of psychopathology. During a four-hour baseline assessment including written questionnaires, interviews, a medical examination, a cognitive computer task and collection of blood and saliva samples, extensive information was gathered about key (mental) health outcomes and demographic, psychosocial, clinical, biological and genetic determinants. Detailed assessments will be repeated after one, two, four and eight years of follow-up.

The findings of NESDA are expected to provide more detailed insight into (predictors of) the long-term course of depressive and anxiety disorders in adults. Besides its scientific relevance, this may contribute to more effective prevention and treatment of depressive and anxiety disorders.

INTRODUCTION

Depressive and anxiety disorders are common at all ages. In addition, their effects on well-being and daily functioning are enormous and comparable to those of major chronic physical illnesses (Buist-Bouwman et al., 2006; Murray and Lopex, 1997). In economic terms, the cost of depressive and anxiety disorders due to loss of productivity and use of health services ranks among the top-fi ve of all disorders (Smit et al., 2006). Consequently, depressive and anxiety disorders are relevant candidates for efforts to improve public health.

During the past decades, progress has been made in the development and testing of different forms of treatment for depressive and anxiety disorders. Although successful treatment is available, a large proportion of those affected remains undiagnosed and untreated (Bijl and Ravelli, 2000), and treatment is not effective for everyone. Moreover, although it is fi rmly established that the duration of episodes can be infl uenced with treatment, it is uncertain whether treatment has effect on the long-term course of depressive or anxiety disorders.

The extremely variable natural history precludes matching interventions accurately to those who are most in need of treatment. This is reflected in current professional treatment guidelines which offer little guidance as to which patients may recover without substantial treatment and which patients may be in need of more intensive interventions. A fi rst requirement for a more accurate matching of limited treatment resources to the projected need of patients is to have detailed knowledge of the factors that determine or predict the prognosis. For this, data on (determinants of) the long-term course and consequences of anxiety and depressive disorders are essential.

We are currently conducting the Netherlands Study of Depression and Anxiety (NESDA), a multi-centre study designed to examine the long-term course and consequences of depressive and anxiety disorders. This paper presents the basic rationales, objectives and methods of NESDA.

KEY RATIONALES

There were four key rationales that guided our design, which will be discussed.

Rationale 1: Insight into long-term prognosis of depressive and anxiety disorders is limited

Both in the literature and in clinical practice, the disease-episode-model for the prognosis of depression and anxiety dominates. Using this model, the median duration of episodes of major depressive disorder (MDD) ranges between 3–6 months, whereas using the prevailing

definition of chronicity of MDD (duration > two years) approximately 20% of episodes becomes chronic (Keller et al., 1992; Spijker et al., 2002). Nevertheless, although remission occurs, the course of MDD is typified by recurrences: in a meta-analysis of studies among depressed patients in psychiatric settings, 76% had one or more recurrent episodes over 10 years (Piccinelli and Wilkinson, 1994). Although several studies of the prognosis of MDD are available, the Collaborative Depression Study (CDS) has probably been the most influential.

In this study, 431 adults with MDD who were treated in academic centres were followed over 12 years. Using the disease-episode-model, the above figures for duration of episodes were reached (Keller et al., 1992; Keller at al., 1984). However, using the life-chart method the prognosis appeared to be pleiomorphic with symptom levels changing frequently; patients were symptomatically ill in 59% of the weeks over 12 years, much of which at the minor, dysthymic or subthreshold level (Judd et al., 1998). Using similar methodology in population- based studies provided rather similar conclusions indicating that depression is a chronic intermittent disorder in the majority of cases (Judd, 1997). Therefore, to describe the longitudinal course, the disease-episode model for the prognosis of affective disorders should be complemented with a dimensional model describing the waxing and waning of symptoms (Duncan-Jones et al., 1990).

For anxiety disorders, the (few) studies examining the course, have also focused on the disease-episode model. The Harvard/Brown Anxiety Research programme (HARP) repeatedly assessed 711 psychiatric outpatients with anxiety disorder (panic, social phobia or generalized anxiety disorder) at 6 to 12 month intervals over 10 years. The course of anxiety disorders appeared to be poor with the smallest probability of recovery for social phobia (Bruce et al., 2005). Only 35% of 232 outpatients with social phobia recovered during 10 years, whereas the recurrence rate once recovery was achieved was 34% (Keller, 2006). In two reviews, it was estimated that the course of panic disorder shows only little to no improvement in 36–40% of the subjects after 1 to 20 years of treatment (Keller and Hanks, 1993; Pollack and Otto, 1997). These results depict anxiety disorders as insidious with low recovery rates and high recurrence rates, and beg for more naturalistic long-term studies that examine episodes as well as symptoms in order to improve our knowledge about the course of anxiety disorders.

Rationale 2: When studying depression and anxiety disorders, different settings and developmental stages should be considered

Although common throughout settings, the prevalence of depressive and anxiety disorders increases as one moves from the community, through primary care, to specialized health care settings (Goldberg and Huxley, 1992). Those with the most severe, complex, recurrent and longstanding disorders are more likely to be referred to specialized mental health care (Bijl and Ravelli, 2000). The setting in which subjects are recruited is therefore crucial to the outcome, since those recruited in specialized mental health care are a selection of those with the least favourable prognosis. Unfortunately, there are no longitudinal studies that have included sufficient subjects representative of those suffering from depressive and anxiety disorders in different health care settings. Studies like HARP and CDS (discussed earlier) provide information on the course of psychiatric outpatients in specialty clinics, but the extent to which this information is generalizable to community and primary care settings – where the majority of cases resides – needs to be determined.

The clinical developmental stage of a disorder has shown to be a key determinant of the course of a depressive or anxiety disorder. This can be best demonstrated by the importance of previous history, duration and severity of the index episode for the prognosis (Spijker et al., 2002). However, these clinical factors do not explain the wide variation in the prognosis: it is highly likely that underlying biological and psychosocial factors, such as genetics or personality, partly determine both the clinical features of index episodes and its subsequent

course. Patients enrolled in specialized health care settings generally have a more progressed developmental stage of their illness than patients in primary care or community settings (Suh and Gallo, 1997; Cooper-Patrick et al., 1994). Consequently, clinical setting and developmental stage of the illness are highly correlated. To obtain a full understanding of the course of depressive and anxiety disorders, it is crucial to design studies that include patients from different settings and developmental stages of illness. Such a study would not only allow comparison of the (prediction of) course between patients from different settings and developmental stages, but would also allow for studies of trajectories of care, focusing on factors determining transitions from informal to different levels of formal care.

Rationale 3: Depressive and anxiety disorders should be studied in concert

Previous studies have shown that comorbidity among depressive and anxiety disorders is rule rather than exception: comorbidity rates range from 30% through 60% (Kessler et al., 1994; Beekman et al., 2000; Angst, 1996; Sartorius et al., 1996; van Balkom et al., 2000; de Graaf et al., 2002). Depressive and anxiety disorders often arise sequentially within the same patient: the order is more likely to start with anxiety, depression commonly arising later (Merikangas et al., 1996; de Graaf et al., 2002). Another line of research shows that patients with both anxiety and depression have more severe symptoms, more disability, a longer duration of illness and are less likely to respond to treatment (Vollrath and Angst, 1989; Bijl and Ravelli, 2000; Hecht and Wittchen, 1990; Roy-Byrne et al., 2000; Bruce et al., 2005; Ormel et al., 1994). Finally, analyses of depression and anxiety comorbidity patterns identified a three-dimensional model underlying these diagnoses that distinguished an externalizing domain as well as an internalizing domain, the latter consisting of a panic/phobia dimension and an affective dimension including depression and generalized anxiety disorder (GAD). (Krueger, 1999; Vollebergh et al. 2001).

Given the debate about the validity of a categorical distinction between anxiety and depression (Goldberg, 1996), and the undisputed close relationship between both, a long-term study should examine anxiety and depression in concert, focusing on comorbidity patterns and employing both a dimensional and a categorical approach to the diagnosis of depressive and anxiety disorders.

Rationale 4: Psychosocial and biological paradigms should be integrated when examining depressive and anxiety disorders

Studies suggest that depressive and anxiety disorders share common risk factors and that similar interventions are effective (Andrews and Stephens, 1990; Brown et al., 1996; Beekman et al., 2000). With regard to risk factors, there is some evidence supporting the idea that depressive and anxiety disorders share longstanding vulnerability factors, with recent stress factors determining the specific disorder (Kendler et al., 1987; Goldberg and Huxley, 1992). An interdisciplinary approach when studying depressive and anxiety disorders is important, since the etiology of these disorders is likely multi-causal. Etiological studies have yielded important findings, but single risk factors only explain modest parts of the etiology. Also for the course of disorders, it is unlikely that there exists one single predictor.

Accurate prediction of the course of depressive and anxiety disorders requires that psychosocial and biological research paradigms be integrated within a common psychiatric epidemiological framework (Merikangas et al., 2002). The rapid technological advances such as genomics have recently allowed such integration which enables research into the interaction between psychosocial and biological determinants.

Recent examples confirm that these domains interact.

For instance, a serotonin transporter genetic polymorphism influences depressiveness only when stressful life events are present (Caspi et al., 2003), and hypothalamic- pituitary-adrenal (HPA) axis dysregulation in depression is most obvious after traumatic childhood exposure (Heim et al., 2002). These observations have indicated that interactions between

determinants are likely contributing to depressive and anxiety disorders, and consequently, may be important as well in determining their course. Ideally, future psychiatric epidemiological studies should be designed to integrate psychosocial and biological paradigms and should be large enough to allow exploration of interaction between domains.

OBJECTIVES

In line with the rationales mentioned earlier, NESDA was designed as a naturalistic, longitudinal cohort study including respondents from different health care settings (community, primary care and specialized mental health care) and in different stages of the developmental history of disorders (normals, high familial risk, subthreshold disorders, first and recurrent episodes).

Depressive and anxiety disorders are studied in concert using both dimensional and categorical measurements.

Central outcomes and determinants are measured in detail at baseline and after one, two, four and eight years of follow-up in a cohort of 2981 adults.

NESDA has three related main study objectives:

(1) Describing the long-term prognosis of depressive and anxiety disorders in terms of course (chronicity, recurrence, development of comorbidity, suicidal behaviour) and public health consequences (disability, mortality, costs).

(2) Examining clinical, psychosocial, biological and genetic determinants of the long-term course and consequences of depressive and anxiety disorders.

(3) Examining 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.

It is important to emphasize that NESDA should be regarded as an overarching research infrastructure intended to foster specific research projects to address focused research questions and hypotheses. Examples of these research projects are, for instance, the examination of disability patterns among patients with different types of anxiety disorders (part of objective 1), the exploration of a gene-environment interaction in predicting the chronicity of depression (part of objective 2), and the examination of received mental health care on the course of depressive and anxiety disorders (part of objective 3). In addition to these specifi c research projects, it is possible to frame some general research hypotheses although these can only be based on limited (indirect) scientific evidence (e.g. Keller et al., 1992; Keller, 2006; Bruce et al., 2005). Three main examples are: (1) the long-term course of anxiety disorders is more chronic than that of depressive disorders, (2) the long-term course of anxiety disorders is more homogeneous and therefore influenced by a lower number of (diverse) determinants than the course of depressive disorders, and (3) comorbidity of anxiety and depressive disorders negatively influences the long-term course and consequences of psychopathology.

In order to judge the interpretation and generalizability of NESDA findings, it is good to place the Dutch mental health care situation in an international perspective.

First, large-scale epidemiological studies have shown that the prevalence of both depression and anxiety disorders in the Netherlands is well in the range of that in other high income countries such as the US, Germany or Canada (Andrade et al., 2003). In addition, the structure of the Dutch Health Care System is comparable to that of several other European countries (e.g. UK, Germany, Italy, Spain) in which the general practitioner serves as the gatekeeper and referrals are needed for access to specialized mental health care. Results from both the World Health Organization (WHO) World Mental Health Surveys and the European Study of the Epidemiology of Mental Disorders confirm that the proportion of diagnosed persons receiving mental health treatment as well as the quality of care received is well comparable to that in other high income countries such as the US, UK, Germany, Spain and Belgium (Wang et al., 2007; Alonso et al., 2004).

Consequently, we have no reason to believe that our study results on the long-term course of (treated) anxiety or depressive disorders are specific to the Dutch situation only *NESDA consortium*

The NESDA study is largely funded through a special grant to stimulate psychiatric research ("Geestkracht") of the Netherlands Scientific Organization as well as through matching funds from participating universities and mental health organizations. A research consortium was established consisting of academic and nonacademic research groups, including the departments of psychiatry, general practice and clinical psychology of the VU University Medical Centre, the Leiden University Medical Centre and the University Medical Centre Groningen, the Centre for Quality of Care Research of Radboud University, the Netherlands Institute for Health Services Research, and the Netherlands Institute of Mental Health and Addiction. This collaboration guarantees access to the diverse expertise of a large group of researchers. External (international) researchers may collaborate and request access to the data.

METHODS

Sampling

NESDA has been designed to be representative of those with depressive and anxiety disorders in different health care settings and stages of the developmental history.

Therefore, the sample is stratified for setting (community, primary care and specialized mental health) and set up to include a range of psychopathology: those with no symptoms or disorders ('controls'), those with earlier episodes or at risk because of subthreshold symptoms or family history, and those with a current first or recurrent depressive or anxiety disorder. The Composite Interview Diagnostic Instrument (CIDI) – lifetime version 2.1 – was used to diagnose depressive and anxiety disorders according to Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) algorithms. The focus is on Dysthymia (Dyst), Major Depressive Disorder (MDD), General Anxiety Disorder (GAD), Panic Disorder (PAN), Social Phobia (SocPhob) and Agoraphobia (AgoraPhob).

Table 1 shows the number of participants recruited by setting and developmental stage of illness. Overall, 807 persons were recruited through mental health care organizations, 564 persons through the community setting and the remaining 1610 through primary care (see later). Across recruitment setting, uniform inclusion and exclusion criteria were used. A general inclusion criterion was an age of 18 through 65 years. In order to maintain representativity, only two exclusion criteria existed: (1) a primary clinical diagnosis of a psychiatric disorder not subject of NESDA which will largely affect course trajectory: psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder, and (2) not being fluent in Dutch since language problems would harm the validity and reliability of collected data.

Recruitment from community samples

The NESDA community sample builds on two cohorts that were already available through prior studies.

The first cohort is from the Netherlands Mental Health Survey and Incidence Study (NEMESIS), a community-based study described in detail elsewhere (Bijl et al., 1998). NEMESIS applied a multistage, stratified sampling procedure using a random sample of private households in 90 Dutch municipalities. The adult household member with the most recent birthday was asked to participate. A total of 7076 respondents (69.7% of those eligible) participated and were interviewed with the CIDI, version 1.1 in 1996. Follow-up interviews were conducted in 1997 (n = 5618) and 1999 (n = 4796). For NESDA, we included participants with a 12-month prevalent depressive (MDD or Dysth) or anxiety disorder diagnosis (GAD, SocPhob, Agora- Phob, PAN) at baseline or a diagnosis during any of the two follow-up NEMESIS assessments who did not have a CIDI diagnosis of any

of the psychiatric diagnoses belonging to the exclusion criteria (e.g. psychosis, bipolar disorder, obsessive-compulsive disorder). Consequently, a total of 766 NEMESIS participants were selected, of whom nine persons had died, eight persons had left the Netherlands, and 87 could not be traced despite several attempts. Of the 662 persons approached, 359 (54.2%) refused to participate, none were excluded because of language problems, and 303 (45.8%) participated in NESDA. Those participating did not differ in terms of age ($p = 0.77$), gender ($p = 0.79$), or type of baseline disorder (anxiety, depression or comorbid disorder, $p = 0.97$) from those not participating. An important advantage of following this NEMESIS cohort within NESDA, is that we have detailed information on the prior 10-year history (since 1996) through repeated (CIDI) assessments. Of the participating 303 persons, 104 had a current (six-month) prevalent depressive or anxiety disorder at the NESDA baseline assessment (see Table 1).

[TABLE 1]

The second cohort exists of participants of the Adolescents at Risk for Anxiety and Depression (ARIADNE) study (Landman-Peeters et al., 2005), a prospective cohort study among 528 biological children (aged 13– 25 years) of parents who were treated for depressive or anxiety disorder as outpatient at a mental health organization.

These children can be considered at high risk to develop depressive or anxiety disorders themselves.

The baseline ARIADNE interview in 2000 consisted of a CIDI interview as well as self-report questionnaires.

Additional follow-up assessments were collected after one year ($n = 487$), two years ($n = 458$) and four years ($n = 413$). After offi cial closure of the ARIADNE study in 2004, 394 participants who were all fl uent in Dutch and who did not have a CIDI diagnosis of excluding psychiatric diagnoses agreed to be contacted for additional research, of whom one died before contact, 10 could not be traced, 122 refused, and 261 participated in NESDA. The 261 participants were more likely to be female (64.0% versus 50.2%, $p = 0.001$) and have a life-time depressive or anxiety disorder (31.0% versus 22.5%, $p = 0.02$) compared to the 267 no-participants, but no age differences were present ($p = 0.43$). An advantage of including this unique cohort is that detailed, prospectively collected data is already available for the four years prior to NESDA.

Recruitment from primary care practices

Primary care patients were recruited from 65 general practitioners (GPs) in the vicinity of the fi eld sites (Amsterdam, Groningen, Leiden). In selecting these GPs, attention was paid to the use of an appropriate electronic patient record databases which allows uniform data extraction for research purposes. This is important since collection of GP health care use information is part of NESDA, especially to address study objective 3.

In the Netherlands, all patients are enlisted at a general practice. For the selection of respondents, a three-stage screening procedure was used. Screening questionnaires were sent to a random sample of 23,750 patients aged 18–65 years who consulted their GP in the last four months irrespective of reason for consultation.

The screening questionnaire consisted of the Kessler-10 (K-10; Kessler et al., 2003) with proven screening qualities for affective disorders (Furukawa et al., 2003; Kessler et al., 2003). Since the K-10 does not contain questions for specific anxiety disorders, five additional questions were added asking for the presence (yes/no) of a panic attack, social phobia, agoraphobia, general anxiety or nervousness, and psychotropic medication use during the last month. A screen-positive score on the K-10 was defined as a validated K-10 score of ε20, (Furukawa et al., 2003) or a positive score on any of the added anxiety questions. A total of 10,706 persons (45%) returned the screener. Those returning the

screener were more likely to be female (59.3% versus 50.0%, $p < 0.001$) and older (44.4 years versus 39.0 years, $p < 0.001$) compared to those not returning the screener.

Of the screeners returned, 4887 were screen-positive (46%) and these persons were approached for a short phone-screen interview consisting of the CIDIshort form sections (MDD, Dysth, GAD, SocPhob, Agoraphob, PAN). Those who fulfilled the CIDI-short form criteria for a current depressive or anxiety disorder during the phone-screen, and who were not treated for psychiatric conditions in a psychiatric mental health care setting, were invited to participate in the NESDA study. In addition, a random selection of the screennegatives (both from the written screener or the phonescreen) were also invited to participate.

Figure 1 depicts the yield of the three-stage primary care screening procedure. A total of 743 participants with a current (six-month recency) and 353 participants with a non-current depressive or anxiety disorder were recruited, as well as 141 persons with subthreshold symptoms (screen-positives not fulfilling diagnostic criteria or a CIDI DSM-IV minor depression diagnosis).

Finally, 373 participants with a screen-negative score and no depressive or anxiety disorder participated and constitute a “healthy control group”.

Recruitment from mental health organizations

The specialized mental health patients were recruited from outpatient clinics of regional facilities for mental health care around the three research sites. For each newly enrolled patient at these outpatient clinics, a mental health professional conducted a standardized intake, which in most, but not all, facilities consisted of a structured psychiatric interview [e.g. Mini International Neuropsychiatric Interview (MINI), Structured Clinical Interview for DSM-IV (SCID)]. Patients who received a primary diagnosis of depressive or anxiety disorder, received brief information about NESDA. The clinic staff of participating mental health care organizations submitted 1597 patients with primary depressive or anxiety disorder for inclusion. Of these, 87 appeared not to fulfil NESDA inclusion criteria when double checked by research staff, 58 could not be reached despite multiple efforts, and 39 were excluded due to language problems during phone contact. Of the other 1413 persons contacted by phone, 606 (43%) refused participation and 807 (57%) participated in NESDA.

Those participating were slightly older (38.0 years versus 36.5 years, $p = 0.04$) compared to the 635 who refused, but there was no gender difference ($p = 0.17$).

Characteristics of study sample

[FIGURE 1]

The overall sample has a mean age of 41.9 years [standard deviation (SD) = 13.0] and consists of 1002 men (33.6%) and 1979 women (66.4%). The respondents have an average of 12.1 years of education (SD = 3.3) and 97% has the Dutch nationality. As shown in Table 1, 1701 persons (57.1%) had a current (six-month) depressive and/or anxiety disorder, whereas 2329 persons (78.1%) had a lifetime history. Table 2 illustrates that within the sample a total number of 3406 current and 5446 lifetime depressive and anxiety disorders are present. Especially the current numbers of MDD ($n = 1115$), PAN ($n = 670$) and SocPhob ($n = 665$) are high. As shown in Table 2, the majority of all cases had an age of onset before age 30. Using the Life Chart method, more than half of the persons with an anxiety disorder and one-third of those with a MDD diagnosis reported symptoms during at least 24 out of the 48 months prior to baseline. At baseline, a total of 748 (25.1% of the total sample) respondents were using antidepressants.

[TABLE 2]

Of these 748 respondents, 518 were using a selective serotonin reuptake inhibitor (SSRI), 80 were using a tricyclic antidepressant (TCA), and 172 were using another antidepressant. In addition, 230 respondents were frequently (εfour days a week) using a benzodiazepine.

Original sample size calculations were based on the examination of course predictors within the smallest subgroups of depressive and anxiety disorders. Beforehand, we calculated that a minimum of 160 persons per subgroup were needed to detect a small difference (RR = 1.5) in a dichotomous outcome (e.g. yes/no poor course with a minimum outcome rate being 25%) given a two-sided test, a model including 10 covariates, a power of 80% and alpha of 0.05. Table 2 shows that our smallest subgroup is 288 (for agoraphobia without panic disorder). For many research questions, however, power will be larger since analyses will be based on the larger disorder groups and on continuous measures.

Measurements

Similar information is collected and similar procedures were used for all participants, regardless of recruitment setting. The baseline assessment lasted on average four hours. Baseline assessments took place at one of the seven clinic sites in the three regions around Amsterdam, Leiden and Groningen. If participants did not want to come to the clinic site, they were offered transportation by taxi. A few persons (n = 60) who live far away from the field site 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.

(Mental) health outcomes

Assessment of psychopathology

The NESDA baseline assessment includes various indicators of presence, symptomatology, and history of depressive and anxiety disorders (see Table 3). The diagnoses of depression [minor depression (MinD), MDD, Dyst] and anxiety disorders (GAD, SocPhob, AgoraPhob, PAN) were established with the CIDI (WHO version 2.1) which classifi es diagnoses according to the DSM-IV criteria (American Psychiatric Association, 2001). The CIDI is used worldwide and WHO fi eld research has found high interrater reliability (Wittchen et al., 1991), high test–retest reliability, (Wacker et al., 2006) and high validity for depressive and anxiety disorders (Wittchen et al., 1989; Wittchen, 1994). Specially trained clinical research staff conducted the CIDI. DSM-IV organic exclusion rules were used in making diagnoses, and hierarchy free diagnoses were made to allow for research into comorbidity. At baseline, the life-time CIDI version was used with added questions to determine the research DSM-IV diagnosis of current minor depression (MinD). The life-time CIDI allows for the determination of the history, recency, duration and age of onset of episodes. As has been feasibly used in other large-scale studies [Epidemiologic Catchment Area (ECA); Eaton et al. 1997] and NEMESIS (Spijker et al., 2004), more detailed fluctuation of depressive and anxiety symptoms during the past four years was assessed with the Life Chart method. This instrument first determines life events in this period to re-fresh memory, and then assesses presence and severity of symptoms during each quarter of the past four years (Lyketsos et al., 1994).

[TABLE 3]

Severity of depressive symptoms was measured with the 30-item Inventory of Depressive Symptomatology self-report version, which has shown high correlations with observer-rated scales and with established responsiveness to change (Rush et al., 1996). Although persons with depression in the course of a bipolar disorder were not included in the study, it was expected that some respondents would report manic symptoms, which was assessed using the Mood Disorder Questionnaire (Hirschfeld et al., 2000). Current suicidality was assessed

with an interviewer-rated five-item scale of current suicide ideation (Beck et al., 1979). Severity of generalized anxiety and panic symptoms was measured using the 21-item Beck Anxiety Inventory (Beck et al., 1988), whereas social and agoraphobia symptoms were measured using the 15-item Fear Questionnaire (Marks and Mathews, 1979).

Given the debate about the validity of categorical distinction between anxiety and depression (Goldberg, 1996) and the undisputed close relationship between both, a dimensional approach to diagnosis was also considered. A shortened Mood and Anxiety Symptom Questionnaire was included, which uses Watson and Clarcks tripartite model as the basis (Watson et al., 1995). This 30-item scale has three subscales consisting of lack of positive affect, negative affect and somatic anxiety symptoms. Somatization and general distress were determined with the validated four-dimensional symptoms questionnaire (Terluin et al., 2006). Finally, since the prevalence of alcohol use disorders was expected to be high, the life-time CIDI-sections for alcohol abuse and dependency were administered as well as the Audit questionnaire to assess high-risk drinking behaviour (Babor et al., 1989).

Assessment of public health consequences

From a patient and public health perspective, the prognosis of mental symptoms should be supplemented with information on well-being, functioning, somatic health and societal costs. Consequently, validated instruments to assess disability (WHO-Disability Assessment Schedule II (Chwastiak and von Korff, 2003), and disability days (Sheehan et al., 2001), loss of productivity at work, and health care utilization (TIC-P; Hakkaart-van Roijen, 2002) were included (see Table 3). An inventory of somatic disease was made by detailed questions of presence of and receiving treatment for 20 chronic illnesses.

Determinants of (mental) health outcomes

Assessment of demographic and personal characteristics

Detailed sociodemographic data were collected, including age, sex, ethnicity, place of living, and household composition. Socio-economic information was collected by asking for education, occupation and income of the respondents and their partner and parents. Personal history questions included a structured inventory of trauma exposure during childhood (emotional neglect, psychological abuse, physical abuse, sexual abuse and important life-events in early life). The Brugha questionnaire (Brugha et al., 1985) assessed exposure to 12 important negative events during life such as death or serious illness of other family members, unemployment and violence experience. Finally, the Daily Hassles Questionnaire measures day-to-day experience of stressful circumstances such as work, private or financial problems or arguments (Kanner et al., 1981).

Psychosocial function

Details about social support from the four most intimate persons is assessed through the social support inventory (Stansfeld and Marmot, 1992) and self-report questionnaires of loneliness and affiliation are used (de Jong-Gierveld and Kamphuis, 1985). The Karasek questionnaire examines work content and environment (Karasek et al., 1998). Personality is operationalized using the NEO personality questionnaire, a 60-item questionnaire measuring five personality domains: neuroticism, extraversion, agreeableness, conscientiousness, and openness to experience (Costa and McCrae, 1995). Locus of control is assessed by a five-item mastery scale (Pearlin and Schooler, 1978).

Cognitions have been hypothesized to be important as predisposing factors for (a poor course of) depression and anxiety disorders. The Leiden index of depression sensitivity assesses the extent in which dysfunctional cognitions (e.g. rumination, hopelessness, aggression) are triggered during normal mood variations (van der Does, 2002). The anxiety sensitivity index explores fear of anxiety-related somatic sensations (Peterson and Reiss,

1992) and the Penn–State Worry Index assesses the extent to which persons worry frequently and extensively (Meyer et al., 1990). Some relevant (implicit) personality constructs are not measurable through questionnaires because they operate in an automatic (unconscious) mode that is not accessible to introspection.

Therefore, implicit trait anxiety and depression were assessed by means of a modified Implicit Association Test (Greenwald et al., 1998) that was designed to measure implicit associations between self items on the one hand and anxiety-related and depression-related items on the other.

Attitude towards health care

The patients' perspective is essential in any effort to reduce long-term effects of disorders. Very little is known about the long-term development in relevant attitudes, expectations and motivation of patients with depressive and anxiety disorders. This is surprising, as depression and anxiety are disorders with high levels of non-adaptive illness behaviour. NESDA included the Quote instrument (Sixma et al., 1998) to measure experience and evaluation of care for mental health and the Perceived Need of Care questionnaire (Meadows et al., 2000) to assess a person's care needs.

(Physiological) health indicators

Depressive and anxiety disorders are strongly associated to somatic health. To account for these associations and to further examine potential underlying biological and behavioural mechanisms, NESDA included (physiological) health and health behaviour indicators (Table 4). The International Physical Activity Questionnaire (IPAQ) calculates energy expenditure based on sports and other daily activities during a regular day (Craig et al., 2003) In addition, sleep behaviour (using the Insomnia Rating Scale; Levine et al., 2003), smoking behaviour and nicotine dependence (Fagerstrom questionnaire; Heatherton et al., 1991) and regular drug and alcohol use were measured. An inventory of 20 somatic conditions was included, and medications used in the prior month were registered (by observation of the containers brought in). Participants who used benzodiazepines in the prior month were questioned about dependency using the Bendep SRQ (Oude Voshaar et al., 2003). Since self-reported disease status may be biased by mood, we also included objective, generic indicators of health status: a peak flow assessment to measure lung function capacity and a handgrip strength assessment using a hand-held dynanometer. Body composition assessment included objective, standardized assessments of height, weight and hip and abdominal circumference.

Systolic and diastolic blood pressure were measured twice in a supine position using an electronic omron phygmomanometer. Doppler assessment of ankle and arm blood pressure allowed calculation of the ankle/ brachial index, an indicator of peripheral atherosclerosis (Newman et al., 1993). Since all baseline assessments took place in the morning, respondents came in after an overnight fast. This allowed the draw of a fasting sample of 50 millilitres of blood, which were immediately transferred to a local laboratory to start processing within one hour. Routine assays included assessment of hemoglobin, hematocrit, creatinine, total, HDL and LDL cholesterol, glucose, triglycerides, ASAT, ALAT, gamma-GT, thyroid stimulated hormone (TSH) and Free T4. Most of the blood sample, however, was processed and stored at -85 °C for later assaying.

Physiological assessment of stress systems

Two important stress systems have been hypothesized to be of importance in the adverse health effects of depressive and anxiety disorders: the HPA axis and the autonomic nervous system. These stress systems may be dysregulated and may determine the long-term course of depressive or anxiety disorders. Activity of the HPAaxis was assessed by free cortisol assessment using seven saliva samples per respondent. As a measure of a natural 'stress' response of the HPA-axis, the morning cortisol awakening response was assessed by taking

saliva samples at awakening time, 30, 45 and 60 minutes later (Wust et al., 2000). To obtain information on basal levels and the circadian rhythm, additional saliva samples were collected at 22 p.m. and 23 p.m. Afterwards, participants were instructed to ingest 0.5 milligrammes of dexamethasone, a specifi c antagonist of the glucocorticoid receptor which inhibits adrenocorticotropic hormone (ACTH) release at the pituitary gland.

Immediately after awakening the next morning, the extent of cortisol inhibition was determined by a seventh saliva sample (Gaab et al., 2002) Respondents collected saliva samples on regular (work) days using cotton swaps which were returned by mail. After receipt, saliva was spun down, stored at –85 °C and assayed.

[TABLE 4]

Physiological signals of the autonomic nervous system were measured using the ambulatory monitoring system (VU-AMS), of which reliability and recording methodology have been described previously (de Geus et al., 1995). Respondents wore the VU-AMS assessment unobtrusively underneath clothing for two hours

during which continuous time series of R wave-to-R wave intervals and respiration rates were registered from a three-lead electrocardiogram and a four-lead impedance cardiogram. From these, valid indicators (e.g. heart rate variability, pre-ejection period, respiration sinus arrhythmia) of parasympathetic and sympathetic cardiac activity were obtained.

Genetic determinants

Depressive and anxiety disorders are highly heritable, with heritability estimates between 35–40% (Sullivan et al., 2000). Consequently, it is likely that underlying genetic factors (in interaction with environmental factors) determine the onset and course of depressive and anxiety disorders. NESDA is therefore set up to provide genetic indicators for future genetic research.

Briefly, for all participants DNA was isolated from the baseline blood sample. Through funding from the fNIH GAIN programme (www.fnih.gov/gain), whole genome scan analysis were conducted for 1860 NESDA participants to be compared with 1860 controls from the Netherlands Twin Registry (see for more details: Boomsma et al., 2008). For all respondents, lymphocytes were stored so that future genomic information can be obtained. In addition, to examine the genome responsiveness at the individual genetic background of individuals, we also set up samples for later geneexpression profiling and proteomics. For this purpose, we stored one heparin tube with blood at –80 °C, and stored another heparin tube after a lipopolysacharride (LPS) challenge had been added and incubated for five hours. After future micro array analyses, geneexpression profiling in unchallenged and challenged samples can for instance be compared between depressed or anxious patients and controls. Finally, family history of depressive and anxiety disorders is explored using the family tree method (Fyer and Weissman, 1999).

Additional data collection

Functional magnetic resonance imaging (fMRI)

Although several functional magnetic resonance imaging (fMRI) studies have now confirmed neurobiological abnormalities among depression and anxiety patients (Anand and Shekhar, 2003; Deckersbach et al., 2006), the specificity of these abnormalities, and associations with e.g. severity and duration have not been fully explored. Also the prognostic importance of (change in) neurobiological parameters for the course of depression and anxiety disorders remains largely unknown, which is the main reason for including fMRI assessments in a subgroup of the NESDA cohort. Both volumetric and functional MRI using a 3 Tesla MRI scanner was performed in fi ve subgroups (total $n = 301$): controls ($n = 69$), and current (one-month recency) cases with MDD ($n = 94$), social phobia ($n = 28$), panic

disorder (n = 26) and in cases with multiple disorders (n = 88). Included paradigms are the Eckman Faces task (Canli et al., 2005), the Tower of London planning task (van den Heuvel et al., 2003) and an episodic memory task of encoding and retrieval (Daselaar et al., 2003). fMRI assessments will be repeated two and four years after baseline.

Information from GPs

For respondents recruited in primary care, additional data from GPs were collected. Participating GPs fi lled out a questionnaire about practice characteristics and their medical experience and attitude towards (mental) health care. In addition, the GP's electronic patient register data were extracted during the NESDA follow up period. This data extraction includes information on medical history, number of and reasons for GP visits, prescribed medication, and referrals starting from the year prior to baseline. This will be used for e.g. data verification of health care utilization and health care costs. Since the charging to the insurance company is connected with completion of the electronic patient record, this information is rather complete. The consequent coding of somatic, social and psychiatric diagnoses in electronic patient records provides reliable information on daily care (Okkes et al., 2002).

Procedures In the baseline assessment, the use of a laptop computer was central. Interviews 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, respondents were compensated with a small incentive (gift certificate of 15 euro and payment of travel costs) for their time and cooperation.

Staff training and supervision

In order to conduct the study, more than 40 research assistants have been trained. The majority of research assistants consisted of psychologists, nurses or residents in psychiatry. Research assistants received one week of training by the fieldwork coordinator. A research assistant was 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 in SPSS.

Data management and control

The NESDA coordinating centre at the Department of Psychiatry of the VU University Medical Centre serves as data monitoring centre. The data management team focuses on data archiving, checking of data errors, creation of (summary) variables and scales, and maintaining and updating central data bases. Electronic data from the interviews were sent on a weekly basis to the coordinating centre, where data were entered in central databases. Data quality checks were routinely carried out to review missing data and check for inconsistencies.

Ethical issues

The study protocol was approved centrally by the Ethical Review Board of the VU University Medical Centre and subsequently by local review boards of each participating centre. After full verbal and written information about the study, written informed consent was obtained from all participants at the start of baseline assessment. This written informed consent asked for permission to use genetic information, to retrieve health care information from physicians, and to link respondent information to external data banks (e.g. mortality or hospitalization databases). Confidentiality of data is maintained by using a unique research ID number for each respondent, which enables to identify individuals without using names.

Only a limited number of persons (principal investigator, data manager) have access to the record that link ID number to identifiable information.

Time line and follow-up assessments

Recruitment of the NESDA sample started in September 2004 and was completed in February 2007. In September 2005 and September 2006, the one-year and two-year follow-up assessments started. The one-year follow-up assessment consists of a written questionnaire containing the most important self-report instruments to determine demographic changes, recent life events and the course and consequences of anxiety and depression symptoms. The two-year follow-up assessment consists of a face-to-face clinic visit, in which baseline assessments – except those concerning stable concepts – are repeated. A few additional assessments were included: the CIDI bipolar disorder section, questions about experienced side effects and effectiveness of used psychotropic medication, a computerized working memory task (N-back; Carlson et al., 1998), a computerized exogeneous cueing task (Koster et al., 2005) to assess attentional bias for depression and anxiety, and an index of seasonality of symptoms (Seasonal Pattern Assessment Questionnaire; Mersch et al. 2004). The four-year and eight-year follow-up assessments will start in September 2008 and 2012, respectively.

CONCLUSION

NESDA is multisite, longitudinal, naturalistic cohort study examining the eight-year course and consequences of depressive and anxiety disorders. Although psychiatric epidemiology has provided us insight into the high prevalence of depressive and anxiety disorders and their large impact on public health, there is relatively much less known about the long-term course of these disorders and its determinants. NESDA's large sample size and detailed assessment of both mental health outcomes and determinants. In sum, NESDA provides a unique opportunity to learn more about the prognosis of two of the most common and burdensome disorders for society. Better prediction of prognosis will allow more accurate and efficient planning of the limited health care resources and thereby ultimately contribute to health improvement of patients with depressive and anxiety disorders.

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DECLARATION OF INTERESTS

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TABLES

Table 1. Overview of the number of NESDA respondents per recruitment setting

	Total (*N*)	*N* without any dep/anx disorder	*N* with current[1] dep/anx disorder	*N* with lifetime[2] dep/anx disorder
Recruited from community				
Subjects with life-time dep/anx disorder[3]	303	0	104	303
Subjects with parents with dep/anx disorder[4]	261	138	47	123
Recruited from primary care				
Controls: no dep/anx symptoms or disorder	373	373	0	0
Subjects with subthreshold symptoms[5]	141	141	0	0
Subjects with non-current dep/anx disorder[1]	353	0	0	353
Subjects with current dep/anx disorder[1]	743	0	743	743
Recruited from mental health organizations				
Subjects with current dep/anx disorder[1]	807	0	807	807
Total	2981	652	1701	2329

Note: Dep/anx disorder = depressive or anxiety disorder.
[1] Current = six-month prevalence.
[2] Lifetime disorders include current diagnoses as well as diagnoses earlier in life.
[3] From NEMESIS (see Methods section).
[4] From the ARIADNE study (see Methods section).
[5] Defined as K-10 score ≥ 20 or positive anxiety screening questions or a DSM-diagnosis of minor depression, but not having a (prior) history of dep/anx disorder according to the CIDI interview.

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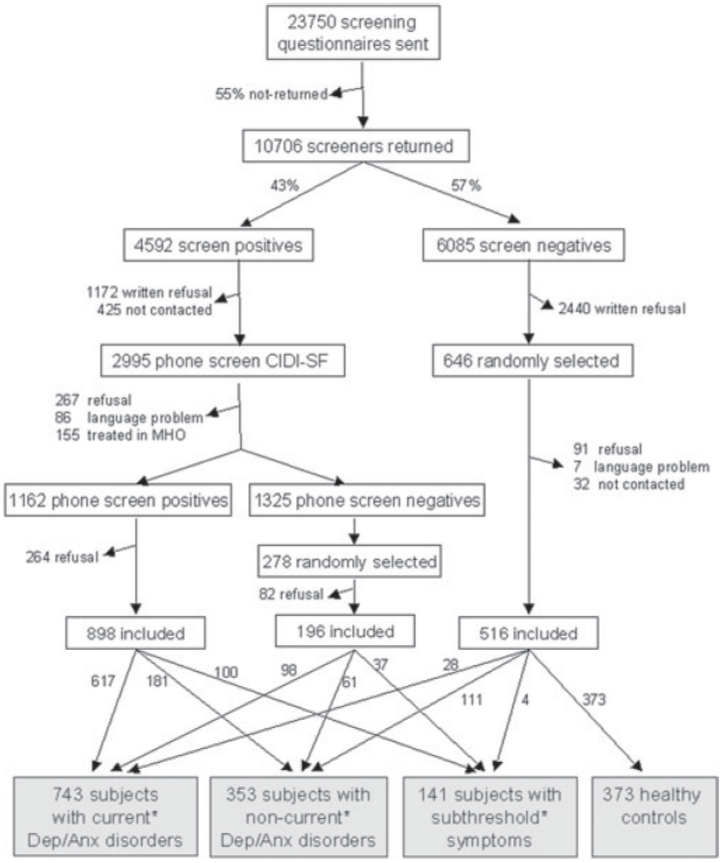

Figure 1. Recruitment flow of NESDA respondents in the primary care setting. *Current = presence during the last six months; non-current = presence before the last six months; subthreshold symptoms are defined as screen-positives or having minor depression according to the CIDI interview.

Table 2. Baseline number of depressive or anxiety disorders among the 2981 NESDA respondents

	Number of Current[1] disorders	Number of Lifetime[2] disorders	Percentage disorders with age of onset <30 years	Percentage disorders[1] with duration >2 years[3]
Major Depressive Disorder (MDD)	1115	1925	56.7	34.1
Dysthymia[3]	305	663	55.8	70.3
Panic disorder with/without agoraphobia	670	878	65.4	53.7
Social Phobia	665	908	82.0	51.7
Generalized Anxiety Disorder (GAD)	464	784	53.7	58.1
Agoraphobia without panic disorder	187	288	58.0	58.1
Total number of disorders	3406	5446		

[1]Current = six-month prevalence.
[2]Lifetime disorders include current as well as diagnoses earlier in life.
[3]Measured using the Life Chart method and defined as reporting symptoms during at least 24 out of the 48 months prior to baseline.

Table 3. Collected baseline information on central (mental) health outcomes in NESDA

Topic	Baseline measurement instrument	Reference	Method
Psychopathology			
Presence of depressive disorder	CIDI: MDD, MinD, Dysth	Wittchen, 1994	Int
Presence of anxiety disorder	CIDI: SocPhob, AgoraPhob, GAD, PAN	Wittchen, 1994	Int
Presence of alcohol disorder	CIDI: alcohol abuse and dependency	Wittchen, 1994	Int
Severity of depression			
–depressive symptoms	Inventory of depressive symptoms	Rush et al., 1996	SR
–bipolar symptoms	Mood Disorder Questionnaire	Hirschfeld et al., 2000	SR
–suicidal ideation	Beck Scale for suicide ideation	Beck et al., 1979	Int
Severity of anxiety			
–GAD/panic symptoms	Beck Anxiety Index	Beck et al., 1988	SR
–phobia symptoms	Fear questionnaire	Marks and Mathews, 1979	SR
Severity of alcohol disorder			
–alcohol dis. Symptoms	Audit	Babor et al., 1989	SR
Dimensional categorization	Mood and anxiety symptoms question.	Watson et al., 1995	SR
General distress	Four-dimensional symptom questionnaire	Terluin et al., 2006	SR
Somatization symptoms	Four-dimensional symptom questionnaire	Terluin et al., 2006	SR
Course of symptoms	Life-chart	Lyketsos et al., 1994	Int
(Public) health consequences			
Disability severity	WHO-Disability Assessment Schedule II	Chwastiak and Von Korff, 2003	SR
Disability days	Disability days	Sheehan et al., 2001	Int
Work productivity	TIC-P	Hakkaart-van Roijen, 2002	Int
Health care use	TIC-P and registration by GPs	Hakkaart-van Roijen, 2002	Int/GP
Medication use	Drug container observation + GP data	n/a	Int/GP
Somatic diseases	Presence + symptoms of disease	n/a	SR/GP
Mortality/causes of death	Information from proxies, GPs and the Netherlands Central Bureau of Statistics	n/a	Proxy, GP/DR

Note: SR = self-report; Int = interview; GP = data collection through general practitioner records; DR = death records.

Table 4. Collected baseline information on important determinants of (mental) health outcomes in NESDA

Topic	Baseline measurement instrument	Reference	Method
Demographic and personal characteristics			
Demographics			
Age, gender, ethnicity	Standard questions	n/a	Int
Partner + household status	Standard questions	n/a	Int
Socio-economic status	Education, income, occupation	n/a	Int
Personal history			
Important life events	Brugha questionnaire	Brugha et al., 1985	Int
Childhood trauma	NEMESIS questionnaire	de Graaf et al., 2002	Int
Daily hassles	Daily Hassles questionnaire	Kanner et al., 1981	SR
Patient's perspective			
Psychosocial function			
Social support and activity	Close Person Inventory	Stansfeld et al., 1992	SR
Work content/environment	Karasek questionnaire	Karasek et al., 1998	Int
Loneliness	De Jong-Gierveld loneliness scale	de Jong-Gierveld and Kamphuis, 1985	SR
Affiliation	Van Tilburg scale	van Tilburg, 1998	SR
Personality	NEO-FFI questionnaire	Costa and McCrae, 1995	SR
Locus of control	Pearlin and Schooler mastery scale	Pearlin and Schooler, 1978	SR
Worry	Penn–State Worry Scale	Meyer et al., 1990	SR
Anxiety cognitions	Anxiety Sensitivity Index	Peterson and Reiss, 1992	SR
Depression cognitions	LEIDS questionnaire	van der Does et al., 2002	SR
Experimental cognitive task	Implicit Association Test	Greenwald et al., 1998	CT
Health care attitude			
Need of care	Perceived Need of Care questionnaire	Meadows et al., 2000	Int
Patient evaluation of care	QUOTE questionnaire	Sixma et al., 1998	SR
(Biological) health and genetic measures			
Health behaviour			
Regular alcohol intake	Drinking behavior questions	n/a	SR
Drugs	Soft and hard drugs questions	n/a	SR
Smoking	Past + current smoking questions	n/a	SR
Nicotine dependence	Fagerstrom questionnaire	Heatherton et al., 1991	Int
Benzodiazepine dependence	Bendep SRQ	Oude Voshaar et al., 2003	Int
Physical activity	IPAQ questionnaire	Craig et al., 2003	SR
(Biological) health markers			
Presence of 20 diseases	Standard self-report questions + GP data	n/a	Int, GP
Pain	Chronic graded pain scale	von Korff, 1992	Int
Sleep	Insomnia Rating Scale	Levine et al., 2003	SR
Pulmonary function	Peak flow measurement	n/a	ME
Muscle strength	Grip strength assessment	n/a	ME
Biomarkers	Fasting blood sample	n/a	Blood
Body composition	Weight, height, waist + hip circumference	n/a	ME
Blood pressure (BP)	Systolic and diastolic BP assessment	n/a	ME
Peripheral atherosclerosis	Doppler assessment of ankle-arm index	n/a	ME
Autonomic nervous system	Electro + impedance cardiography	de Geus et al., 1995	ME
HPA-axis (salivary cortisol)	Seven saliva samples, including DST test	n/a	Saliva
Genetic measures			
Family history	Family tree inventory	Fyer and Weissman, 1999	Int
DNA/lymphocytes	Full blood	Boomsma et al., 2008	Blood
Proteomics	Serum	Boomsma et al., 2008	Blood
Gene-expression (RNA)	Before + after LPS-challenge	Boomsma et al., 2008	Blood

Note: SR = self-report; Int = interview; GP = data collection through general practitioner records; Blood = data collection via fasting blood sample; CT = computer task; ME = medical examination.