The interplay between depression, anxiety and objectively measured physical function

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2021

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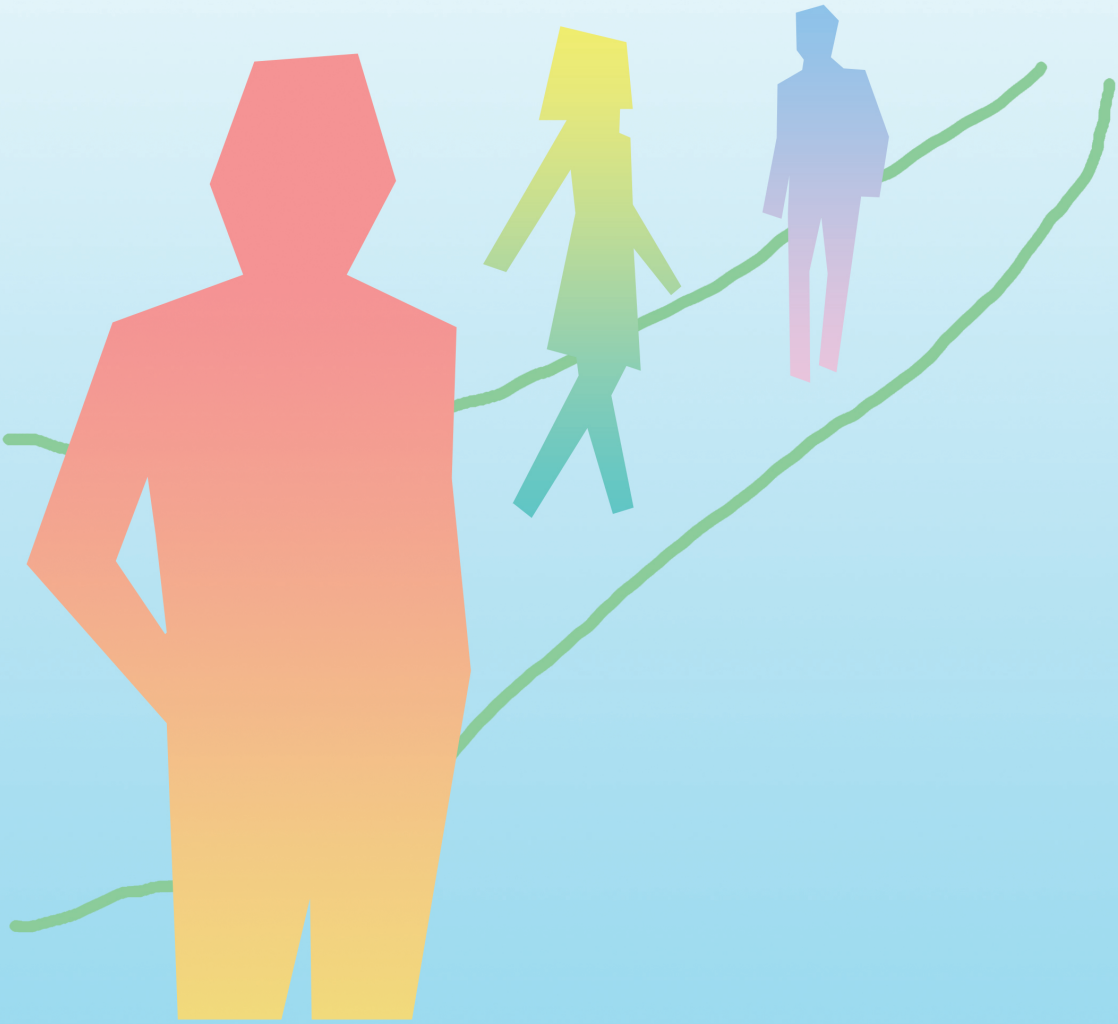

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This thesis was prepared at the Department of Research and Innovation at GGZ inGeest, and the Department of Psychiatry, Amsterdam UMC, VU University Amsterdam, within the Amsterdam Public Health research institute.

Financial support for the publication and distribution of this thesis was kindly provided by the Department of Psychiatry, Amsterdam UMC, VU University Amsterdam.

Cover design	Laurens Teunen | Laurens Fotografie
Layout	Renate Siebes | Proefschrift.nu
Printed by	ProefschriftMaken | De Bilt
ISBN	978-94-6423-443-5

VRIJE UNIVERSITEIT

The interplay between depression, anxiety and objectively measured physical function

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor of Philosophy
aan de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. V. Subramaniam,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op dinsdag 16 november 2021 om 11.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

Bianca Arianne Lever-van Milligen

geboren te Alphen aan den Rijn

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CHAPTER 1

General introduction

GENERAL INTRODUCTION

This dissertation examines the relationship between depressive and anxiety disorders and objective physical function. First, both elements of this relationship will be defined. Following this, the rationale for studying the association between depressive and anxiety disorders and physical function will be described. The Chapter concludes with formulating the specific aims that this dissertation will address and the research approach that will be used for this.

1. Depressive and anxiety disorders

Depressive and anxiety disorders are common mental disorders. Worldwide, the lifetime prevalence of depressive disorders and anxiety disorders is approximately 20% [1, 2]. These mental disorders are often comorbid (40-65%) [3] and have substantial impact on daily functioning [4]. More women are affected than men. Most prevalent depressive and anxiety disorders are major depressive disorder (MDD), dysthymia, social phobia, generalized anxiety disorder, and panic disorder with and without agoraphobia [5]. Psychiatric disorders are typically classified and diagnosed based on criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM; fourth edition in this dissertation). The DSM is widely used by clinicians to categorize mental symptoms [6]. A description of the psychiatric disorders included in the presented studies in this dissertation is given below.

MDD is characterised by a depressed mood and/or loss of interest in almost all activities during the largest part of the day for at least two consecutive weeks. In total at least five out of 9 core depression symptoms need to be experienced by the patient and at least one of the symptoms is either depressed mood or loss of interest or pleasure. The other depressive symptoms include loss or increase of weight or appetite, insomnia or hypersomnia, psychomotor retardation or agitation, fatigue or loss of energy, feelings of worthless or inappropriate guilt, difficulty concentrating or decision making, and recurrent thoughts about dead and/or suicide. Symptoms need to be present during a major part of the day, resulting in limitations in daily functioning. Dysthymia is a more milder type of depression, but with a chronic duration as symptoms are continuously present during at least two years.

Social phobia is expressed by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The fear exists of acting in a way that will be humiliating

or embarrassing and could lead to social or occupational impairment. Generalized anxiety disorder (GAD) is characterized by worrying about a number of everyday situations for at least six months. This worrying could lead to restlessness, fatigue, difficulty concentrating, irritability, increased muscle tension or sleep disturbance. These worry and physical symptoms cause clinically significant distress or impairment in daily functioning. Panic disorder consists of recurrent unexpected anxiety attacks which are paired with extreme fear and which may be accompanied with avoidance of the feared places (agoraphobia). Furthermore, persistent concerns about having additional attacks, the consequences of the attacks or significant change in behavior related to the attacks are present during at least one month after a panic attack.

The World Health Organization (WHO) states that depressive and anxiety disorders are leading causes of disability worldwide and that depression and anxiety are major contributors to the overall global burden of disease [7]. As we know from earlier research, depressive and anxiety disorders are accompanied with an increased risk of somatic comorbidity, mortality, disability, work loss and sick days and use of health care which contributes to high societal costs [8]. An underlying problem of the increase of these accompanying factors could be a deterioration of physical function, as this is strongly associated with somatic disorders [9, 10], mortality [11] and disability [12]. However, its link with depressive and anxiety disorders asks for a structured and well-measured evaluation. Therefore, it is important to increase our knowledge about the relationships between depressive and anxiety disorders and physical function in order to better prevent and treat functional consequences of depressive and anxiety disorders.

2. Physical function

The ICF (International Classification of Function, Disability and Health [12]) identifies three levels of human functioning: functioning at the level of body or body part (physiological function of body systems and anatomical parts of the body), the whole person, and the whole person in a social and environmental context. This is a multi-perspective approach to the classification of functioning and disability as an interactive and evolutionary process. Figure 1.1 presents the ICF biopsychosocial model of disability.

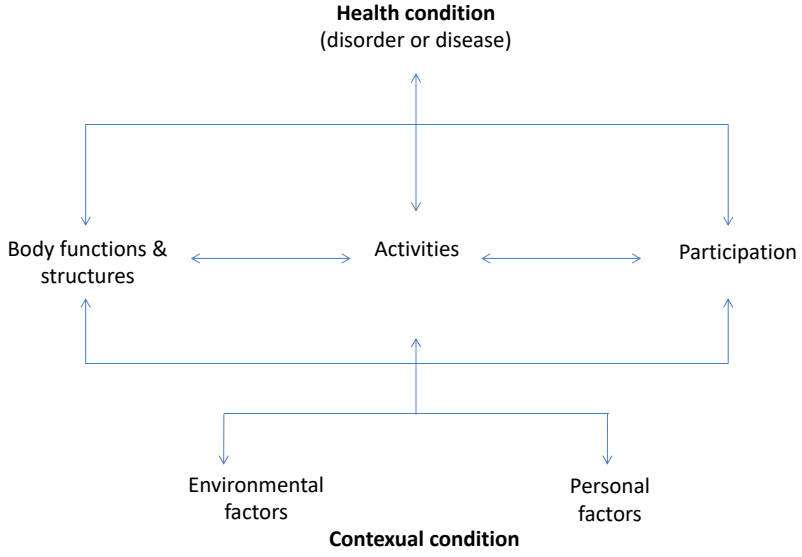

Figure 1.1. WHO ICF biopsychosocial model of disability.

Disability is any continuing condition that restricts every day activities. It is a complex phenomenon and contains interactions between health and contextual conditions. Health conditions include disorders, diseases and injuries while contextual conditions include environmental factors (the physical, social and attitudinal environment such as social attitudes and climate) and personal factors (such as age, gender, coping styles and other factors that influence how disability is experienced by the individual).

Functioning at the level of the body function and structures focuses on impairments (e.g. problems in body function or structure such as conceptualized in poor muscle strength, poor balance and low walking speed), whereas functioning in terms of limitations in activity (for example climbing the stairs) or participation restrictions (such as absenteeism or presenteeism at work) focus more on the whole person.

For this dissertation, the focus is on physical function as determined at the impairment level – so (dys)function assessed at the body level. Physical function at this level is defined as the ability to perform the basic actions that are essential for maintaining independence and carrying out more complex activities such as mobility, muscle strength and endurance [13]. Physical function increases during childhood and adolescence, peaks during early adulthood and then declines linearly with advancing age [14]. One of the most important predictors of physical function is physical activity which has a positive effect on physical function [15], while a sedentary lifestyle and

chronic diseases impact physical function negatively [16]. A high level of physical functioning is related to high quality of life, better cognitive function [17, 18] and lower mortality rates [19]. It is also associated with less injuries or accidents such as falling and with less somatic health complaints [20, 21].

Overall, physical function seems to start to decrease at age 30 to 40 [14, 22] with a steeper decline starting after 50 years of age, which means that this group could already experience disabilities. Moreover, experiencing a disease can have a negative impact on physical function with consequently more decline of physical function. It is well-known that somatic diseases negatively influence physical functioning, although the literature also increasingly shows evidence for the negative impact of mental disorders on physical function. For example, higher severity of depression seems to be associated with poor function [23]. To prevent large physical deterioration at older age, it is important to identify important determinants of decreased physical function in an adult populations [24].

Measuring physical function at the body level is important to identify those with vulnerability for disability. Targeting decrease of physical function might help to select interventions focusing at increasing physical function to prevent physical disability.

Methods of measuring physical function are diverse in research. Clearly, physical function is mostly measured in terms of limitations in activity or participation restrictions. For this, most studies use self-report measures such as the WHO-DAS or the SF-36 instruments [25, 26]. Such self-reported physical function may be biased by current mood, cognition or personality, since these assessments can be influenced by the self-perception of functioning. This may especially be an issue in psychiatric populations, where self-reports may be skewed towards negative bias [27]. There is much less focus within the psychiatric research field on the physical function at the body level, by measuring impairments. However, there are standardized and validated objective performance-based measures such as walking speed, hand grip strength or chair rise tests [28]. Although objective performance-based measurements may also partly depend upon subject's motivation to perform, several studies suggested that objective measures provide qualitatively better information compared to self-reports. Brach et al. [29] showed that using performance-based physical function measures identified more limitations in physical function than self-report measures did in a sample of community-dwelling older women. This was confirmed by the study of Goldman et al. [30] that showed that using objective physical function measures to predict all-cause mortality had an incremental value beyond self-reports. Furthermore,

Cesari et al. [28] also confirmed better prediction of mortality by performance-based measures compared to self-report questionnaires. Objective performance-based tests may be more likely than self-report questionnaires to capture the integrated and multisystemic effects of aging, comorbidity, disease severity, malnutrition, motivation and cognition [15]. Therefore, using objective measurements of physical function may provide a more objective, integrative tool for evaluating functional limitations for clinical and research purposes. However, most objective performance-based tests were developed for use in older persons, but may not be sensitive enough for finding differences in functional capacity in younger and high functioning older populations [13]. For example, the 6-meter walk test or sit-up-and-go test have ceiling effects in younger age groups [31]. Two examples of objective measures which in earlier research have shown to be valid in younger populations are hand grip strength and lung function. These are measures that will be used as assessments in this dissertation. Both these measures can be interpreted as objective physical function indicators, since they have shown to predict higher disability and mortality in older and also in middle-aged populations [17, 19, 30, 32].

Hand grip strength

Hand grip strength is one of the most widely reported and recommended objective performance-based measurements [33]. This instrument gives a good indication of overall bodily muscle strength and is therefore often used as a global index of muscular strength. It has an important role in the evaluation of functionality. Hand grip strength is influenced by age, sex, height, weight and hand dominance [34]. Hand grip strength is found to be correlated to self-report measures such as 'The Disability of the arm, shoulder and hand outcome measure' (DASH) [35].

However, the indicator of hand grip strength does not just reflect upper extremity function. A review of Chainani et al. [36] shows evidence for hand grip strength as an important predictor for overall mortality. Furthermore, hand grip strength was found to predict overall disability [37]. The literature also shows proof of an association between poorer hand grip strength and cognitive decline [18, 38] and between poorer hand grip strength and the prevalence of cardiovascular diseases [39]. Following this, hand grip strength has been suggested to play an important role in detecting health problems and seems to be a good instrument for measuring objective physical function.

In the studies presented in this dissertation, hand grip strength was measured with a Jamar hand held dynamometer [40] which is considered to be the golden standard

among handgrip strength dynamometers [33]. It is a hydraulic instrument that measures grip strength in kilograms or pounds of force. The inter-rater and test-retest reliabilities are high, it is fast and easy to perform and produces a result which is simple to record.

Lung function

As earlier mentioned, physical function decreases already at age 30-40 years, and reaching a higher lung function capacity at this age will prevent large decline in later life. The literature shows that lung function during life time is positively influenced by younger age, lower BMI, more physical activity, healthy environment, less smoking and in minor proportions better socio-economic factors [41].

Strong evidence was found for associations of lung function and general physical health [42]. Poor lung function was associated with subsequent disability, somatic diseases and mortality [43, 44]. The literature shows also evidence for a relationship between poor lung function and cognitive decline in which neurological problems, heart failure and obesity are underlying mechanisms [45]. Lung function was correlated with self-report measures of physical function [30].

Spirometry is a method to objectively measure lung function [46] and is used to detect changes in ventilatory performance and tracking respiratory illness [47]. One of the most common spirometric parameters is the peak expiratory flow, which is defined as the maximum flow achieved during expiration delivered with maximal force starting from maximal lung inflation [48]. A peak flow meter is inexpensive, the inter-rater and test-retest reliability are high and it is simple to use [49]. Optimal lung function is needed for adequate performance in daily life. Lung function increases during early adulthood and some studies have indicated that during growth, stage and development of anthropometric characteristics play a fundamental role in the determination of the spirometry muscle strength [50] and therefore in the growth of lung function. It can be concluded that a spirometry lung function measurement seems to be a good instrument for measuring physical function and is used in the studies in this dissertation.

Beyond hand grip strength and lung function, one chapter in this dissertation is focused on examination of hemoglobin level in relationship to mental health. A good health condition may prevent disability in case of an impairment. However, a poor health condition could worsen the disability level and could even cause large problems in

daily functioning. To identify problems in health to further prevent disability, it is important to measure health. There are multiple options to measure somatic health. As just one example, we examined a generic mechanism of somatic health through measurement of hemoglobin level.

Deviated hemoglobin level could be an indicator of a chronic disease or vitamin deficiency which both have been linked to disability [51]. Hemoglobin is a protein molecule in red blood cells that contains an iron molecule and carries oxygen from the lungs to the body tissues and returns carbon dioxide back to the lungs. Reference values of hemoglobin are 12.5-15.0 g/dl for women and 13.5-17.5 g/dl for men.

Abnormal values of hemoglobin can lead to health problems of which clinically low hemoglobin level (anemia) is the most prevalent. Anemia is a global health problem in both developed and developing countries [52, 53]. Main causes of anemia are iron deficiency, blood loss due to a disease e.g. cancer or trauma, or somatic diseases such as kidney disease or red blood cell synthesis problems. Effects of anemia can be tremendous e.g. weakness, shortness of breath, pale skin, chest pain or restless legs syndrome. However, also high hemoglobin can have effects on the body's health. Most evidence, however, has been published about low hemoglobin level which has been linked to diabetes, hypertension, cardiovascular diseases, kidney disease [54] and cognitive impairment [55, 56].

The literature shows important evidence for associations between low hemoglobin level (anemia) and poor physical function [57–59]. However, these studies were mostly performed in the elderly in which anemia is more present since hemoglobin level decreases by increasing age [60]. However, less research has been done that examined the relationship between abnormal values of hemoglobin and mental problems. In the elderly, lower hemoglobin levels were associated with depression [61]. However, in adult populations the association between hemoglobin level and mental disorders remains unclear.

3. The association between depressive and anxiety disorders and objective physical function

Depressive and anxiety disorders are accompanied with more physical disability due to functional impairments in daily life. These effects of depression and anxiety are chronic, and are comparable to the effects of somatic diseases on physical disability [62]. The study of Quiñones et al. [63] shows that multimorbidity of both somatic

and mental conditions are associated with substantially greater prospective disability. They have shown that the presence of depression or cognitive impairment increases disability. Other studies confirmed these results and found that multimorbidity is linked to poorer quality of life [64]. More specific research focused on the relationship between mental disorders and physical disability is growing and results show overall increased disability in mentally diseased patients [65–67].

There is large evidence showing that persons with depressive and anxiety disorders have poorer physical function compared to healthy persons [68–70], based on self-report measures. These outcomes are clinically relevant since these patients who did experience poorer functioning reported more impairments in daily life compared to those with better physical functioning, resulting in more health care use and less working days [71, 72]. However, as earlier mentioned, using objective physical function measures instead of self-reported questionnaires, can overcome bias of mood [27]. In the last decade, literature focused on the relationship between objectively measured physical function and depressive and anxiety disorders has been mostly focused at the elderly. In this age group, evidence for poorer objectively measured physical function in depressed and anxious persons has been growing [73–75]. However, research focusing on objectively measured physical function and depressive and anxiety disorders in adult populations where mental health disorders are actually very frequent, is scarce. Some interesting relationships are shown in the literature such as poorer hand grip strength and lung function in those with mental health problems [32, 73, 76–78]. Furthermore, earlier research was often cross-sectional. It is unclear how the longitudinal relationship between depressive and anxiety disorders and objective physical function is in adults.

It is relevant to examine physical function in depressed and anxious patients from a number of reasons. First, it is necessary to examine to what extent objective physical impairments are really poorer in affective disorder patients. Second, it is important to determine the longitudinal nature of such association, in order to understand whether poorer physical function is driving disease (course) or whether poorer physical function is also a consequence of disease. Third, detecting poor physical function during depression or anxiety could help the practitioner to address physical function and e.g. zoom in with such patients on potential benefits of exercise and other strategies for preventing physical disability. This dissertation contributes to this research field, by examining the relationship between objective physical function and depressive and anxiety disorders.

4. Potential underlying mechanisms connecting poorer physical function and depression/anxiety disorders

When delving into the relationship between depression, anxiety and objective physical function, the questions arises which mechanisms are potential underlying in these associations. The literature show evidence for unhealthy lifestyles, such as physical inactivity, smoking, alcohol drinking, poorer self-management and adherence to treatment, as linking variables to depression and anxiety as well as to physical disability [79, 80]. Another potential underlying mechanisms may be dysregulated physiological stress systems, such as higher levels of inflammation, dysregulation of the HPA-axis and disturbed autonomic nervous system (ANS) functioning, which have shown to be present in depressive and anxiety disorders [81–85]. Such biological stress system dysregulations could also be linking pins to poorer physical health and function.

Experiencing acute or chronic stress can result in physiological changes in the body. In a stress situation, a stress reaction could arise based on sensory input and processing. The hypothalamus is then activated and stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH stimulates the adrenal glands to produce the hormone cortisol. Cortisol enables the body to maintain steady supplies of blood sugar and helps to cope with the stressor and also helps the body to return to normal. The hypothalamus also activates the autonomic nervous system (ANS). This system acts as a control system to maintain homeostasis in the body. These activities are generally performed without conscious control. The ANS system secretes the hormone adrenaline which gets the body ready for a fight or flight response. Adrenaline leads to the arousal of the sympathetic nervous system and reduced activity of the parasympathetic nervous system. Adrenaline creates changes in the body such as decreases in digestion and increases of sweating, increased pulse and blood pressure. The immune system is overactive as well in a stressful situation. Especially higher levels of C-reactive protein (CRP), Interleukin-6 (IL-6) and TNF-α were found in persons experiencing stress. Chronic low-grade inflammation is linked to cardiovascular diseases and mortality [86, 87].

Furthermore, the literature shows, in less extent, some evidence for a role of these dysregulations (inflammation [88], HPA-axis [89] and ANS [90]) also in poorer objective physical function. Consequently, research is necessary to understand the impact of dysregulation of stress systems on depression, anxiety and on physical function, and examine whether stress dysregulations could explain the potential depression/anxiety and physical function association.

5. Clinical view

Mental health organizations give limited attention to physical function and the role of lifestyle. However, looking at the guidelines of general practitioners and mental health for depressive and anxiety disorders, prevention and treatment interventions are stepwise constructed. The first step is a focus on healthy lifestyle and getting structure in daily life. In the following steps, self-management of the problems, psychotherapy, antidepressants medication and intensive treatment programs will follow. During the first step, namely lifestyle, the focus is on smoking, alcohol and exercise. In the next steps, also running therapy is mentioned as an effective intervention for depressive and anxiety disorders. Exercise in daily life and running therapy could help the patients to get physically stronger and should be an important intervention in the total treatment program of depressive and anxiety disorders. However, widespread implementation of running therapy is lacking. The literature shows proof of the effectiveness of running therapy as an intervention, both as single as well as add-on treatment, for patients with depressive and anxiety disorders [91–93]. Running therapy is included in the multidisciplinary guidelines of depression and anxiety and seems to be comparable with antidepressants in effectiveness for depression and anxiety disorders [91]. However, the evidence of these effects of running therapy is less examined than for example the impact of antidepressant or cognitive behavior therapy. Also, the effects of running therapy and other established treatments, such as antidepressant use, have hardly been directly compared. Finally, we know little about the exact pathways through which these different interventions are effective, so studies that evaluate and compare different treatments should measure not only mental health outcomes but also physical and potentially underlying biological outcomes in order to increase our understanding of mechanisms of action.

So, our research team conducted an intervention study, MOTAR (Mood Treatment with Antidepressants or Running therapy) for patients with depressive or anxiety disorders in which the patients received antidepressants (Selective Serotonergic Reuptake Inhibitors, SSRIs) or running therapy (3 times a week) during 16 weeks. Before and after treatment, research assessments were taken including a psychiatric diagnostic interview, blood samples (including e.g. physiological stress markers), hemoglobin level, hand grip strength, lung function and various other variables. Chapter 7 includes the published study protocol of the MOTAR study.

6. Study used in this dissertation: NESDA cohort

All studies in this dissertation are based on data from the Netherlands Study of Depression and Anxiety (NESDA). NESDA is a large ongoing longitudinal cohort study designed to examine the course and consequences of depressive and anxiety disorders. A total of 2981 respondents, aged 18-65 years, were recruited from the general population (19%), primary care (54%) and mental health organizations (27%) to represent various settings and stages of psychopathology. Exclusion criteria were not being fluent in Dutch and having a primary diagnosis of psychotic, obsessive compulsive, bipolar or severe addiction disorder. At baseline, 57% of the respondents had a current depressive and/or anxiety disorder, 21% of the respondents had a remitted disorder and 22% had no lifetime depressive and/or anxiety disorders. The NESDA protocol was approved by the Ethical Committee of participating universities and all respondents provided written informed consent. Baseline assessments took place between 2004 and 2007 and every few years another assessments took place (2, 4, 6 and 9 years). The 4-hour face-to-face assessments consisted of a medical examination, written questionnaires, a diagnostic interview, computer tasks and a collection of blood, saliva or hair. Specially trained clinical research staff conducted the assessments. This dissertation used data of baseline and two-, four- and six-year follow-up. Follow-up assessments had response rates of 87.1% (N = 2595) at two-year follow-up, 80.6% at four-year follow-up and 75.7% at six-year follow-up. A detailed description of the rationale, methods and recruitment strategy is reported elsewhere [94].

7. Aims and outline of this dissertation

The overall main goal of this dissertation is to examine the relationship between depressive and anxiety disorders and objective physical function in a middle-aged sample with (subclinical) depressive and anxiety disorders and healthy controls. This sample, originated from the NESDA study, is large and representative for persons with depressive and anxiety disorders since these persons were recruited in various settings with different stages of psychopathology. Furthermore, the NESDA study included two objective physical function measures (hand grip strength and lung function), a blood collection with determination of e.g. hemoglobin level, various indicators of different physiological stress systems and important covariates. This comprehensive dataset provides us the opportunity to answer our research questions.

In particular, the ***first aim*** is to examine the cross-sectional association between depressive and anxiety disorders and objective physical function. In *Chapter 2* the association between hemoglobin level and depressive and anxiety disorders will be examined. *Chapter 3* describes the association between objective physical function measured with hand grip strength and lung function and depressive and anxiety disorders.

The ***second aim*** was to describe the longitudinal association between depressive and anxiety disorders and physical function. In *Chapter 4* we examine whether objective physical function at baseline is a predictor for the persistence of depressive and/or anxiety disorders at two-year follow-up. *Chapter 5* investigated the six-year trajectory of objective physical function in persons with depressive and/or anxiety disorders.

The ***third aim*** was to investigate the potential underlying mechanisms of the relationship between depressive and anxiety disorders and objective physical function. More precisely, in *Chapter 6* we evaluate whether physiological stress systems are associated with objective physical function.

In *Chapter 7* the design of the MOod Treatment with Antidepressants or Running (MOTAR) study is described. Finally, in *Chapter 8* the main findings are discussed, clinical implications are made and suggestions for further research are presented.

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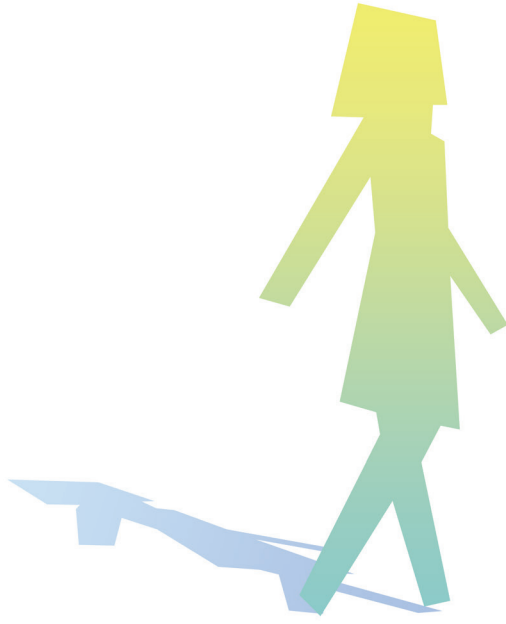

CHAPTER 2

Hemoglobin levels in persons with depressive and/or anxiety disorders

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Published in Journal of Psychosomatic Research 76 (2014):317-321.

ABSTRACT

Objective: Both low and high hemoglobin levels lead to more physical diseases, and both are linked to mortality. Low hemoglobin, often classified as anemia, has also been linked to more depressive symptoms, but whether both hemoglobin extremes are associated with depressive disorder and potentially also with anxiety disorder, has not been examined before. This study examines to which extent hemoglobin levels are associated with depression and anxiety disorders in a large cohort.

Methods: The study sample consisted of 2920 persons from the Netherlands Study of Depression and Anxiety. Hemoglobin levels were determined after venipuncture. Depressive and anxiety disorders were determined according to a DSM-IV based psychiatric interview. Clinical psychiatric characteristics included severity of depression and anxiety, duration of symptoms, the age of onset and the antidepressant use.

Results: Higher hemoglobin levels were found in those with current depressive and/or anxiety disorders after sociodemographic adjustment and both higher, and lower hemoglobin levels were found in persons with higher depression and anxiety severity. However, after full adjustment for sociodemographics, disease indicators and lifestyle, associations were no longer significant.

Conclusions: This cohort study showed that there is no independent association between depressive and/or anxiety disorders and hemoglobin levels or anemia status.

Key words: depression, anxiety, hemoglobin, anemia.

1. INTRODUCTION

Extreme hemoglobin levels (Hb), both low and high levels, lead to deteriorated quality of life [1, 2], have been associated with greater mortality in elderly persons [2, 3] and have been linked to the development of diseases, such as heart failure or cardiovascular diseases (for low hemoglobin levels) [4, 5] and hypertension or thrombosis (for high hemoglobin levels) [6].

Beyond these physical health problems, previous research has shown that low hemoglobin level (anemia) is associated with more depressive symptoms [7-11]. Such an association could be expected since symptoms of low hemoglobin level (paleness, fatigue, dizziness, shortness of breath during physical activity, higher heart beat in resting state and heart fluttering) also often occur when having depressive (or anxiety) symptoms. This association between low hemoglobin level and depression could potentially be explained by underlying poorer physical health status such as fatigue [12-14], reduced levels of brain oxygen [15], vitamin B12 deficiency [16-18] or higher inflammatory levels [19-21]. Earlier studies on anemia and depression included elderly or diseased persons only, and did generally not consider the presence of psychiatric disorders but used self-report measures of depressive symptomatology. Consequently, whether low hemoglobin levels are associated with psychiatric depression in a younger adult sample needs to be clarified. In addition, whether an association between anemia and mental health extends to anxiety disorders, a highly comorbid condition to depression with partly shared pathophysiology, needs to be established as well. Furthermore, whether high hemoglobin levels are also associated with depressive and anxiety disorders, has not been examined before. Such an association could be expected since both high hemoglobin and depressive and anxiety disorders are associated with vascular disease [6, 22, 23] and smoking [24, 25] probably due to increased blood viscosity [26].

This cohort study examines the association between hemoglobin levels and the presence of depressive and anxiety disorders in an adult population. Both the low end and high end of the hemoglobin spectrum will be distinguished, considering the fact that both ends have been associated with poorer health. We also examined whether an association between low or high hemoglobin levels and psychiatric disorders is dependent on clinical psychiatric characteristics, such as severity, duration, age of onset of the depressive or anxiety disorder and antidepressant use.

2. METHODS

Study sample

The Netherlands Study of Depression and Anxiety (NESDA) is an ongoing longitudinal cohort study that investigates the long-term course and consequences of depressive and anxiety disorders. During a 4-hour measurement, a wide range of data were collected, including assessment of demographics, a diagnostic psychiatric interview and a medical examination including blood collection. All respondents signed an informed consent. The NESDA protocol was approved by the ethical review board of all participating universities. A total of 2981 respondents, aged 18-65 years, were recruited from the general population (19%), primary care (54%) and mental health care organizations (27%) to represent various settings and stages of psychopathology. General population based persons had previously participated in the Netherlands Mental Health Survey and Incidence Study (NEMESIS) (27) or the Adolescents at Risk for Anxiety and Depression (ARIADNE) study [28]. The NEMESIS participants were selected when a 12-months recency diagnoses of depressive or anxiety disorder was met at baseline or during follow-up. A total of 776 participants of NEMESIS were selected and 662 were approached. Of these, 303 persons were willing to participate in NESDA. The ARIADNE participants (*N* = 528) were asked for participating in NESDA when they did not have a CIDI diagnosis of excluding psychiatric diagnoses, were fluent in Dutch and were willing to participate in NESDA (*N* = 261). Primary care patients were identified through a three-stage screening procedure. Screening questionnaires were sent to a random sample of 23750 patients aged 18-65 years who consulted their general practice in the last 4 months irrespective of reason for consultation. The screening questionnaire consisted of the Kessler-10 [29] with proven qualities for affective disorders. A screen-positive score on the K-10 was defined as a validated K-10-score of ≥ 20 or a positive score on one of the five added anxiety questions. A total of 10706 persons returned the screener and 4887 were screen-positive. These persons were approached for a short phone-screen interview consisting of the CIDI-short form sections of depression and anxiety. 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. A total of 743 participants with a current (6 months recency) and 353 participants with a non-current depressive or anxiety disorder were recruited, as well as 141 persons with subtreshold symptoms (screen-positives not fulfilling diagnostic criteria). Furthermore, a random selection

of the screen-negatives (both from the written screener and phone-screen) also participated (373 participants) and constituted a 'healthy control group'. Mental health care patients were recruited when newly enrolled in the participating mental health organizations with a primary depressive or anxiety diagnoses (*N* = 1597). Of those, 807 persons with a current depressive or anxiety disorder were willing to participate in NESDA. Exclusion criteria for the NESDA study were not speaking Dutch and a known primary clinical diagnosis of bipolar disorder, obsessive-compulsive disorder, severe addiction disorder, psychotic disorder or organic psychiatric disorder. A description of the rationales, methods and recruitment strategy is reported elsewhere [30].

To evaluate the association between hemoglobin levels and depression and anxiety, persons with missing hemoglobin levels were excluded (*N* = 61) resulting in a sample of 2920 persons consisting of healthy controls (22%) and patients with depressive and/or anxiety disorders (78%). No significant differences in basic characteristics (age, sex and years of education) were found between included and excluded persons.

Hemoglobin levels

Fasting blood samples were drawn early in the morning using venipuncture. On the same day, blood was sent to the laboratory where hemoglobin levels were determined using standard laboratory methods. Anemia was defined according to the World Health Organization (WHO) criteria as a hemoglobin (Hb) concentration < 12 g/dl (7.5 mmol/l) in women and < 13 g/dl (8.1 mmol/l) in men. High hemoglobin level was determined following the literature [2, 3] as a hemoglobin level ≥ 3.1 g/dl above the cut off value of anemia (women: ≥ 15.1 g/dl (9.3 mmol/l) and men: ≥ 16.1 g/dl (9.9 mmol/l)). As suggested by earlier studies [12, 13, 31], a categorical variable of hemoglobin was created so that the association between both low and high hemoglobin level could be examined; (1) Hb below the anemia cutoff (= anemia); 2) Hb level: 0.1-2 g/dl above anemia cutoff (reference group, considered as optimal Hb levels based on earlier studies); 3) Hb level: 2.1-3 g/dl above anemia cutoff (slightly increased hemoglobin level); and 4) Hb level: ≥ 3.1 g/dl above anemia cutoff (high hemoglobin level).

Diagnoses of depressive and anxiety disorders

Depressive disorders (including major depressive disorder and dysthymic disorder) and anxiety disorders (including social phobia, panic disorder, agoraphobia and generalized anxiety disorder) were established using the Composite International Diagnostic Instrument (CIDI, WHO version 2.1) according to the *Diagnostic and Statistical Manual*

of Mental Disorders, Fourth edition (DSM-IV). The CIDI is a valid and reliable instrument to assess depressive and anxiety disorders [32] and was administered by specially trained research staff. Participants were categorized as lifetime healthy controls (*N* = 640), remitted depressive and/or anxiety disorders (*N* = 614) and current (6-month recency) depressive and/or anxiety disorders (*N* = 1666). Depressive and anxiety disorders were analyzed together since they largely share same pathophysiology and since there was a high percentage of comorbidity (60%) in this sample.

Clinical psychiatric characteristics of depressive and anxiety disorders

Several clinical characteristics of depressive and anxiety disorders were selected to explore whether specific aspects are associated with hemoglobin levels. The severity of depression was measured with the Inventory of Depressive Symptoms (IDS, a 30-item self-report questionnaire [33]). The severity of anxiety was measured with the Beck Anxiety Inventory (BAI, a 21-item self-report questionnaire [34]). Antidepressant use was determined through drug container inspection of all drugs used in the past month and classified according to the Anatomical Therapeutic Chemical (ATC) classification: tricyclic antidepressants (ATC-code N06AA), selective serotonin re-uptake inhibitors (ATC-code N06AB) and other antidepressants (ATC-code N06AF/N06AX). The duration of depressive and anxiety symptoms was evaluated using the Life Chart method [35], in which the presence of symptoms of depressive and anxiety disorders during 4 years prior to baseline was assessed. The duration of symptoms was expressed as the percentage of time in which symptoms were present. The age of onset was retrospectively derived from the CIDI interview and when multiple disorders were present; the earliest onset was used in the analyses.

Covariates

Sociodemographics included age (in years), sex and education (in years). In addition, various disease indicators and lifestyle characteristics were considered as covariates since these have been linked to both depression/anxiety and hemoglobin levels. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. A count of the number of chronic somatic diseases for which a respondent receives treatment (including lung disease, diabetes, cardiovascular disease, cancer, osteoarthritis, intestinal disorder, liver disease, epilepsy and thyroid gland diseases) was made based on self-report. Creatinine clearance in milliliters per minute was used to account for effects of renal function and was calculated using plasma creatinine

based on the CKD-EPI formula [36]. Smoking status was defined as current or no current smoker. Alcohol intake was categorized as non-drinking (< 1 drink/week), moderate drinking (1-14 (women)/1-21 (men) drinks/week) and heavy drinking (> 14 (women)/> 21 (men) drinks/week). Physical activity was measured with the International Physical Activity Questionnaire (IPAQ) [37] and expressed in MET minutes (ratio of energy expenditure during activity compared to rest times the number of minutes performing the activity) per week.

Statistical analyses

Data were analyzed using SPSS 20.0. Sample characteristics were compared across hemoglobin level categories using one-way ANOVA for continuous variables and chi-square tests for categorical variables. Multinomial logistic regression analyses were used to examine associations between psychiatric status (no, remitted and current depressive/anxiety disorder) as predictor and hemoglobin level categories as the outcome with the Hb 0.1-2 g/dl above anemia cutoff group as the reference group. First, analyses were adjusted for sociodemographics (sex, age and education). In a second step, additional adjustments for disease indicators and lifestyle characteristics (BMI, somatic diseases, creatinine clearance, smoking status, alcohol intake and physical activity) were made. To test for possible sex interactions, age interactions and setting interactions, a sex × psychiatric status, an age × psychiatric status and a setting × psychiatric status interaction term were added to the model. Next, ANCOVAs and multinomial logistic regression analyses were performed to explore the association between hemoglobin level categories and clinical psychiatric characteristics (severity, duration and age of onset) and antidepressants use with basic and full adjustment. A *p*-value lower than 0.05 was considered as significant.

3. RESULTS

The mean age of the study sample was 41.9 ± 13.1 years, 66.3% was women and the mean years of education was 12.2 ± 3.3 years. The mean hemoglobin level was 13.9 g/dl (SD = 1.3 g/dl), 7.3% had anemia according to the WHO cutoff and 7.9% had high hemoglobin levels (Hb ≥ 3.1 g/dl above anemia cutoff). Table 2.1 shows characteristics of the study sample across the different hemoglobin categories. The hemoglobin groups differed from each other: those with anemia were younger, were more often women, had more years of education, had lower BMI, smoked less and had lower alcohol intake

Table 2.1. Sample characteristics across hemoglobin level categories (*N* = 2920)

	Hb below cutoff (anemia) (*N* = 214)	Hb 0.1-2 g/ dl above cutoff (*N* = 1784)	Hb 2.1-3 g/ dl above cutoff (*N* = 692)	Hb ≥ 3.1 g/ dl above cutoff (*N* = 230)	*p*-value
Demographics					
Age in years (mean (SD))	40.0 (12.6)	41.8 (13.0)	42.5 (13.2)	43.0 (13.2)	.05
Sex (% women)	89.3	74.3	49.9	33.0	< .001
Education in years (mean (SD))	12.4 (3.3)	12.4 (3.3)	11.7 (3.2)	11.2 (3.0)	< .001
Inclusion setting (%)					
General population	15.4	18.2	20.5	19.6	
Primary care	53.3	56.7	49.9	49.1	.02
Mental health organization	31.3	25.1	29.6	31.3	
Health & lifestyle variables					
BMI in kg/m2 (mean (SD))	24.8 (5.9)	25.3 (4.9)	26.3 (5.0)	26. 3 (4.7)	< .001
Nr. of somatic diseases (mean (SD))	0.8 (1.1)	0.6 (0.9)	0.6 (0.8)	0.7 (0.8)	.01
Creatinine clearance in ml/min(mean (SD))	105.9 (18.8)	104.2 (15.8)	103.8 (15.1)	103.1 (15.5)	.28
Current smoking (% yes)	30.8	35.5	46.5	47.8	< .001
Alcohol intake (%)					
< 1 drink/ week	47.6	31.2	31.7	29.8	
1-14/21 drinks/ week	46.7	57.1	56.1	54.8	< .001
> 14/21 drinks/ week	5.7	11.7	12.2	15.4	
Physical activity in MET minutes (mean (SD))	3652 (2927)	3616 (2992)	3669 (3255)	3921 (3620)	.59
Clinical psychiatric characteristics					
Psychiatric status (%)					
Healthy controls	20.6	23.2	19.8	20.0	
Remitted dep/anx	19.2	21.5	21.4	18.3	.31
Current dep/anx	60.3	55.4	58.8	61.7	
Depression severity (IDS) (mean (SD))	23.5 (14.5)	20.7 (13.8)	22.5 (14.6)	22.4 (14.8)	.004
Anxiety severity (BAI) (mean (SD))	10.9 (1.5)	9.5 (1.1)	10.5 (1.3)	10.9 (1.3)	.02
Antidepressants use (% yes)					
SSRI use	19.2	17.1	16.1	16.1	
TCA use	3.3	2.4	1.9	4.3	.35
Other antidepressant use	3.8	4.9	6.2	7.0	
Duration (% of time) (mean (SD))*	42.3(3.1)	41.5 (3.3)	42.8 (3.3)	47.4 (3.6)	.21
Age of onset in years (mean (SD))*	21.2 (11.7)	22.1 (12.3)	23.9 (13.6)	23.2 (12.7)	.01

One-way ANOVA was used to compare continuous variables and chi square analyses were used to compare categorical variables. * Within persons with a current or remitted depressive /anxiety disorder (*N* = 2280).

than those with normal hemoglobin levels, while those with high hemoglobin levels showed the opposite pattern. Those with lower hemoglobin levels were more often included from the primary care and less often included from the general population compared to those with higher hemoglobin levels. Furthermore, those with low or high hemoglobin level were more often included from mental health care organizations

compared to the intermediate hemoglobin levels. The number of somatic diseases was increased among both those with anemia and those with the highest hemoglobin levels compared with intermediate categories. Furthermore, those with more extreme values of hemoglobin (both low and high levels) had higher depression and anxiety symptom severity compared to the reference group with optimal hemoglobin levels, but there were no significant differences in psychiatric status. In addition, among those with a depressive or anxiety disorder (*N* = 2280), those with anemia had a lower age of onset of the depressive and/or anxiety disorder compared to those with higher hemoglobin levels.

Depressive and anxiety disorders and hemoglobin levels

Adjusted associations between psychiatric status and hemoglobin level categories are presented in Table 2.2. The results show that after basic adjustment (adjustment for age, sex and education) those with a current depressive and/or anxiety disorder have a significant higher odds ratio for having a Hb 2.1-3 g/dl above cutoff (OR = 1.26, 95% CI = 1.00-1.59, p = .05) compared to healthy controls. The odds for a Hb ≥ 3.1 g/dl above the cutoff was even larger for those with a current depressive and/or anxiety disorder (OR = 1.31, 95% CI = 0.90-1.88, p = .16), but this was not statistically significant probably due to a smaller sample size. However, after full adjustment (adjustment for age, sex, education, BMI, somatic diseases, creatinine, smoking, alcohol use and physical activity) no significant associations were found between current or remitted depressive and anxiety disorders and hemoglobin levels. This was mainly due to including creatinine clearance and alcohol use for anemia and to including smoking for high hemoglobin into the multivariate models, which had most impact on reducing the association between psychiatric status and hemoglobin levels. To test whether results differed for depressive versus anxiety disorders, depression and anxiety were also examined separately. These analyses yielded comparable results (data not shown). The interaction terms for sex × psychiatric status, age × psychiatric status and setting × psychiatric status were added but were not significant after adjustment for all covariates for both remitted and current disorders (all interaction p-values > 0.10) indicating that no sex, age or setting differences in the association between depressive and/or anxiety disorders and hemoglobin levels exist.

Table 2.2. Associations of depressive/anxiety disorders with hemoglobin level categories

	N	Hb below cutoff (anemia) OR (95% CI)	Hb 0.1-2 g/dl above cutoff OR (95% CI)	Hb 2.1-3 g/dl above cutoff OR (95% CI)	Hb ≥ 3.1 g/dl above cutoff OR (95% CI)
Basic adjustment					
No dep/anx disorder	640				
Remitted dep/anx disorder	614	0.96 (0.61-1.51)	Reference	1.27 (0.96-1.69)	1.12 (0.71-1.77)
Current dep/anx disorder	1666	1.17 (0.81-1.68)	Reference	1.26 (1.00-1.59) [1]	1.31 (0.90-1.88)
Full adjustment					
No dep/anx disorder	640				
Remitted dep/anx disorder	614	0.96 (0.60-1.55)	Reference	1.18 (0.88-1.58)	1.12 (0.69-1.79)
Current dep/anx disorder	1666	1.02 (0.69-1.51)	Reference	1.17 (0.92-1.50)	1.26 (0.85-1.90)

Multinomial logistic regression analyses were used. Reference group included persons with a hemoglobin level 0.1-2 g/dl above anemia cutoff (*N* = 1784). Basic adjustment: analyses adjusted for age, sex and education. Full adjustment: analyses adjusted for age, sex, education, BMI, somatic diseases, creatinine clearance, smoking, alcohol intake and physical activity. [1] $p = .05$.

Clinical psychiatric characteristics and hemoglobin levels

Next, we examined the association between clinical psychiatric characteristics and hemoglobin level categories in the total sample using ANCOVA and multinomial regression analyses (Table 2.3). Subjects with anemia (IDS = 23.5 (SE = 1.0), $p = .01$) and those with Hb 2.1-3 g/dl above cutoff (IDS = 22.2 (SE = 0.5), $p = .04$) had higher depression symptom severity as compared to the reference group (Hb 0.1-2 g/dl above anemia cutoff, (IDS = 20.9 (SE = 0.3)) after basic adjustment. Furthermore, those with Hb 2.1-3 g/dl above cutoff (BAI = 10.6 (SE = 1.0), $p = .02$) and Hb ≥ 3.1 g/dl above cutoff (BAI = 10.8 (SE = 1.0), $p = .06$) showed higher anxiety symptoms severity compared to the reference group (BAI = 9.5 (SE = 1.0)) after basic adjustment. Although anxiety symptom severity was also higher in persons with anemia (BAI = 10.6 (SE = 1.0)), this was not statistically significant ($p = .11$). No associations were found between the level of hemoglobin and the duration of the disorder or age of onset of the disorder. Furthermore, we examined the association between antidepressants use and hemoglobin levels; however, no significant associations were found (data not shown).

Subsequently, after full adjustments for all covariates no significant associations were found for depression or anxiety severity.

Table 2.3. Clinical psychiatric characteristics and hemoglobin level categories

	Hb below cutoff (anemia) (*N* = 214)		Hb 0.1-2 g/dl above cutoff (*N* = 1784)		Hb 2.1-3 g/dl above cutoff (*N* = 692)		Hb ≥ 3.1 g/dl above cutoff (*N* = 230)	
	Adjusted mean (SE)	*p*-value	Adjusted mean (SE)	*p*-value	Adjusted mean (SE)	*p*-value	Adjusted mean (SE)	*p*-value
Depression severity								
Basic adjustment	23.5 (1.0)	.01	20.9 (0.3)	Ref	22.2 (0.5)	.04	21.8 (0.9)	.35
Full adjustment	22.6 (1.0)	.11	20.9 (0.3)	Ref	21.9 (0.5)	.14	21.8 (0.9)	.38
Anxiety severity								
Basic adjustment	10.6 (1.0)	.11	9.5 (1.0)	Ref	10.6 (1.0)	.02	10.8 (1.0)	.06
Full adjustment	10.2 (1.0)	.37	9.5 (1.0)	Ref	10.4 (1.0)	.06	10.7 (1.0)	.09
Duration (% months)*								
Basic adjustment	43.5 (2.7)	.59	42.0 (1.0)	Ref	41.8 (1.5)	.94	45.6 (2.7)	.21
Full adjustment	41.6 (0.1)	.94	41.8 (0.1)	Ref	42.2 (0.1)	.85	47.2 (0.1)	.07
Age of onset *								
Basic adjustment	22.5 (0.9)	.87	22.3 (0.3)	Ref	23.3 (0.5)	.11	22.1 (0.9)	.76
Full adjustment	22.6 (0.9)	.80	22.4 (0.3)	Ref	23.1 (0.5)	.23	21.5 (0.9)	.36

Based on ANCOVA. Each line represents a single analysis. Basic adjustment: adjusted for sex, age and education. Full adjustment: adjusted for sex, age, education, BMI, somatic diseases, creatinine clearance, smoking, alcohol intake and physical activity. * Within persons with a current or remitted disorder (*N* = 2280) only.

4. DISCUSSION

This large cohort study comprehensively examined the role of hemoglobin levels in depression and anxiety. The current study provides no clear evidence for an association between depression/anxiety and hemoglobin levels. Higher hemoglobin levels were found in those with current depressive and/or anxiety disorders after sociodemographic adjustment and both higher and lower hemoglobin levels were found in persons with higher depression and anxiety severity. However, after full adjustment for important covariates, such as creatinine clearance and alcohol use for low hemoglobin and smoking for high hemoglobin which had most impact, associations were no longer significant.

Earlier research found higher depression severity in elderly persons with anemia [9], higher risk for postpartum depression in women with early postpartum anemia [38] and higher depression severity after 3 weeks in anemic patients with acute coronary syndrome [10]. The populations included in these earlier studies can be expected to have more disturbed hemoglobin levels than our sample, which might partly explain why these studies found more convincing associations between depression and anemia. However, our study shows that associations between depression (and also anxiety) and anemia largely disappear after adjustments for disease indicators and lifestyle, suggesting that health status might be explaining a spurious association between depressive (or anxiety) symptoms and anemia. Furthermore, depressive and anxiety disorder diagnoses as well as depression and anxiety severity were found to be associated with a high hemoglobin level. However, again, after adjustment for disease indicators and lifestyle the associations of psychiatric status disappeared, indicating that also these associations might be spurious. This is further corroborated by the fact that overall we found somewhat stronger associations for self-reported symptom scales than for depressive and anxiety disorder diagnoses. The depression and anxiety severity questionnaires include somatic symptoms such as fatigue, pain and decreased energy level which are all also symptoms of a disturbed hemoglobin level. Associations between depressive and anxiety symptom severity and hemoglobin levels might thus possibly be explained by this symptomatic overlap, while no clear association is seen when examining true diagnoses and taken health status into account.

The strengths of this study are a very large adult sample, the use of diagnoses of depression and anxiety disorders and the probability for examining high hemoglobin levels. However, some limitations of this study should also be mentioned. Due to the cross-sectional design of this study, no causal directions in the association between

depression/anxiety and hemoglobin level could be investigated. A longitudinal design might elucidate a possible causal relationship and this should be checked in follow-up research. Furthermore, our study used hemoglobin categories which were arbitrarily created. However, the categories of hemoglobin level in this study were based on earlier studies of hemoglobin levels in which these categories were associated with health risks [12, 13, 31].

In conclusion, after taking disease indicators and lifestyle into account, no clear evidence for an association between depressive and/or anxiety disorders and hemoglobin levels or anemia status was found. Further research might examine whether the course of depression and anxiety is related to the course of hemoglobin levels.

Conflict of interest

All authors declare that they have no competing interests to report.

Acknowledgements

The infrastructure for the NESDA study is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (ZonMw, grant number 10-000-1002) and is supported participating universities and mental health care organisations (VU University Medical Center, GGZinGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, IQ Healthcare, Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos). Study sponsors had no further role in study design; in the collection, analyses and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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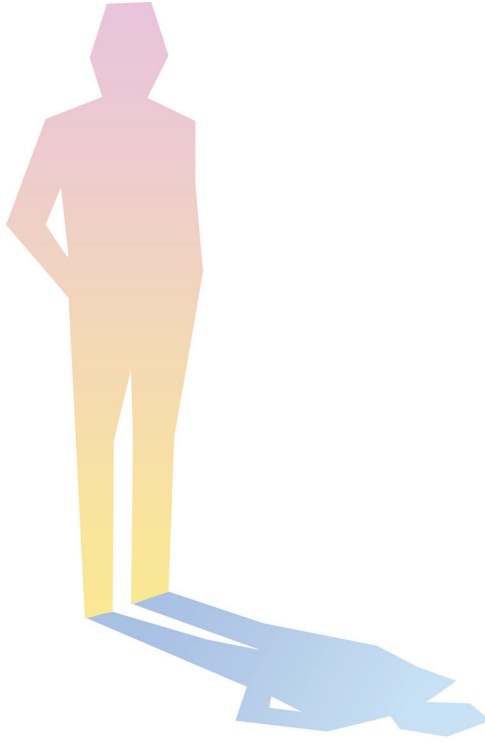

CHAPTER 3

Objective physical functioning in patients with depressive and/or anxiety disorders

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Published in Journal of Affective Disorders 131 (2011):193-199.

ABSTRACT

Background: Poorer physical function in patients with depressive or anxiety disorders has been reported, but is often measured by self-reports which may be biased by mood. This study examined the association between depression and anxiety and physical function using objective measures in a large cohort, and investigated which psychiatric characteristics are associated with physical function.

Methods: Baseline data from the Netherlands Study of Depression and Anxiety were used, including persons with current depressive and/or anxiety disorders (*N* = 1629) and healthy controls without lifetime diagnoses (*N* = 629). Psychiatric characteristics studied included type of disorder, duration, severity, age of onset, and antidepressant use. Hand grip strength and lung function were used as general objective measurements of physical function.

Results: Women with depressive or anxiety disorders had significantly poorer physical function – both lower grip strength and lung function – compared to healthy controls, especially those with a late age of onset (≥ 40 years). Poorer lung function was present among the women using antidepressants, those with higher symptom severity, and those with depression compared to anxiety disorder. In men, depressive or anxiety disorder was associated with better lung function but not with hand grip strength.

Limitations: Due to the cross-sectional design no causal relationships could be established.

Conclusions: In women, depressive or anxiety disorders were associated with objective indicators of poorer physical function. Since this association was most pronounced for later onset disorders, it suggests a larger role of physical function in depressive and anxiety disorders at later age.

Key words: physical function, depressive disorder, anxiety disorder, hand grip strength, lung function.

1. INTRODUCTION

Previous studies indicate that patients with depressive or anxiety disorders reported poorer physical functioning compared to healthy controls [1, 2]. Poorer physical functioning could ultimately result in disabilities [3], which have observed to be more prevalent with increasing severity of the depressive or anxiety disorder [1, 4]. Furthermore, patients with depressive disorders have been shown to report greater disability than those with anxiety disorders [1]. Monitoring physical function related to depression and anxiety may be an important point of intervention to prevent disability in patients with a depressive and/ or anxiety disorder [5].

A limitation of previous studies however, is that physical functioning is usually measured by self-reported questionnaires or self-report during face to face interviews which may be biased by mood since symptoms of depression and anxiety seem to influence the self-perception of functioning [6]. Although objective performance measurements may also partly depend upon the subject's motivation to perform, several studies suggested that these measures provide qualitatively better information compared to self-reports [7, 8]. Therefore, using objective measurements of physical function seems more appropriate to evaluate the association between depressive and anxiety disorders and physical function for clinical and research purposes. An advantage of objective physical function assessments is that they pick up variation in rather young, non-diseased samples.

Examples of such objective measurements are hand grip strength and lung function assessments. Hand grip strength gives an indication of overall bodily muscle strength [9]. It is the most widely reported and recommended measure of muscle strength [10], the inter-rater and test-retest reliability are high, it is fast, easy to perform, and produces a result which is simple to record [11]. Lung function measured with peak expiratory flow is the maximum flow achieved during expiration delivered with maximal force starting from the level of maximal lung inflation [12]. This instrument is inexpensive, the inter-rater and test-retest reliability are high and it is simple to use [12, 13]. Both measurements can be interpreted as objective physical function indicators since they have shown to predict poorer physical function, higher disability and mortality [9, 14, 15] even in middle-aged populations [3]. Using both hand grip strength and lung function, extended indication of physical function will be provided.

Some aging studies [9, 16] showed negative associations between hand grip strength and depression. In adults, only one study investigated the association between depressive symptoms and hand grip strength and found a marginal negative association

[17]. Studies exploring associations between hand grip strength and anxiety disorders could not be identified. Goodwin et al. [18] examined the association between lung function and mental health problems in adults and found higher scores on a depression symptom scale, but not on an anxiety symptom scale, for those with lower lung function. Another study examining depressive symptoms found higher depression symptom scores at three-year follow-up in persons with lower lung function at baseline [19]. Because previous studies used symptom assessments and did not include the diagnoses of depressive or anxiety disorders, and because most studies focused on elderly, the association between depressive and anxiety disorders and objective physical function indicators in middle-aged populations remains unclear.

This study examined the association between physical functioning and the presence of depressive and anxiety disorders in adults using hand grip strength and lung function measurements in a large cohort study. Whether specific psychiatric characteristics further differentiate in physical function is largely unknown. Consequently, an additional aim was to further explore the role of basic psychiatric characteristics (type of disorder, severity, age of onset, duration and use of anti-depressants) in the association with physical functioning.

2. METHODS

Study sample

The Netherlands Study of Depression and Anxiety (NESDA) is a longitudinal cohort study that investigates the long-term course of depressive and anxiety disorders. During a four-hour baseline measurement a wide range of data was collected, including assessment of demographics, a diagnostic psychiatric interview and a medical examination. All respondents signed an informed consent at baseline assessment. A description of the rationales, methods and recruitment strategy is reported elsewhere [20]. The NESDA protocol was approved by the Ethical Review Board of all participating universities. A total of 2981 respondents, aged 18-65, were recruited from the general population (19%), primary care (54%) and mental health care organizations (27%) to represent various settings and stages of psychopathology.

To evaluate the association between physical function and the presence of depression and anxiety, only respondents with a current depressive and/ or anxiety disorder based on six-month diagnoses (N = 1701) and healthy controls without lifetime diagnoses (N =

652) were included in current analyses. Respondents with missing values on hand grip strength and/ or lung function (*N* = 95, because of medical reasons no measurement, measured on non-dominant hand or other reasons) were excluded from the analyses resulting to a total sample of 2258 persons.

Diagnoses of depressive and anxiety disorders

The presence of depressive disorder (major depressive disorder and dysthymia) and anxiety disorder (social phobia, generalized anxiety disorder, panic disorder with and without agoraphobia, and agoraphobia) was established using the Composite International Diagnostic Instrument (CIDI, WHO version 2.1) according to the Diagnostic and Statistical Manual of Mental Disorders – Fourth edition (DSM-IV) algorithms. The CIDI is a valid and reliable instrument to assess depressive and anxiety disorders [21] and was administered by specially trained research staff.

Hand grip strength

Hand grip strength was measured twice by a Jamar hand held dynamometer. This is a hydraulic instrument that measures grip strength in kilograms or pounds of force. The Jamar dynamometer has been shown to be an accurate and reproducible instrument [10]. It correlates high with elbow flexion strength, knee extension strength and trunk extension strength [16]. The standard position for testing was used: sitting in a straight-backed chair with the feet flat on the floor, shoulders adducted in neutral position, arms unsupported, elbows flexed at 90˚, forearm rotation neutral and wrist 0-30˚ dorsiflexion and 0-15˚ ulnar deviated [22]. Hand grip strength was assessed for the dominant hand. The interviewer used a verbal encouragement to improve the maximum value [23]. The respondent had to sustain the hand grip for 5 s to record the maximal effort [24]. For the analyses, the maximum of the force from two trials was used because the highest realizable result of the respondent represents the physical strength exquisitely [23, 24]. Poor hand grip strength is a predictor for unfavourable health outcomes like physical disability and mortality [3, 16].

Lung function

Lung function was determined by measuring the peak expiratory flow (PEF) using a mini Wright peak flow meter. This is an accurate and reliable instrument [13]. The standard method to measure peak flow – to stand with the peak flow meter held in a horizon position – was used. The interviewer encouraged the respondent to blow as hard and

as fast as possible. PEF was defined in litre per minute and was measured twice. For the analysis, the maximum peak flow from two trials was used [25]. Poor lung function is a predictor for unfavourable health outcomes like physical disability and mortality [14, 15].

Psychiatric characteristics

Several basic characteristics of psychopathology were selected to explore whether specific aspects of depressive and anxiety disorders are associated with physical function. Baseline duration of the depressive and anxiety symptoms was evaluated using the Life Chart method [26], in which the presence of symptoms of depressive and anxiety disorders during the four years prior to baseline was assessed. Duration of symptoms was expressed as the percentage of time in which symptoms were present. Age of onset was retrospectively derived from the CIDI interview and the earliest onset was used in analyses. Severity of depressive and anxiety symptoms was assessed by the total score of the Inventory of Depressive Symptoms (IDS) [27], which also includes items on anxiety symptoms. Antidepressant treatment was determined through drug container inspection of all drugs used in the past month and classified according to the Anatomical Therapeutic Chemical (ATC) classification; tricyclic antidepressants (ATC-code N06AA), selective serotonin re-uptake inhibitors (ATC-code N06AB) and other anti-depressants (ATC-code N06AF/N06AX).

Covariates

Socio-demographics included age, sex and years of education. In addition, various lifestyle characteristics and confounding disease indicators were considered as covariates since these have been linked to both depression/ anxiety and hand grip strength/ lung function. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Lung medication (ATC-code R03) was used as an indicator of lung condition (dichotomous variable ‘yes’ or ‘no’). A count of the number of chronic somatic diseases (included lung disease, diabetes, cardiovascular disease, cancer, osteoarthritis, intestinal disorder, liver disease, epilepsy and thyroid gland diseases for which a respondent received treatment) was made based on a self-report questionnaire. Smoking status was defined in pack years (one pack year is equal to smoking 20 cigarettes per day over a course of one year). Physical activity was measured with the International Physical Activity Questionnaire (IPAQ) [28] and expressed in MET-minutes (ratio of energy expenditure during activity compared to rest times the number of minutes performing the activity) per week.

Statistical analyses

Data were analyzed using SPSS 15.0. Characteristics of the depressive/ anxiety group and the healthy control group were compared using the Student's t-test for continuous variables and chi-square test for categorical variables. ANCOVA was used to assess the difference in hand grip strength and lung function for persons with depressive and/ or anxiety disorders and healthy controls before and after adjustment for selected socio-demographic (age, years of education), health status (BMI, lung medication, chronic diseases) and lifestyle (smoking status, physical activity) covariates. All analyses were stratified by sex as commonly done in studies using these outcomes [11, 29], since large differences in physical function measures in men and women exist [30, 31]. Effect sizes were calculated using Cohen's *d* for those associations that were significant. Linear regression analyses were used to explore the association of psychiatric characteristics with hand grip strength and lung function in persons with a current depressive and/ or anxiety disorder. For each characteristic a separate regression analysis was performed, corrected for covariates.

3. RESULTS

The mean age of the study sample was 41.1 years (SD = 13.1), 65.2% were women and 72.1% had a depressive and/ or anxiety disorder. In both men and women, those with a depressive and/ or anxiety disorder were more often smokers, had more chronic diseases and had less years of education compared to healthy controls. Only in women, those with a depressive and/ or anxiety disorder had lower hand grip strength and peak expiratory flow compared to controls (Table 3.1).

Figure 3.1 presents the adjusted mean hand grip strength and lung function across psychiatric status. In women, hand grip strength and lung function were significantly lower in persons with depressive and/ or anxiety disorders compared to healthy controls (resp. $p = .01$, effect size = 0.03 and $p = .001$, effect size = 0.05). In men, no differences were found in hand grip strength between those with depressive and/ or anxiety disorders and healthy controls. A significantly higher lung function was found in men with depressive and/ or anxiety disorders compared to healthy controls ($p = .03$, effect size = 0.03). Sex*psychiatric status interaction terms were significant for both lung function ($p < .001$) and grip strength ($p = .01$) indicating that findings were significantly different for men versus women in this study.

Table 3.1. Sample characteristics by psychiatric disorder

	Men			Women		
	Healthy controls (*N* = 242)	Depression and/or anxiety (*N* = 543)	*p*-value	Healthy controls (*N* = 387)	Depression and/or anxiety (*N* = 1086)	*p*-value
Sociodemographic variables						
Age mean years (SD)	41.90 (± 15.2)	43.25 (± 11.6)	.18	40.34 (± 14.4)	40.03 (± 12.6)	.69
Education mean years (SD)	12.87 (± 3.2)	11.79 (± 3.2)	< .001	12.70 (± 3.2)	11.79 (± 3.3)	< .001
Health variables						
BMI in kg/m^2 (SD)	25.65 (± 4.5)	26.25 (± 4.6)	.09	24.77 (± 4.8)	25.38 (± 5.6)	.05
Lung medication (% yes)	5.0	6.0	.50	6.5	8.7	.19
Mean nr of chronic diseases (SD)	0.51 (0.8)	0.67 (0.9)	.03	0.45 (0.7)	0.65 (0.9)	< .001
Lifestyle variables						
Smoking status in pack years (SD)	9.97 (± 16.8)	16.54 (± 21.6)	< .001	5.27 (± 10.4)	10.73 (± 15.2)	< .001
Physical activity mean MET-min/week (SD)	4053 (± 3450)	3551 (± 3375)	.06	3699 (± 2895)	3486 (± 2982)	.24
Clinical characteristics						
Depression only (*N*)	NA	131	NA	NA	244	NA
Anxiety only (*N*)	NA	177	NA	NA	349	NA
Comorbid (*N*)	NA	235	NA	NA	493	NA
Duration (%)	NA	49.92	NA	NA	46.25	NA
Age of onset (SD)	NA	23.87 (± 13.6)	NA	NA	20.76 (± 11.9)	NA
Severity IDS score (SD)	NA	29.16 (± 12.9)	NA	NA	29.05 (± 12.2)	NA
Antidepressants (% yes)	NA	40.0	NA	NA	37.5	NA
Physical function variables (unadjusted)						
Hand grip strength in mean kg (SD)	50.12 (± 8.8)	50.49 (± 9.7)	.61	33.48 (± 7.6)	32.25 (± 6.7)	.003
Peak exp flow in l/min (SD)	565.95 (± 102.6)	575.82 (± 103.0)	.22	442.48 (± 70.1)	422.86 (± 78.0)	< .001

Age of onset: first age of onset of disorder present in past 6 months. NA = not applicable. P-values based on chi-square statistics for categorical variables and analyses of Students t-test for continuous variables.

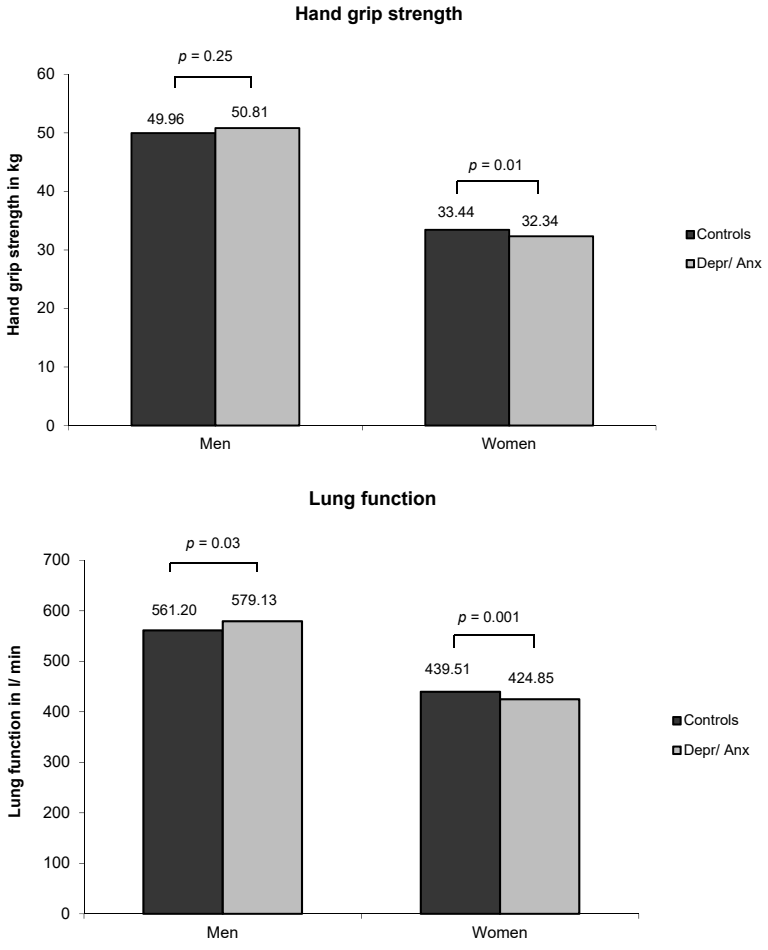

Figure 3.1. Adjusted mean (adjusted for age, education, BMI, lung medication, chronic diseases, smoking, physical activity) values for hand grip strength and lung function according to depression and anxiety in men and women.

Table 3.2 shows the results from linear regression analyses examining psychiatric disorder characteristics and hand grip strength in persons with a depressive or anxiety disorder. In men, no associations between hand grip strength and basic psychiatric characteristics were found. In women, later age of onset was marginally associated with lower hand grip strength. Similarly, later age of onset in both men and women were respectively marginally and significantly associated with poorer lung function (Table 3.3). In addition, women with a pure anxiety disorder had better lung function than those with a pure depressive disorder. In line with dose-response expectations, women with higher depressive symptom severity and women using antidepressants had significantly poorer lung function.

Table 3.2. Associations* of hand grip strength and basic psychiatric characteristics

	Men (*N* = 543)		Women (*N* = 1086)	
	B (± S.E.)	*p*	B (± S.E.)	*p*
Type of disorder				
Depression	Reference		Reference	
Anxiety	0.15 (± 1.1)	.89	-0.26 (± 0.6)	.64
Comorbid	-0.38 (± 1.1)	.72	0.03 (± 0.5)	.96
Duration (%)	-1.67 (± 1.2)	.17	0.46 (± 0.6)	.47
Age of onset	0.03 (± 0.03)	.39	-0.04 (± 0.02)	.06
Severity (IDS)	-0.02 (± 0.03)	.55	-0.01 (± 0.02)	.50
Use of antidepressants	0.96 (± 0.9)	.26	-0.21 (± 0.4)	.61

* Based on linear regression analyses. All values are adjusted for age, education, BMI, lung medication, chronic diseases, smoking, physical activity. Each line represents a single analysis.

Table 3.3. Associations* of lung function and basic psychiatric characteristics

	Men (*N* = 543)		Women (*N* = 1086)	
	B (± S.E.)	*p*	B (± S.E.)	*p*
Type of disorder				
Depression	Reference		Reference	
Anxiety	-9.36 (± 11.6)	.42	17.00 (± 6.5)	.01
Comorbid	-9.44 (± 11.1)	.40	3.22 (± 6.2)	.60
Duration (%)	-1.07 (± 12.9)	.93	8.11 (± 7.4)	.28
Age of onset	-0.64 (± 0.4)	.07	-0.42 (± 0.2)	.05
Severity (IDS)	-0.57 (± 0.4)	.11	-0.67 (± 0.2)	.001
Use of antidepressants	7.08 (± 8.9)	.43	-10.94 (± 4.9)	.03

* Based on linear regression analyses. All values are adjusted for age, education, BMI, lung medication, chronic diseases, smoking, physical activity. Each line represents a single analysis.

Because other studies [32, 33, 34] also found remarkable results in the age of onset and the results of this study consistently indicated that later age of onset of the disorder seems to be an important determinant of hand grip strength in women and lung function in men and women, age of onset was further explored. In line with other studies [33] we divided persons with disorders into those with earlier age (< 40 years) and later age of onset (≥ 40 years). After adjustment for covariates, significantly higher hand grip strength was found in healthy women compared to women with earlier age of onset ($p < .001$, effect size = 0.24) and women with later age of onset ($p < .001$, effect size = 0.49) (Figure 3.2). For lung function significantly higher values were found in healthy women compared to women with earlier and later age of onset ($p = .001$, effect size = 0.20 and $p < .001$, effect size = 0.44, respectively) (Figure

3.2). In men, significantly higher lung function was found in persons with earlier age of onset compared to healthy controls (p = .02, effect size = 0.18) but no differences were found in men with later age of onset compared to healthy controls and persons with an earlier onset (data not shown).

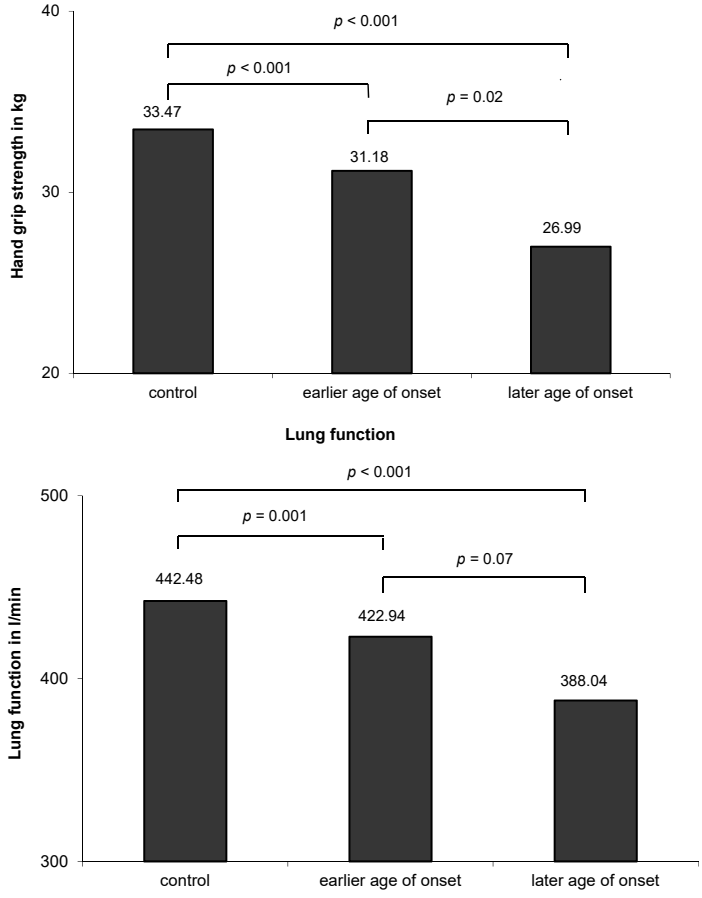

Figure 3.2. Hand grip strength and lung function in women according to age of onset of depressive and anxiety disorder (all values are adjusted for age, education, BMI, lung medication, chronic diseases, smoking, physical activity).

4. DISCUSSION

We examined the association between depressive and anxiety disorders and physical function using two objective health indicators in a large cohort of adults. Results showed that women with depressive and/or anxiety disorders had poorer physical function in terms of lower hand grip strength and lung function in comparison with

healthy women. The presence of pure depression (compared to pure anxiety), higher severity and the use of antidepressants were significantly associated with poorer lung function in women. For both lung function and grip strength, performance was poorer in women with later age of onset of depressive or anxiety disorder compared to women with earlier age of onset and healthy controls. In men, contrary to our expectations, depressive or anxiety disorders were associated with higher lung function but no association was found for hand grip strength.

Poorer physical function was found in depressive and anxious women which may imply that these women have higher risk of mortality and disability compared to healthy controls, since hand grip strength and lung function have been associated with higher risk of mortality and disability [3, 9, 14, 15, 25]. Consequently, poorer physical function among women may contribute to the overall increased mortality and disability risk observed among persons with depressive or anxiety disorders [35, 36]. Our results among women are consistent with previous studies which examined physical function with subjective questionnaires [1, 2, 37] or in elderly [3, 38]. In men, no consistent difference was found for hand grip strength between depressive or anxious persons and healthy controls, and even an unexplainable higher lung function was found among depressive or anxious men. These results in men were against our expectations and were inconsistent with other studies [3, 38]. The reason for not finding a consistent association in men could be due to the fact that the grip strength measurements used in this study to assess physical function may not be sensitive enough in men. Our sample is relatively young (average age is 41 years) and scores rather high on physical function measures compared to the older age groups that are commonly used in studies of hand grip strength and lung function. Additional analyses in a subsample of older men (aged > 50 years, $N = 257$), however, did not yield stronger evidence for an association between psychopathology and physical function (hand grip strength: $F = 0.46$, $p = .50$, effect size = 0.09, lung function: $F = 0.41$, $p = .50$, effect size = 0.08). However, the small sample size of older men and the still rather relatively young men are the limiting factors. Consequently, we may have reached a ceiling effect in our grip strength measurements for men, which could be more noticeable in men than in women because of higher scores in men. An alternative explanation would be that there truly is a sex difference and that objective physical function is more strongly associated with depression/anxiety status in women than in men. As shown before, women and men may differ in physiological reaction to depressive and anxious symptoms, potentially partly because of hormonally difference [39]. The reason for finding even a higher lung function in men, but not in women, with depressive or anxiety disorders

compared to healthy men could not be explained and has not been found in other studies. Longitudinal analyses, in which decline in objective function indicators is being investigated are necessary to further explore this observed sex difference.

Purely depressed women had a poorer lung function than women with a pure anxiety disorder, which is consistent with findings of poorer function in depression than anxiety in a previous study of Ormel et al. [40]. The fact that more depression symptoms and use of antidepressants are associated with poorer lung function is in line with a dose-response expectation and provides further proof of an association. Other studies [4, 36, 38, 41] also found that higher severity of depression and anxiety was associated with lower physical functioning, which was comparable to our results in women. These characteristics associated with lung function were not found in hand grip strength, which could be due to the fact that lung function measurement is probably a more sensitive measurement compared to hand grip strength.

A remarkable observation is that associations between depression or anxiety disorders and objective physical function tended to be more strongly present when disorders arise at later age of onset. In line with other suggestions, this may indicate that especially later onset of depression or anxiety disorders may represent a more 'reactive' type of disorder in which underlying somatic dysregulations play a larger role [42, 43]. Others have already pointed out that when depressive disorders arise at later age, somatic etiologic factors play a larger role [33]. Our findings provide further evidence for this suggestion.

A limitation of our study should be noted. The use of cross-sectional data provides no evidence of causal direction in the association between depressive and/or anxiety disorder and physical function. It is both possible and plausible that poor physical function causes depressive and anxiety symptoms, as well as that psychopathology causes declining physical function. Using longitudinal data may provide further insight into the association. Further, significant differences in physical functioning between healthy controls and depressive/ anxious women were found although the overall effect sizes were only small to moderate. An important strength of this study is that we studied DSM-IV diagnoses of depressive and anxiety disorders, while other studies often used symptom scales for depression and anxiety. Also by using objective indicators to measure physical health, bias by mood was decreased.

To conclude, this study showed evidence for poorer physical health in women with depressive or anxiety disorders, but not in men. This association was especially

present among women with a later age of onset, which suggests that physical health plays a larger role in depression and anxiety disorders in later life. Consequently, a later onset of depressive or anxiety disorder may represent a more somatic type of depressive or anxiety disorder. Although longitudinal studies should explore the causal ordering of poor physical health and depressive and anxiety disorders in more detail, our findings clearly indicate that especially for women with late-onset depressive or anxiety disorder, underlying poorer physical health may cause poorer subsequent health outcomes.

Role of funding source

Study sponsors had no further role in study design; in the collection, analyses and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest

All authors declare that they have no competing interests to report.

Acknowledgements

The infrastructure for the NESDA study is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (ZonMw, grant number 10-000-1002) and is supported participating universities and mental health care organisations (VU University Medical Center, GGZinGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, IQ Healthcare, Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos). Study sponsors had no further role in study design; in the collection, analyses and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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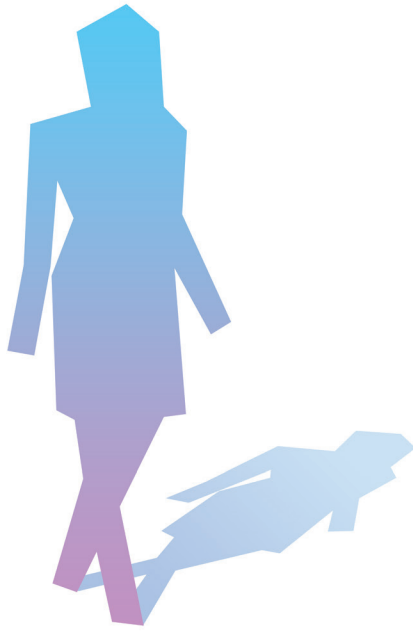

CHAPTER 4

Physical function as predictor for the persistence of depressive and/or anxiety disorders

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Published in Journal of Affective Disorders 136 (2012):828-832.

ABSTRACT

Introduction: Depressive and anxiety disorders often involve a chronic course. This study examined whether objective physical function is a predictor for the persistence of depressive and anxiety disorders.

Method: The study sample consisted of 1206 persons with depressive and anxiety disorders at baseline. Hand grip strength and lung function were used as objective physical function measurements and were determined at baseline. Outcome variable was a 6-month depressive and/or anxiety diagnosis after two years of follow-up.

Results: Lower hand grip strength predicted the persistence of depressive and/or anxiety disorders at 2-year follow-up (per SD increase: OR = 0.82, 95% CI = 0.69-0.99, p = .04). Associations were consistent for depressive and anxiety disorder persistence. Poorer lung function was associated with the persistence of depressive disorders (per SD increase: OR = 0.83, 95% CI = 0.70-0.98, p = .03) but not with anxiety disorders.

Limitations: Follow-up was limited to two years.

Conclusions: Objectively measured poorer physical function predicted the persistence of depressive and/or anxiety disorders.

Key words: depression, anxiety, hand grip strength, lung function, physical function.

1. INTRODUCTION

Depressive and anxiety disorders are common disorders and often involve a chronic course. As compared to non-chronic disorders, chronic disorders have been associated with more burden of the disorder, more disability and more health care utilisation [1, 2]. The strongest identified predictors for persistence of depressive and/or anxiety disorders are clinical characteristics such as higher severity and longer duration of previous episodes [3-5]. Early identification of worse courses of depressive and/or anxiety disorders is important for a better understanding of these disorders and for clinical practice [4].

Also physical function may have an impact on the course of depressive and/or anxiety disorders. Previous research shows that depressive and/or anxious persons have more physical disabilities and poorer physical functioning compared to healthy controls [6, 7]. However, in these studies physical illnesses and disability were measured with subjective questionnaires which may be biased by mood, report defaults or social desirability. We previously confirmed with objectively assessed general physical function indicators (hand grip strength and lung function) that especially women with poorer objective function were more likely to have a depressive and/or anxiety disorder [8]. These objective function indicators have been associated in other studies with an increased onset of physical disability and mortality [9, 10].

Whether a poorer physical function also adds to the course trajectory of depressive and anxiety disorders has not been largely examined. It can be hypothesised that poorer physical functioning at baseline forms a limiting factor in the recovery of patients either because of underlying somatic conditions, increased helplessness feelings, lower opportunities for social or physical activities and more experienced hassles in daily life. Some studies indeed show that more chronic illnesses and lower physical function [4, 11, 12] predict the persistence of depression or anxiety. However, again, these studies did not use objective indicators for physical function and used rather small samples. As far as we know, no longitudinal study has examined whether objective physical function impacts on the chronicity of depressive and/or anxiety disorders.

The present study examines whether a poorer objective physical function at baseline is associated with the persistence of depressive and/or anxiety disorders after 2 years of follow-up in a large group of depressive and anxious patients.

2. METHODS

Study sample

Data of the Netherlands Study of Depression and Anxiety (NESDA) were used. NESDA is a longitudinal cohort study investigating the long-term course of depressive and anxiety disorders. A total of 2981 respondents, aged 18-65 years, were recruited from the general population, primary care and mental health care organisations to represent various settings and stages of psychopathology. This included persons with a current or past depressive and/or anxiety disorder and healthy controls. The NESDA protocol was approved by the Ethical Committee of participating universities and all respondents provided written informed consent. A detailed description of the NESDA design and sampling procedures is reported elsewhere [13].

For the purpose of this study, persons with a 6-month depressive and/or anxiety diagnosis who confirmed symptoms in the month prior to baseline at either the CIDI questions (Compact International Diagnostic Instrument, WHO version 2.1 [14] according to the DSM-IV criteria or the Life Chart Interview [15] and participated at follow-up were included (*N* = 1456). At 2-year follow-up, 83.0% of the respondents participated (*N* = 1209). Non-response was higher in those with younger age, with lower education, in non-North European ancestry and in those with a depressive disorder, but not in those with an anxiety disorder [16]. Three persons were excluded because of missing values of both hand grip strength and lung function, leaving 1206 persons for the present analyses.

Persistence of depressive and/or anxiety disorders

The persistence of depressive (major depressive disorder and dysthymia) and anxiety disorders (social phobia, generalised anxiety disorder, panic disorder and agoraphobia) was established by using the CIDI [14] according to the DSM-IV criteria. Persistence was defined as a 6-month depressive and/or anxiety diagnosis at the 2-year follow-up.

Physical function

Hand grip strength and lung function were used as objective measures for physical function at baseline. Hand grip strength was measured with a Jamar hand held dynamometer in kilograms of force and was assessed for the dominant hand. Lung function was determined by measuring the peak flow expiratory flow (PEF in liter per

minute) using a mini Wright peak flow meter. Both measurements have been shown to be accurate and reproducible instruments [17, 18]. For the analyses, the maximum value for hand grip strength and lung function from two trials was used.

Covariates

Baseline socio-demographics included age, sex and years of education. Body mass index (BMI), number of somatic diseases, lung medication, physical activity and smoking were considered as potential confounders at baseline since these variables have been linked to both depression/anxiety and physical functioning. BMI was calculated as weight in kilograms divided by height in meters squared. The number of somatic diseases was classified in three groups (0 diseases, 1 disease or ≥2 diseases). The use of lung medication (ATC-code R03) was used as an indicator of lung condition (dichotomous variable 'yes' or 'no'). Physical activity was measured with the International Activity Questionnaire (IPAQ) [19] and expressed in MET-minutes (ratio of energy expenditure during activity compared to rest times the number of minutes performing the activity) per week. Smoking was defined in pack years (one pack year is equal to smoking 20 cigarettes per day over a course of 1 year).

Statistical analyses

Characteristics of persons with a persistent versus a remitted disorder were compared using chi-square analyses for categorical variables and independent sample t-tests for continuous variables. Logistic regression analyses were used to explore the association between objective physical function and the persistence of depressive and/or anxiety disorders after 2 years. Additional logistic regression analyses were conducted to examine the association between objective physical function and the persistence of a depressive disorder and the persistence of an anxiety disorder separately. Sex and age-interaction terms were added to explore whether found associations were consistent across sex and age groups.

3. RESULTS

The mean age of the sample was 42.0 (SD = 12.3) years and 66.0% were women. After 2 years, 61.4% (*N* = 741) of the sample had still a 6-month diagnosis of depressive and/or anxiety disorder (persistent disorder). Those with a persistent disorder had more smoking years than those with a remitted disorder but no differences were found in

any other sample characteristic (Table 4.1). The mean hand grip strength of the total sample at baseline was 38.4 (SD = 11.5) kg and the mean lung function was 475.2 (SD = 113.5) l/min.

Table 4.1. Sample characteristics at baseline (*N* = 1206)

	Remitted disorder (*N* = 465)	Persistent disorder (*N* = 741)	*p*-value [a]
Age (years), mean (SD)	41.3 (12.7)	42.5 (12.1)	.09
Sex (% women)	65.8	66.1	.91
Education (years), mean (SD)	12.0 (3.1)	11.7 (3.4)	.11
BMI, mean (SD)	25.5 (5.1)	25.9 (5.5)	.18
Somatic disease (%)			.15
0 diseases	55.1	52.1	
1 diseases	30.8	29.4	
≥ 2 diseases	14.1	18.5	
Use of long medication (% yes)	8.4	8.0	.79
Physical activity (MET-min/ week), mean (SD)	3574 (3068)	3396 (3154)	.35
Smoking status (pack years), mean (SD)	11.0 (15.5)	14.3 (20.1)	.02
Hand grip strength (kg), mean (SD)	38.9 (11.9)	38.0 (11.2)	.19
Lung function (l/min), mean (SD)	477.8 (112.6)	473.6 (114.1)	.54

[a] Chi-square analyses for categorical variables and independent sample t-tests for continuous variables.

Table 4.2 shows adjusted associations between physical function and the persistence of depressive and/or anxiety disorders. After full adjustment for potential confounders, poorer hand grip strength was associated with the persistence of depressive and/or anxiety disorders at follow-up (per SD increase: OR = 0.82, 95% CI = 0.69-0.99, p = .04). No associations were found for lung function. No sex and age interaction effects for hand grip strength and lung function were found (all p > .40).

Table 4.2. Adjusted associations* between baseline physical function and the persistence of depressive and/or anxiety disorders at 2-years follow-up

	Persistent depressive/anxiety disorder[a] OR (95% CI)	*p**	Persistent depressive disorder[a] OR (95% CI)	*p**	Persistent anxiety disorder[a] OR (95% CI)	*p**
Hand grip strength	0.82 (0.69-0.99)	.04	0.81 (0.67-0.98)	.03	0.80 (0.66-0.96)	.02
Lung function	0.96 (0.82-1.13)	.59	0.83 (0.70-0.98)	.03	0.98 (0.84-1.15)	.81

* Logistic regression analyses were used; ORs are given per SD increase (hand grip strength: SD = 11.5, lung function: SD = 113.5). Each row represents a single analysis.
[a] Adjusted for age, sex, education, body mass index, somatic diseases, use of lung medication, physical activity and smoking.

Additional analyses were conducted to examine whether results were similar for the persistence of depression versus the persistence of anxiety by focusing on specific outcomes at follow-up (Table 4.2). Of all persons, 39.8% had a persistent depressive disorder (with or without an anxiety disorder) at follow-up (*N* = 480) and 46.6% had a persistent anxiety disorder (with or without a depressive disorder) at follow-up (*N* = 562). Hand grip strength was both associated with the persistence of depressive disorders (per SD increase: OR = 0.81, 95% CI = 0.67-0.98, *p* = .03) and with persistent anxiety disorders (per SD increase: OR = 0.80, 95% CI = 0.66-0.96, *p* = .02). Poorer lung function was associated with persistent depressive disorder (per SD increase: OR = 0.83, 95% CI = 0.70-0.98, *p* = .03) but not with persistent anxiety disorders.

4. DISCUSSION

This study examined the association between objective physical function and the 2-year persistence of depressive and anxiety disorders in patients with a depressive and/or anxiety disorder. Lower hand grip strength predicted persistence of depressive and/or anxiety disorders after 2 years. Associations were consistent with depressive and anxiety disorder persistence. Lower lung function predicted persistence of depressive disorders after 2 years but not anxiety disorders.

Our results for hand grip strength are consistent with a previous study which showed that self-reported poor physical function predicted a poorer course of depressive and anxiety disorders [12]. Further, the association between lung function and depressive disorders was partly comparable to the results of the study of Giltay et al. [10], which shows that poor lung function at baseline was associated with the onset of depressive symptoms at follow-up. Our study adds significant evidence that an objective measure of physical function predicts the persistence of depressive and anxiety disorders.

Our finding, that poorer physical function predicts worse course of depression and/or anxiety may be explained by both biological and behavioural mechanisms. First, in a previous study evidence was found that hand grip strength is a predictor for poorer somatic health consequences [9] which may negatively impact on the course of depressive and anxiety disorders. Otherwise, depression and anxiety may also negatively impact on somatic health. Further, increased helplessness feelings [12], fewer social activities [4] or fatigue caused by poorer physical function, may further negatively impact the course of depression and anxiety. In addition, also direct underlying biological mechanisms may play a role. Previous studies have indicated

that poorer physical function is observed among those with chronic inflammation [20] and metabolic dysfunctions [21], which also have been implicated in poorer mental health trajectories [22]. On the other hand exercise training has been associated with reductions of depression and anxiety symptoms [23, 24]. Likely, those with more exercise training have higher scores on physical function.

A notable observation in this study is that lung function is only a predictor for depressive disorders and not for anxiety disorders. We expected to find rather similar results for both disorders as we did in our previous study in which both depressive and anxiety disorders were cross-sectionally associated with objective health indicators in women [8]. Lung function may be more influenced by smoking, physical activity and somatic diseases which may have more impact on the persistence of depressive compared to anxiety disorders. Further research should examine the consistence of different objective physical function measures in their predictive value for depression and anxiety course trajectories.

Some study limitations should be noted. First, the follow-up period was only 2 years. However, this time period often shows the most variation. Second, we only used baseline physical function to predict the course of depression and anxiety and no data of physical function at follow-up. Third, hand grip strength and lung function were determined as objective measurements but they might also be influenced by mood and motivation derived from depressive and/or anxiety disorders. Fourth, physical activities were measured with a subjective questionnaire and not with an objective treadmill test. Finally, a relatively young sample was used in this study and therefore our results may not be generalised to older persons. However, this study adds significantly to the literature by showing that even in a relatively young sample, poor physical function has a negative impact on the persistence of depressive and/or anxiety disorders. An important strength of this study is that to our knowledge, this is the largest study to examine whether objective physical function measures are predictors of depressive and anxiety disorder course and not merely symptoms of depression/ anxiety. Another strength is that by using objective instruments, potential bias by mood, report defaults or social desirability were decreased.

In conclusion, poorer hand grip strength was found to be a significant predictor of the persistence of depressive and/or anxiety disorders and poorer lung function was a significant predictor of the persistence of depressive disorders. This may suggest that a check for physical function in depressive and/or anxious persons might contribute to predict their prognosis. Further research is needed to understand underlying

biological or behavioural mechanisms of the relationship of hand grip strength and lung function as predictors for the persistence of depressive and/or anxiety disorders. When underlying mechanisms are known, this raises further questions whether improvement of physical function by e.g. exercise training, could further improve remission of depression and anxiety disorders.

Role of funding source

Study sponsors had no further role in study design; in the collection, analyses and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest

All authors declare that they have no competing interests to report.

Acknowledgements

The infrastructure for the NESDA study is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (ZonMw, grant number 10-000-1002) and is supported participating universities and mental health care organisations (VU University Medical Center, GGZinGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, IQ Healthcare, Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos). Study sponsors had no further role in study design; in the collection, analyses and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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CHAPTER 5

Six-year trajectory of objective physical functioning in persons with depressive and anxiety disorders

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Published in Depression & Anxiety 2017; 34(2):188-197.

ABSTRACT

Background: Depression and anxiety have been related to poorer self-reported physical functioning over time; however, objective measures of physical function are less frequently examined. This study assessed the 6-year trajectory of hand grip strength and lung function in persons with depressive and/or anxiety disorders.

Methods: At four waves (baseline, 2, 4 and 6 years) hand-grip strength and lung function were assessed in 2480 participants, aged 18-65 years, of the Netherlands Study of Depression and Anxiety. Linear mixed models were used to examine the association between baseline psychiatric status (current and remitted depression and anxiety, healthy controls) and physical function during 6-year follow-up, adjusted for sociodemographics, lifestyle, and health indicators.

Results: Although there were no differences in the rate of decline over time, women with current, but not remitted, depression and anxiety had poorer hand-grip strength (B = -1.34, $p < .001$) and poorer lung function (B = -11.91, $p = .002$) compared to healthy women during the entire 6-year follow-up. Associations with depression and anxiety severity measures confirmed dose-response relationships with objective physical function. In men, stronger 6-year decline of lung function was found in those with current disorders (current diagnosis-by-time: B = -11.72, $p = .002$) and even in those with remitted disorders (remitted diagnosis-by-time: B = -10.11, $p = .04$) compared to healthy men.

Conclusions: Depression and anxiety are associated with consistently poorer hand-grip strength in women and poorer lung function in women and men over 6 years of time, implicating their long-lasting impact on physical functioning.

Key words: anxiety, depression, hand-grip strength, lung function, physical function.

1. INTRODUCTION

Lower levels of physical functioning have been found in depressed and anxious patients compared to healthy persons [1-3] which could result in more disabilities, more somatic diseases and worse quality of life. However, most studies have used self-administered questionnaires to measure physical functioning which may be prone to bias caused by mood and personal or health characteristics [4,5]. Although objective performance-based measurements may also partly depend on persons' motivation to perform, using these measurements will overcome self-report limitations. Hand-grip strength and lung function are objective, general physical function indicators that predict subsequent mortality and disability [6-8]. Earlier cross-sectional studies showed poorer hand-grip strength and lung function in depressed and anxious persons compared to healthy persons [9-11].

While cross-sectional associations have been well established, only a few studies have evaluated the longitudinal course of objectively measured physical function in depressed and anxious patients. Results have been conflicting. Everson-Rose and colleagues [12] found poorer objectively measured physical function during the entire follow-up in older persons with depressive symptoms but no difference in the rate of decline in those with and without depressive symptoms. No difference in decline of physical performance was also found in another study including older persons with and without anxiety symptoms [13]. In contrast, two studies found greater decline of objectively measured physical function over time in older persons with depression [14, 10]. In addition to the presence of a diagnosis, the persistence or recovery of depression and anxiety over time may have influence on the parallel trajectory of physical decline. Only few studies confirmed higher decline of objectively measured physical function in those with persistent depressive symptoms compared to those who remitted or who had no depressive symptoms [15,16], however, they all included older persons.

Overall, most research into the trajectory of objectively measured physical function in depressed or anxious persons has been conducted in the elderly and most studies used symptom scales to measure the presence of depression or anxiety rather than Diagnostic Statistical Manual of Mental Disorders - fourth edition (DSM-IV) based depressive or anxiety diagnoses. This study therefore examined (1) the 6-year trajectory of objectively measured physical function (hand-grip strength and lung function) in a large adult sample with depression and anxiety disorders compared to healthy controls, and (2) the impact of persistence and recovery of depression and anxiety on objectively measured physical function over time.

2. METHODS

Study sample

Data of the Netherlands Study of Depression and Anxiety (NESDA) were used. NESDA is an ongoing longitudinal cohort study investigating the long-term course of depressive and/or anxiety disorders. A total of 2981 respondents, aged 18-65 years, were recruited from the general population (19%), primary care (54%) and mental health organizations (27%) to represent various settings and stages of psychopathology. Exclusion criteria were not being fluent in Dutch and having a primary diagnosis of psychotic, obsessive compulsive, bipolar or severe addiction disorder. A detailed description of the rationale, methods and recruitment strategy is reported elsewhere [17]. The NESDA protocol was approved by the Ethical Committee of participating universities and all respondents provided written informed consent. Baseline assessments took place between 2004 and 2007 and follow-up assessments were conducted every 2 years after the baseline assessment. Follow-up assessments had a response of 87.1% (*N* = 2596) at 2-year follow-up, 80.6% (*N* = 2402) at 4-year follow-up and 75.7% (*N* = 2256) at 6-year follow-up.

For the purpose of this study, persons without baseline physical function indicators were excluded (*N* = 121) as well as persons without any follow-up data on physical function (*N* = 380). This led to a sample size of 2480 persons. Of those, 357 persons had only 1 follow-up assessment, 459 persons had 2 follow-up assessments, and 1664 persons had complete data. Excluded persons (*N* = 501) were comparable in age, sex and psychopathology status at baseline but had less years of education (11.4 (SD = 3.3) vs. 12.3 (SD = 3.3) years) compared to included persons.

Psychiatric diagnoses and severity

At each assessment, the presence of depressive and anxiety disorders was established using the Composite International Diagnostic Instrument (CIDI, version 2.1) [18], according to the DSM-IV algorithms. The CIDI is a valid and reliable instrument to assess depressive and/or anxiety disorders [19] and was administrated by specially trained research staff. Depressive disorders included Major Depressive Disorder (MDD) and dysthymia whereas anxiety disorders included social phobia, generalized anxiety disorder, panic disorder and agoraphobia. For the present study, the sample was divided in three subgroups, based on the baseline diagnoses: (1) healthy controls (no lifetime depressive or anxiety disorders, *N* = 557), (2) persons with remitted disorders (a lifetime

but no current depressive and/or anxiety disorder, *N* = 537) and (3) persons with current disorders (6-month recency depressive and/or anxiety disorders, *N* = 1386).

Depression and anxiety severity in the past week was assessed at each wave. Severity of depression was measured using the 30-item Inventory of Depressive Symptomatology (IDS-SR30) [20] with an overall score ranging from 0 to 84. Severity of anxiety was measured with the 21-item Beck Anxiety Inventory (BAI) [21], with an overall score ranging from 0 to 63. For both scales higher scores mean higher symptom severity.

Furthermore, to examine whether the 6-year trajectory of physical function during follow-up parallels recovery or chronicity of depressive and anxiety disorders, six groups were created based on diagnostic status across all waves: (1) controls, (2) new onset, (3) persistent remitted, (4) remission, (5) relapse and (6) chronic.

Physical function indicators

Hand-grip strength and lung function were used as indicators of physical function and were measured at baseline and at 2-, 4- and 6-year follow-up assessments. Hand-grip strength was measured with a Jamar hand held dynamometer in kilograms of force and was assessed for the dominant hand. Hand-grip strength gives an indication of overall bodily muscle strength [22] and is the most widely reported and recommended measure of muscle strength [23]. The standard position for testing was used: sitting in a straight-backed chair with feet on the floor, shoulders adducted in neutral position, arms unsupported, elbows flexed at 90°, forearm rotation neutral and wrist 0-30° dorsiflexion and 0-15° ulnar deviation [24]. Lung function was determined by measuring the maximum peak flow during expiration (in liter per minute) delivered with maximum force starting from the level of maximal lung inflation using a mini Wright peak flow meter. Lung function gives an indication of ventilatory performance. Peak flow was measured while standing with the peak flow meter in horizontal position.

The interviewer encouraged the respondent to perform to the best of their ability. Both instruments have been shown to be accurate and reliable [23, 25] and are both strongly associated with subsequent mortality and disability [6-8]. Maximum performance from two efforts for both hand-grip strength and lung function was used in analyses [11].

Covariates

Baseline *sociodemographic* covariates included age (in years) and education level (in years). In addition, baseline *health and lifestyle indicators* were selected a priori on

the basis of previously reported associations between objectively measured physical function and depression and anxiety [11, 26]. Body mass index (BMI) was calculated as weight in kilogram divided by height in meters squared. A count of the number of chronic somatic diseases for which the respondent receives treatment (including lung disease, diabetes, cardiovascular disease, cancer, osteoarthritis, intestinal disorder and thyroid gland disease) was made. Lung medication (ATC-code R03) was used as an indicator of lung condition (yes/no and only for analyses of lung function). Physical activity was measured with the International Physical Activity Questionnaire (IPAQ) and expressed in 1000 MET minutes per week (metabolic equivalent of task: ratio of energy expenditure during activity compared to rest times and the number of minutes performing the activity) [27]. Smoking status was defined as current or no current smoker as well as in pack years (one pack year is equal to smoking 20 cigarettes per day over a course of one year). Alcohol intake was categorized as nondrinking (< 1 drink/week), moderate drinking (1-14 (women)/ 1-21 (men) drinks/week) and heavy drinking (> 14 (women)/ > 21 (men) drinks/week).

Statistical analyses

Sample characteristics at baseline were compared across the three subgroups (current, remitted, control) using analyses of variance (ANOVA) for continuous variables, chi-square analyses for categorical variables and Kruskal-Wallis Test for variables with a nonparametric distribution.

First, we explored the effect of all a priori determined covariates with physical functioning over time using linear mixed model analyses (LMM) [28]. LMM takes into account the dependency of the repeated observations from the same participant over time and missing values, which reduces bias due to selective loss to follow-up. All analyses were stratified for sex since large differences in physical function measures in men and women exist [29,30] and earlier results showed a stronger relationship between psychopathology and physical functioning in women compared to men [11]. We also checked association between baseline hand-grip strength/ lung function and change during 6-year follow-up which could not be performed by LMM, so linear regression analyses, adjusted for sociodemographics were used.

Associations with physical function using all time points available were analyzed using LMM. Baseline psychopathology status (current, remitted, control) or symptom severity (IDS or BAI), time and baseline covariates were entered as fixed factors with physical function indicators (hand-grip strength or lung function) as dependent variables.

Covariates were entered in stepwise models: (1) included sociodemographics and (2) additionally included health and lifestyle indicators. Furthermore, to examine whether the strength of decline of physical function over time was comparable for persons with current disorders, remitted disorders or healthy controls, a group-by-time interaction term was additionally added. Sensitivity analyses were performed to check whether the results were comparable for depression and anxiety separately. The robustness of the analyses was checked by a complete case analysis including 1664 persons.

To examine the effect of chronicity and remission of depression and anxiety disorders over 6 years, ANCOVAs with adjustment for baseline covariates and physical function tested whether different course patterns of depression and anxiety (Table 5.4) were associated with change in physical function over 6 years (6-year value minus baseline value).

All statistical analyses were performed in SPSS 20.0 and results of the analyses were considered significant if $p < .05$. We calculated effect sizes (Hedge's g) for all significant associations to easy interpretation of results.

3. RESULTS

The mean age of the study sample was 41.9 years (SD = 13.1), 65.7% were women and the mean years of education was 12.3 (SD = 3.2). All baseline characteristics used in this study were significantly different between the three psychopathology groups, and baseline hand-grip strength and lung function were lower in those with current or remitted disorders compared to healthy controls (Table 5.1). Furthermore, men had higher baseline hand-grip strength and lung function than women (hand-grip$_{men}$ = 50.64 kg (SD = 9.30) vs. hand-grip$_{women}$ = 32.90 kg (SD = 7.17), $p < .001$ and lung function$_{men}$ = 574.98 l/min (SD = 103.62) vs. lung function$_{women}$ = 431.82 (SD = 76.16), $p < .001$). Hand-grip strength and lung function decreased during 6-year follow-up (change hand-grip$_{women}$ = -0.55 kg (SD = 6.97), change lung function$_{men}$ = -25.98 l/min (SD = 92.37), change lung function$_{women}$ = -46.85 l/min (SD = 64.19)), except for hand grip strength in men which increased slightly (change hand-grip$_{men}$ = 0.03 kg (SD = 8.17)).

Of the baseline covariates, older age, having more somatic diseases, more pack years of smoking and higher alcohol intake were associated with a larger decline of hand-grip strength (age × time$_{men}$: B = -0.06, $p < .001$; age × time$_{women}$: B = -0.03, $p < .001$; somatic diseases × time$_{men}$: B = -0.34, $p = .05$); somatic diseases × time$_{women}$: B = -0.21, $p = .02$;

pack years of smoking × $time_{men}$: B = -0.03, $p < .001$; pack years of smoking × $time_{women}$: B = -0.01, $p = .02$; alcohol use × $time_{men}$: B = -0.61, $p = .01$; alcohol use × $time_{women}$: B = -0.22, $p = .04$). Significant baseline determinants of larger decline of lung function were lower BMI (BMI × $time_{women}$: B = 0.69, $p < .001$) and current smoking in women only (current smoking × $time_{women}$: B = -6.04, $p = .01$). Baseline hand-grip strength and lung function were strong predictors of change of hand-grip strength and lung function during 6-year follow-up (B = -0.46, $p < .001$ and B = -0.30, $p < .001$, respectively).

Table 5.1. Baseline sample characteristics (N = 2480)

	Healthy controls *N* = 557	Remitted dep/ anx *N* = 537	Current dep/anx *N* = 1386	*p*-value*
Sociodemographics				
Age in years, mean (SD)	40.8 (14.6)	43.9 (13.0)	41.6 (12.4)	< .001
Sex (% women)	60.3	70.9	65.9	.001
Education in years, mean (SD)	12.9 (3.2)	12.7 (3.2)	11.9 (3.2)	< .001
Psychiatric status				
Depressive disorder	0	44.1%	26.0%	NA
Anxiety disorder	0	17.3%	31.0%	NA
Comorbid disorder	0	38.5%	43.1%	NA
Depressive severity (IDS), mean (SD)	7.9 (7.0)	13.6 (8.5)	28.3 (12.2)	< .001
Anxiety severity (BAI), mean (SD)	3.8 (4.5)	6.8 (6.1)	16.3 (10.3)	< .001
Health and lifestyle indicators				
BMI, mean (SD)	25.0 (4.6)	25.9 (4.8)	25.6 (5.2)	.01
No. of somatic disease (%)				
0 diseases	68.2	61.5	54.6	
1-2 diseases	29.8	35.6	40.8	< .001
≥ 3 diseases	2.0	3.0	4.6	
Use of lung medication (% yes)	4.7	6.0	7.9	.02
Physical activity in 1000 MET-min/ week, median (IQR)	3.1 (3.5)	3.1 (3.7)	2.6 (3.7)	.001
Current smoking (% yes)	27.5	34.3	41.6	< .001
Smoking in pack years	7.0	9.6	12.5	< .001
Alcohol intake %				
< 1 drink/ week	22.3	26.8	35.6	
1-14/21 drinks/ week	66.7	61.5	52.2	< .001
> 14/21 drinks/ week	11.1	11.7	12.3	
Physical function indicators				
Hand-grip strength in kg, mean (SD)	40.5 (11.5)	38.6 (11.5)	38.5 (11.6)	.001
Lung function in l/min, mean (SD)	494.3 (103.4)	477.3 (108.4)	476.9 (112.9)	.01

* Based on ANOVA for continuous variables, chi-square tests for categorical variables and Kruskal-Wallis Test for nonparametric variables.

Depressive and/or anxiety disorders and the course of physical function over 6 years

Hand-grip strength and lung function significantly declined over time in all three psychopathology groups during 6-year follow-up (all time effects: $p < .05$). LMM analyses corrected for sociodemographics showed that women with current depressive and/or anxiety disorders had lower hand-grip strength (B = -1.34, $p < .001$, $g = .23$) and lower lung function (B = -11.91, $p = .02$, $g = .15$) compared to controls at all follow-up measurements. Women with remitted diagnosis did not differ from healthy women in hand-grip strength and lung function across all measurements (Table 5.2 and 5.3).

Table 5.2. Longitudinal associations[a] between psychiatric status at baseline and hand-grip strength (kg) during 6-year follow-up (*N* = 2480)

	Hand grip strength					
	Men			Women		
	B	SE	*p*-value	B	SE	*p*-value
Depressive and/or anxiety disorders						
Group						
Controls (reference)						
Remitted disorders	0.71	0.88	.42	-0.21	0.42	.62
Current disorders	0.07	0.69	.92	-1.34	0.36	< .001
Time	-0.16	0.13	.22	-0.20	0.07	.004
Time*group[b]						
Controls (reference)						
Remitted disorders	0.07	0.39	.85	-0.09	0.20	.67
Current disorders	-0.12	0.30	.69	-0.17	0.18	.32
Severity of depression						
IDS	-0.01	0.20	.56	-0.04	0.01	< .001
Time	-0.17	0.13	.18	-0.21	0.07	.002
Time*IDS[b]	-0.01	0.01	.53	-0.004	0.01	.43
Severity of anxiety						
BAI	-0.002	0.03	.95	-0.06	0.01	< .001
Time	-0.17	0.13	.18	-0.22	0.07	.001
Time*BAI[d]	-0.002	0.01	.85	-0.01	0.01	.38

Distribution of the groups in men: controls *N* = 221, remitted *N* = 156, current *N* = 473 and in women: controls *N* = 336, remitted *N* = 381, current *N* = 913. IDS, Inventory of Depressive Symptomatology; BAI, Beck Anxiety Inventory; SE, Standard Error.

[a] Analyses were based on linear mixed models, adjusted for time and sociodemographics.

[b] Model with time, group, sociodemographics and time × group/severity score interaction term.

Table 5.3. Longitudinal associations[a] between psychiatric status at baseline and lung function (l/min) during 6-year follow-up (*N* = 2480)

	Lung function					
	Men			Women		
	B	SE	*p*-value	B	SE	*p*-value
Depressive and/or anxiety disorders						
Group						
Controls (reference)						
Remitted disorders	-2.01	11.56	.86	-1.46	5.79	.80
Current disorders	-4.66	9.07	.61	-11.91	4.96	.02
Time	-15.58	1.60	< .001	-25.62	1.01	< .001
Time*group[b]						
Controls (reference)						
Remitted disorders	-10.11	4.82	.04	1.46	2.99	.62
Current disorders	-11.72	3.76	.002	-1.26	2.57	.62
Severity of depression						
IDS	-0.23	0.27	.39	-0.22	0.15	.14
Time	-15.31	1.60	< .001	-25.81	1.01	< .001
Time*IDS[b]	-0.06	0.11	.57	0.15	0.08	.05
Severity of anxiety						
BAI	-0.54	0.37	.14	-0.54	0.20	.01
Time	-15.32	1.60	< .001	-25.82	1.01	< .001
Time*BAI[b]	-0.07	0.15	.64	-0.06	0.10	.59

Distribution of the groups in men: controls *N* = 221, remitted *N* = 156, current *N* = 473 and in women: controls *N* = 336, remitted *N* = 381, current *N* = 913. IDS, Inventory of Depressive Symptomatology; BAI, Beck Anxiety Inventory; SE, Standard Error.

[a] Analyses were based on linear mixed models, adjusted for time and sociodemographics.

[b] Model with time, group, sociodemographics and time × group/severity score interaction term.

Adjusting for health and lifestyle indicators did not influence the associations between a current diagnosis at baseline and hand-grip strength over time (B = -0.99, *p* = .01, *g* = .16), but the association between a current baseline diagnosis and lung function was no longer significant (B = -6.31, *p* = .21; not tabulated). In men, comparable values of hand grip strength and lung function at all measurements were found in the different psychopathology groups (Table 5.2 and 5.3).

Nonsignificant group-by-time interaction terms in women for both hand-grip strength and lung function showed that the three baseline diagnostic groups showed similar rates of decline. Also in men, the three diagnostic groups were similarly associated with hand-grip strength over time. In contrast, for lung function, men with current (time interaction: B = -11.72, *p* = .002 or remitted (time interaction: B = -10.11, *p* =

.04) depressive and/or anxiety disorders showed a larger decline over time compared to healthy men (Tables 5.2 and 5.3).

Figure 5.1 illustrates the overall better performance in men compared to women, a poorer level of hand-grip strength and lung function in women with current depressive and/or anxiety disorders compared to healthy women, and a larger decline of lung function over time in current depressed or anxious men compared to healthy men.

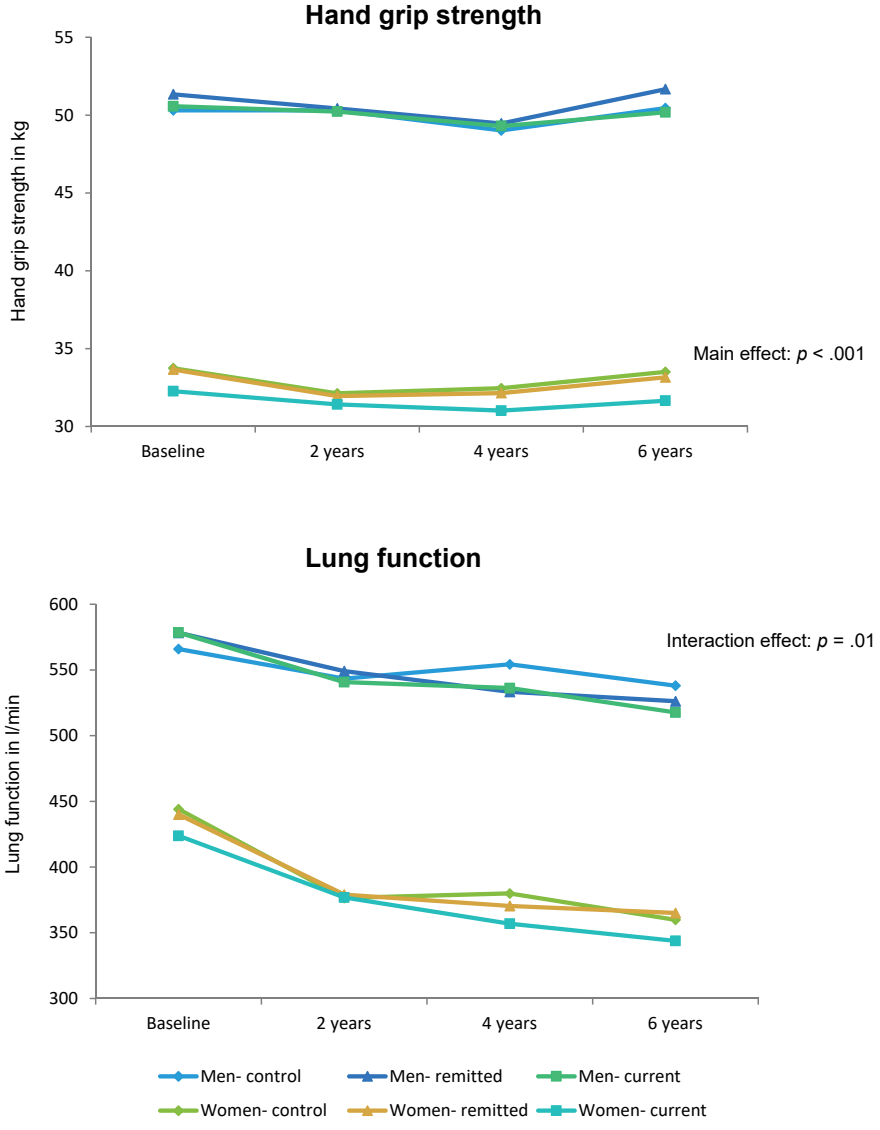

Figure 5.1. Six-year trajectory of physical function (*N* = 2480).

Sensitivity analyses showed that associations were comparable when depression and anxiety were analyzed separately (data not shown). Complete case analyses for checking the robustness of the results (N = 1664) confirmed earlier findings that women with current depressive and/or anxiety disorders had lower physical function (both hand-grip strength and lung function) compared to healthy women, and that men with current and remitted disorders had a larger decline of lung function. In contrast, a significant higher lung function (B = 17.73, p = .05, g = 0.19) was found in men with current disorders compared to healthy controls.

Previous research has shown that the association between physical function and depressive and/or anxiety disorders was stronger in older than in younger persons. Therefore, an interaction term of time × age × diagnoses of psychopathology was added in which age was dichotomized at the mean age (42 years). Interaction terms were not significant (all p-values > .05) indicating that the association between psychopathology and physical function over time was comparable for older and younger persons in our sample.

Severity of depression/ anxiety and the course of physical function over 6 years

LMM analyses corrected for sociodemographics showed that in women baseline severity ratings of depression were negatively associated with lower hand-grip strength (B = -0.04, p < .001) but not with lung function (B = -0.22, p = .14) over the entire follow-up period. Furthermore, higher baseline severity of anxiety was associated with lower hand-grip strength (B = -0.06, p < .001) and lower lung function (B = -0.54, p = .01) in women (Tables 5.2 and 5.3). The association between depression and anxiety severity and hand-grip strength in women remained significant after additional adjustment for health and lifestyle indicators (IDS: B = -0.004, p = .01, BAI: B = -0.04, p = .01). However, anxiety severity was no longer significantly associated with lung function after full adjustment (B = -0.25, p = .23). In men, no significant associations of hand grip strength and severity of depression and anxiety were found (Table 5.2 and 5.3). Group-by-time terms showed comparable decline of physical function in the different severity ratings in both men and women as indicated by non-significant interaction terms (Tables 5.2 and 5.3).

Course of depressive and anxiety diagnoses and the change of physical function during 6 years

No differences in change of hand-grip strength between course patterns (Table 5.4) were found in both men and women, with the exception of women with a relapse during follow-up who had slightly poorer hand-grip strength (B = -0.86, *p* = .07) during 6 year follow-up compared to healthy women (Table 5.5). This result remained the same after adjustment for health and lifestyle indicators (B = -0.83, *p* = .08). Furthermore, no difference in change of lung function was found between different course trajectories in women. In men however, higher decline of lung function was found in those with a new onset of depressive and/or anxiety disorders during follow-up (B = -49.75, *p* = .01) and in those with a relapsing or chronic depressive and/or anxiety disorder (B = -21.08, *p* = .02, B = -26.83, *p* = .01, respectively) compared to healthy men (Table 5.5). After adjustment for health and lifestyle indicators, these results remained significant (new onset: B = -49.14, *p* = .01, relapse: B = -17.97, *p* = .05, chronic: B = -25.12, *p* = .02).

4. DISCUSSION

This large longitudinal cohort study is the first study to our knowledge that examined the 6-year course of objectively measured physical function in adults with a diagnosis of depressive and/or anxiety disorders. The results showed poorer hand-grip strength and lung function during a 6-year follow-up in those with current depressive and/or anxiety disorders compared to healthy persons, however, effect sizes were rather small. Associations were comparable for both depression and anxiety and, in line with a dose-response association, higher severity of depression and anxiety was associated with poorer physical function over time. In women, poorer physical function among those with depressive or anxiety disorders was present consistently over 6 years, but in men, the patterns for poorer lung function in those with current depressive or anxiety disorders were progressing over 6 years. In line with this, men with a new disorder onset or with a relapsing or chronic disorder over 6 years had a higher rate of decline of lung function compared to healthy men.

These longitudinal results of poorer physical function agree with earlier cross-sectional and longitudinal research in which poorer physical function was found in depressive and anxious persons compared to healthy persons [9-12, 14, 31]. The effects of poor physical function may contribute to the observed poorer subsequent health outcomes such as mortality and disability in persons with current depressive or anxiety disorders,

Table 5.4. Course groups based on the course of depressive and anxiety disorder diagnosis status over 6 years follow-up (*N* = 2480)

Status	*N* (men)	*N* (women)	Description
Controls	196	277	No lifetime diagnosis at each assessment.
Persistent remitted	92	182	Non-current lifetime diagnosis at baseline and no other diagnosis during any of the follow up assessments.
New onset	32	68	No lifetime diagnosis at baseline, with at least one new onset of diagnosis during one of the follow up assessments.
Remission	98	172	Current diagnosis at baseline and no diagnosis during any of the follow up assessments.
Relapse	317	688	Current or non-current diagnosis at baseline and at least one diagnosis during one of the follow-up assessments.
Chronic	115	243	Current diagnosis at baseline as well as at the 2-, 4- and 6-year follow up assessments.

Table 5.5. Associations between 6-year change in depression and anxiety status and 6-year[a] change in physical function as the outcome (N = 2480)

	Men			Women		
	B	SE	*p*	B	SE	*p*
	Change in hand-grip strength			Change in hand-grip strength		
Depressive and/or anxiety disorders[b]						
Controls (reference)						
Persistent remitted	0.95	0.99	.34	0.22	0.62	.72
New onset	-0.48	1.52	.75	1.29	0.86	.14
Remission	-0.90	1.06	.40	-0.22	0.66	.74
Relapse	0.36	0.74	.63	-0.86	0.47	.07
Chronic	0.06	0.89	.95	-0.61	0.55	.27
	Change in lung function			**Change in lung function**		
Depressive and/or anxiety disorders[b]						
Controls (reference)						
Persistent remitted	-19.02	12.06	.12	9.09	6.00	.13
New onset	-49.75	18.05	.01	-3.22	8.40	.70
Remission	-20.58	12.85	.10	-4.01	6.41	.53
Relapse	-21.08	9.02	.02	1.92	4.53	.67
Chronic	-26.83	10.80	.01	2.02	5.34	.71

Notes: IDS, Inventory of Depressive Symptomatology; BAI, Beck Anxiety Inventory.

[a] Change was calculated by subtracting baseline values from 6-year values.

[b] Results were based on ANCOVAs and were adjusted for baseline socio-demographics, baseline hand grip strength or lung function.

since poorer hand-grip strength and lung function were found to be strongly associated with increased mortality, higher disability, impaired quality of life and prolonged length of hospital stay [7, 23, 32].

In women, our main findings indicated that those with current depressive or anxiety disorders show poorer hand-grip strength and lung function over 6 years, but the change over time is not different across psychiatric groups or across groups with different course patterns. The latter findings are against our expectations and the literature [9-12, 14, 31]. However, these results may indicate the rather high stability of physical function in women over time, and suggest that in our rather healthy young sample with a mean age of 42 years, deterioration over time was limited. Hand-grip strength in men did not show any associations- static or time dependent- with psychiatric status, which could be because we reached a ceiling effect in our grip strength measurements in men. In contrast, for lung function, we found more decline over time in men with depressive and anxiety disorders. In addition, men with a new disorder onset or with a relapsing or chronic disorder had a larger decline of lung function compared to healthy men, which is in line with other studies in the elderly [33].

Validity of 6-year patterns of hand-grip strength and lung function was confirmed by the fact that other sociodemographic and health indicators impacted on these patterns. Our results show that higher age, more somatic diseases, more smoking and a higher alcohol intake at baseline were associated with poorer hand grip strength during 6-year follow-up. To find decreased muscle strength in older persons was expected [34,35] as well as in those with more somatic diseases [36] and could be caused by age-related muscle cell shrinking, fatigue or vascular-related damage to musculoskeletal and peripheral nervous systems [35, 37, 38]. Furthermore, poorer hand-grip strength over time in smoking persons has been demonstrated before and could be due to reduced oxygen delivery and impair of mitochondrial function caused by circulating smoke [39]. Only small effects were found previously of having poorer physical function in those with higher alcohol intake [38] which could be caused by pathophysiological pathways such as higher inflammation rates [40]. Furthermore, lower BMI and current smoking in women, but not in men, were associated with poorer lung function over time. Although lower BMI could be a marker of an underlying disease, most other studies demonstrate higher BMI to be related to poorer lung function [41]. Furthermore, poorer lung function over time in current smoking women has been demonstrated before and could be due to increased pathophysiological damage to lung tissue due to smoking [42–44]. To check whether these indicators might mediate the associations over time, the analyses were repeated including time-varying covariates (BMI, number

of somatic diseases, physical activity, alcohol use, smoking and use of lung medication). However, the associations between the diagnostic groups and physical function over time were comparable to the original analyses including only baseline covariates and these health and lifestyle indicators were not significant and so, did not explain our results.

However, even when adjusting for all these other determinants, we found that current depression and anxiety disorders additionally impacted on poorer physical functioning over a 6-year pattern. This indicates that it is likely not just the impact of life style that explains why depression and anxiety contribute to poorer physical functioning. Other contributing mechanisms could be multiple pathophysiological pathways such as inflammation and oxidative stress which have been found to be increased in both persons with depression and anxiety [45-48] and in those with poorer physical function [49-52].

Limitations of this study are (1) possible missing relapsing periods of depression and anxiety due to 2-year sampling sequence, (2) 6 years of follow-up in a rather healthy and young baseline sample may have been too short to find the clinically most relevant decline of physical function, (3) missing values of physical function at one or more assessments may have biased our longitudinal effects, (4) only two objective physical function measures were available which might be limited and (5) rather small effect sizes of our main results were found which interpreted small implications for the clinical setting. However, by using linear mixed models, the dependency of the repeated observations from the same participant over time and missing values was taken into account. Strengths of this study are its large sample size with DSM-IV based diagnoses of depressive and anxiety disorders and the availability of multiple repeated objective physical function indicators above self-reports of functioning which provide less biased information about physical function.

To conclude, this study found evidence for poorer physical function over time in persons with current depressive and anxiety disorders compared to healthy persons. These results imply a long-term impact of depressive and anxiety disorders on physical health, since hand-grip strength and lung function have been associated with subsequent disability, impaired quality of life, prolonged length of stay in hospital as well as increased mortality. Furthermore, the knowledge that physical function was consistently poorer over a 6-year period in persons with current depression or anxiety highlights the need for detecting physical decline as part of routine integrated clinical care and for promoting healthy lifestyle including e.g. regular physical activity.

Conflict of interest

All authors declare that they have no competing interests to report.

Acknowledgements

The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (ZonMw, grant number 10–000–1002) and is supported by participating universities and mental health care organisations (VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, IQ Healthcare, Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos). FL has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° PCIG12-GA-2012-334065. Penninx has received research funding from Jansen Research.

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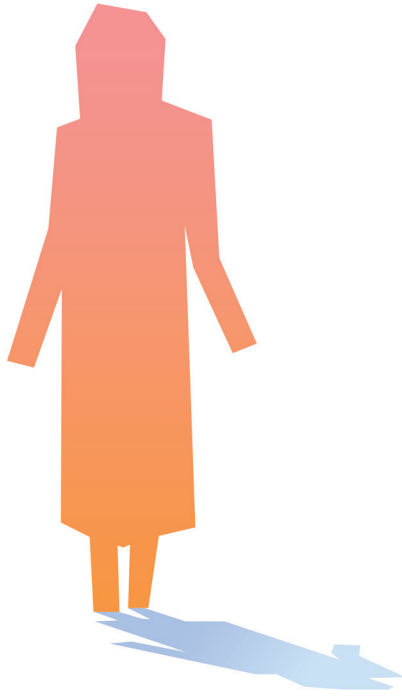

CHAPTER 6

Physiological stress markers, mental health and objective physical function

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Published in Journal of Psychosomatic Research 2020; 133 109996.

ABSTRACT

Objective: The observed poorer physical function in persons with mental disorders could partly be due to dysregulation in physiological stress systems. However, an integrated picture of the role of physiological stress systems on objective physical function is lacking. This study examined the association of multiple physiological stress systems with objective physical function, and explored whether these stress systems contribute to the relationship between depression/anxiety and poorer physical function.

Methods: Data of 2860 persons of the Netherlands Study of Depression and Anxiety was used. Physical function was indicated by hand grip strength assessed using a hand-held dynamometer and lung function assessed using a peak flow meter. Inflammatory markers (CRP, IL-6, TNF-α), salivary cortisol (cortisol awakening response (AUCg, AUCi), evening cortisol) and ANS markers (heartrate, PEP, RSA) were determined. Depression/anxiety disorders were determined using psychiatric interviews. Linear regression analyses were adjusted for sociodemographics, health and lifestyle factors.

Results: Higher inflammation levels were associated with lower hand grip strength (B_{CRP} = -0.21 (SE = 0.06), $p < .001$) and lower lung function (B_{CRP} = -2.07 (SE = 0.66), p = .002), $B_{TNF-\alpha}$ = -3.35 (SE = 1.42), p = .022). Higher salivary cortisol levels were associated with lower lung function ($B_{evening\ cortisol}$ = -2.22 (SE = 0.59), $p < .001$). The association, in women, between depression/anxiety disorders and poorer physical function did not significantly diminish after adjustment for physiological stress markers.

Conclusion: This large cohort study showed that stress system dysfunction (especially the immune-inflammatory system and HPA-axis) contributes to poorer objective physical function. Stress system dysfunction did not explain the poorer physical function observed in persons with depression/anxiety disorders, suggesting that other pathways are involved to explain that association.

Key words: anxiety, depression, hand grip strength, lung function, physical function, physiological stress.

1. INTRODUCTION

The deterioration of physical function that occurs with ageing is associated with increased disability, the development of more somatic diseases and a higher mortality risk [1]. However, although the role of chronological age is important, a large amount of variation exists in the deterioration of physical function within the population. In addition to impact of genetic make-up and lifestyle factors on objective physical function, there is increasing evidence that the impact of mental health is also substantive. In our previous work, poorer objective physical function, as indicated by poorer hand grip strength and lung function, was found in depressed and anxious persons than in healthy controls [2, 3]. Also, others have confirmed that stress-related mental disorders are associated with poorer physical function over time [4, 5].

An underlying mechanism explaining the deterioration of poorer physical function in persons with mental disorders could be dysregulation of physiological stress systems. Examples of such stress systems are the immune-inflammatory system, the hypothalamus-pituitary-adrenal (HPA)-axis and the autonomic nervous system (ANS). Dysregulation of these systems could lead to systemic inflammation, hyperactivity of the HPA-axis and more sympathetic and less parasympathetic activation. To examine whether physiological stress is an underlying mechanism of the deterioration of physical function in depressed and anxious persons, the relationship between physiological stress and physical function needs to be demonstrated.

Multiple reviews suggested that there is a bidirectional link between depressive and anxiety disorders and inflammation [6, 7] and show higher levels of inflammation in depressed and anxious patients. Depression and anxiety disorders have also been linked to a dysregulated HPA-axis since in particular high cortisol awakening response is more often found in depressed and anxious patients [8, 9]. Furthermore, the ANS system was found to be affected in patients with psychiatric disorders with higher heart rate and lower heart rate variability, although some found that this is mainly due to antidepressant use and not disease status itself [10]. In summary, dysfunction of the physiological stress systems was associated with having a psychiatric disorder.

The literature also shows evidence for associations for some of the physiological stress dysregulations with physical function. However, only a few studies used objective physical function indicators instead of subjective questionnaires that could be affected by mood-related reporting bias. Although objective performance-based measurements may also partly depend on a persons' motivation to perform, using such objective

measurements will largely overcome self-report limitations. The literature shows associations between higher levels of inflammation markers and poorer physical function in persons with cardiovascular risk [11] and in elderly samples [12, 13]. Furthermore, a meta-analysis of Gan et al. [14] showed that reduced lung function was associated with increased levels of systemic inflammation in persons with chronic obstructive pulmonary disease. However, until now it is unclear whether there is a relationship between inflammation and physical function in a non-somatic diseased, adult sample. Dysregulated HPA-axis was associated with slower walking speed, but not with hand grip strength in an individual participant meta-analysis by Gardner et al. [15] of six elderly cohorts (aged 50-90 years). However, it is unclear whether these results could also be extended to younger persons. Also, research on the association between ANS activity and physical function is scarce. In an older sample from the least developed rural regions of Ghana it was found that low heart rate variability, but not heart rate, was linked to poorer hand grip strength [16]. However, the above mentioned studies often only focused on one specific physiological stress system and often included single markers. It is known that (dys)regulation of various physiological stress systems are interrelated [17-19] and therefore the cumulative impact of dysregulations in multiple stress systems on physical function could be larger than the impact of (a single indicator of) one stress system. However, the cumulative impact of multiple markers per stress system or across different stress systems has not yet been examined in connection to physical function and its link with mental health.

This study examined whether physiological stress markers are associated with objective physical function in a large cohort of adults. Two objective physical function indicators were used, namely hand grip strength and lung function, which both predict mortality and subsequent disability onset [20-22]. Both instruments are widely recommended as objective measures of physical function even in middle-aged persons. Various physiological stress markers of the immune-inflammatory system (C-reactive Protein (CRP), Interleukin-6 (IL-6), Tumor necrosis factor (TNF-a)), the HPA-axis (saliva cortisol awakening curve and evening levels) and ANS activity (heart rate, heart rate variability and pre-ejection period) were included. Furthermore, the extent to which stress markers explained earlier observed relationship between depressive and/or anxiety disorders and poorer objective physical function was examined.

2. METHODS

Study sample

Data of the Netherlands Study of Depression and Anxiety (NESDA) were used. NESDA is an ongoing longitudinal cohort study investigating the long-term course of depressive and/or anxiety disorders. A total of 2981 respondents, aged 18-65 years, were recruited from the general population (19%), primary care (54%) and mental health organizations (27%) to represent various settings and stages of psychopathology. Exclusion criteria were not being fluent in Dutch and having a primary diagnosis of psychotic, obsessive compulsive, bipolar or severe addiction disorder. A detailed description of the rationale, methods and recruitment strategy is reported elsewhere [23]. Baseline assessments took place between 2004 and 2007 and consisted of a 4-h appointment consisting of a psychiatric interview and a medical examination including blood and saliva collection.

For the purpose of this study, subjects without data on physical function indicators or missing data on all physiological stress markers were excluded (N = 121). This led to a total sample size of 2860 persons. Excluded persons were older (46.0 vs 41.7 years, $p < .001$) compared to included persons, but did not differ in education and sex.

Measurements

Physiological stress systems

Of the *immune-inflammatory system*, CRP, IL-6 and TNF-α were assayed. Fasting blood samples were taken in the morning and kept frozen at -80 °C [24]. CRP and IL-6 were assayed at the Clinical Chemistry Department of the VU University Medical Center. High-sensitivity plasma levels of CRP were measured in duplicate by an in-house ELISA based on purified protein and polyclonal anti-CRP antibodies (Dako, Glostrup, Denmark). Intra- and inter-assay coefficients of variation were 5% and 10%, respectively. Plasma IL-6 levels were measured in duplicate by a high sensitivity ELISA PeliKine CompactTM ELISA, Sanquin, Amsterdam, The Netherlands). Intra- and inter-assay coefficients of variation were 8% and 12%, respectively. Plasma TNF-α levels were assayed in duplicate at Good Biomarker Science, Leiden, The Netherlands, using a high-sensitivity solid phase ELISA (Quantikines HS Human TNF-α Immunoassay, R&D systems, Minneapolis, MN, USA). Intra- and inter-assay coefficients of variation were 10% and 15%, respectively.

HPA-axis variables included the cortisol awakening response and evening cortisol levels from saliva. Saliva samples were taken at the respondent's home on a regular

(preferably working) day shortly after the assessment [25]. Saliva samples were obtained using Salivettes (Sarstedt, Nümbrecht, Germany) and respondents were asked to write down the exact sampling time. Samples were stored in refrigerators and returned by regular mail. After receipt, salivettes were centrifuged at 2000 x *g* for 10 min, aliquoted and stored at -80 °C. Cortisol analysis was performed by competitive electrochemiluminescence immunoassay (Roche, Basel, Switserland) [26]. The detection limit was 2.0 nmol/l and the intra- and inter-assay variability coefficients were < 10%. The cortisol awakening response (CAR) is based on 4 sampling points; at awakening (T1) and at 30 (T2), 45 (T3), and 60 (T4) minutes later. Using CAR, the area under the curve with respect to the ground (AUCg) and with respect to increase (AUCi) were calculated using formulas by Pruessner et al. [27]. The AUCg is an estimate of the total cortisol secretion over the first hour after awakening and predicts mean cortisol levels throughout the day, and the AUCi is a measure of the dynamic of the CAR, more related to the sensitivity of the system and emphasizing changes over time. Evening cortisol was calculated by the mean of T5 (collected at 10.00 pm) and T6 (collected at 11.00 pm) [28] since these values were highly correlated. Evening cortisol level is considered to reflect basal cortisol secretion; the ability of HPA-axis to return to lower levels of cortisol toward the end of the day after the morning peak levels of the cortisol awakening response [29].

Variables of the *autonomic nervous system* were gathered by using the Vrije Universiteit Ambulatory Monitoring System (VU-AMS). The VU-AMS is a lightweight portable device that measures changes in thorax impedance and electrocardiograms from a six-electrode configuration [30, 31]. From these data, interbeat interval time series were extracted to determine mean heart rate (HR) which reflects the combined effect of sympathetic and parasympathetic activity. From the respiration signal, the Respiratory Sinus Arrhythmia (RSA) was calculated by subtracting the shortest inter-beat interval during heart rate acceleration in the inspirational phase from the longest inter-beat interval during deceleration in the inspirational phase for all breaths as described elsewhere [31] and reflects parasympathetic activity. Pre-ejection period (PEP) was defined as the interval between the upstroke (B-point) of the thorax, indicating onset of left ventricular electrical activity, and the dZ/dt(min) point, indicating the beginning of blood ejection trough the aortic valve [31] and reflects the sympathetic activity.

Within each stress system, individual markers were highly correlated ($\beta = 0.09\text{-}0.47$, all markers: $p < .001$) [19], which justifies combining markers into a cumulative index for each stress system [18]. These indices represent the complex and coordinated network of a stress system and by including the cumulative indices in the analyses, the

cumulative impact of the multiple stress markers on physical function can be analyzed [32]. Cumulative indices included the number of markers for which the respondent fell within the highest risk quartile (total score 0-3). For all markers of inflammation and HPA-axis and for HR, the highest quartile was the highest risk quartile. For PEP and RSA, the lowest quartile was labelled as highest risk quartile.

Physical function

Hand grip strength and lung function were used as indicators of physical function and both instruments have been shown to be accurate and reliable [33, 34]. Hand grip strength was measured with a Jamar hand held dynamometer in kilograms of force and gives an indication of overall bodily muscle strength [35]. It was assessed twice for the dominant hand and the maximum performance was used in further analyses. Hand grip strength is the most widely reported and recommended measure of muscle strength [34]. The standard position for testing was used: sitting in a straight-backed chair with feet on the floor, shoulders adducted in neutral position, arms unsupported, elbows flexed at 90°, forearm rotation neutral and wrist 0-30° dorsiflexion and 0-15° ulnar deviation [34]. The interviewer encouraged the respondent to perform to the best of their ability. Lung function was determined by measuring the maximum peak flow during expiration (in liter per minute) delivered with maximum force starting from the level of maximal lung inflation using a mini Wright peak flow meter. Lung function gives an indication of the ventilatory performance. Peak flow was measured while standing with the peak flow meter in a horizontal position. It was assessed twice and the maximum performance was used in further analyses.

Psychiatric diagnoses and severity

The presence of current depressive and anxiety disorders was established using the Composite International Diagnostic Instrument (CIDI, version 2.1), according to the Diagnostic Statistical Manual of Mental Disorders- fourth edition (DSM-IV) algorithms. The CIDI is a valid and reliable instrument to assess depressive and/or anxiety disorders and was administrated by specially trained research staff. Depressive disorders included Major Depressive Disorder (MDD) and dysthymia, whereas anxiety disorders included social phobia, generalized anxiety disorder, panic disorder and agoraphobia.

Severity of depression in the past week was assessed using the 30-item Inventory of Depressive Symptomatology (IDS-SR30) [36] with an overall score ranging from 0 to 84. Higher scores mean higher symptom severity. We previously found associations

between current depressive and anxiety disorder status as well as IDS severity scores with objective indicators of physical function. However, for both grip strength as well as lung function, these associations were significantly stronger for women than for men [2].

Covariates

Covariates age (in years), sex and education level (in years) were collected during the assessment. Body mass index (BMI) was calculated as weight in kilogram divided by height in meters squared. A count of the number of chronic somatic diseases for which the respondent receives treatment (including lung disease, diabetes, cardiovascular disease, cancer, osteoarthritis, intestinal disorder and thyroid gland disease) was made. Frequent medication use (> 50% of the time) was registered from the respondent's medication container inspection and classified using the World Health Organization anatomical therapeutic chemical classification: cardiac medication including beta-blocking agents (C07), antihypertensives (C01-C05, C08, C09), anti-inflammatory medication (M01A, M01B, A07EB, A07EC), and lung medication (ATC-code R03) (lung medication only was used in analyses of lung function). Physical activity was measured with the International Physical Activity Questionnaire (IPAQ) and expressed in 1000 MET minutes per week (Metabolic Equivalent of Task: ratio of energy expenditure during activity compared to rest times and the number of minutes performing the activity) [37]. Smoking status was defined in pack years (one pack year is equal to smoking 20 cigarettes per day over a course of one year). Alcohol intake was categorized as non-drinking (< 1 drink/week), moderate drinking (1-14 (women)/1-21 (men) drinks/week) and heavy drinking (> 14 (women)/> 21 (men) drinks/week).

Statistical analyses

Due to high attrition rates of saliva sampling (38%), HPA-axis data was imputed using a multiple imputation procedure. Markers of inflammation and of the autonomic nervous system were also imputed in these analyses although the percentages of missing values were much lower (resp. 2% and 4%). We followed the guidelines for Multiple Imputation of Van Buuren et al. [38], and performed 100 imputations based on missing at random (MAR). The assumptions of missing at random (MAR) were considered met since missingness was not related to performance on the physical function measures (independent variables), and all other variables used in this study were included in the Multiple Imputation analyses to obtain the required predicted values. Pooled estimates are shown in the results.

To examine the association between physiological stress systems and physical function (hand grip strength and lung function in separated models), single linear regression analyses were conducted for each stress marker (CRP, IL-6, TNFa, AUCg, AUCi, evening cortisol, heart rate, PEP, RSA) adjusting for age, sex, education, BMI, somatic diseases, use of medication, physical activity, smoking and alcohol. To check whether associations were comparable for men and women, interaction terms with sex were added. ANCOVAs were used to determine mean hand grip strength and mean lung function for each of the cumulative index variables with adjustment for all covariates. Excluding those with imputed data, complete case analyses were conducted to check the robustness of the results.

We conducted subsequent analyses to examine whether physiological stress markers explained the earlier observed association between depressive and anxiety disorders and poorer physical function [2]. Linear regression analyses were used with depressive and/or anxiety disorder status and severity of symptoms (IDS) as independent variables, hand grip strength and lung function as dependent variables and age, education, somatic diseases, BMI, medication use, physical activity, smoking and alcohol use as covariates. The impact of additional adjustment of cumulative indexes of inflammation, HPA-axis and autonomic nervous system were examined in subsequent models. Analyses were conducted separately for men and women. All analyses were conducted using SPSS version 24.0 and a significance level of .05 was used.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The NESDA protocol was approved by the Ethical Committee of participating universities and all respondents provided written informed consent.

3. RESULTS

Table 6.1 shows the characteristics of the sample. Mean age of the sample was 41.7 (SD = 13.1) years, 66.2% were female and the mean years of education was 12.2 (SD = 3.3). Mean hand grip strength was 38.7 (SD = 11.6) kg and mean lung function was 478.4 (SD = 110.3) l/min.

Table 6.1. Sample characteristics (*N* = 2860)

Sociodemographics	
Age in years, mean (SD)	41.7 (13.1)
Sex (% women)	66.2
Education in years, mean (SD)	12.2 (3.3)
Health and lifestyle indicators	
BMI, mean (SD)	25.6 (5.0)
No. of somatic diseases (%)	
0 diseases	58.8
1-2 diseases	37.6
≥ 3 diseases	3.6
Cardiac medication (% yes)	14.5
Anti-inflammatory medication (%yes)	4.1
Lung medication (% yes)	5.8
Physical activity in 1000 MET-min/wk, median (IQR)	3.1 (1.4-5.0)
Smoking in pack years, mean (SD)	11.0 (16.6)
Alcohol intake (%)	
< 1 drink/week	32.1
1-14/21 drinks/week	56.2
> 14/21 drinks/week	11.7
Depression/ Anxiety status	
Current depression or anxiety diagnosis (% yes)	58.2
IDS severity score, mean (SD)	21.4 (14.1)
Physical function indicators	
Hand grip strength in kg, mean (SD)	38.7 (11.6)
Lung function in l/min, mean (SD)	478.4 (110.3)
Physiological stress markers	
Inflammation	
CRP (mg/L), median (IQR)	1.2 (0.5-3.0)
IL-6 (pg/ml), median (IQR)	0.7 (0.5-1.3)
TNF-α (pg/ml), median (IQR)	0.8 (0.4-1.1)
HPA-axis	
AUCg (nmol/L/hr), mean (SD)	18.9 (6.9)
AUCi (nmol/L/hr), mean (SD)	2.1 (6.2)
Mean evening cortisol (nmol/L), median (IQR)	4.8 (3.3-6.6)
Autonomic nervous system	
Heart rate (bpm), mean (SD)	72.0 (9.6)
PEP (ms), mean (SD)	120.2 (17.8)
RSA (ms), median (IQR)	38.9 (29.3-55.6)

Abbreviations: SD, standard deviation; BMI, Body Mass Index; IDS, Inventory Depressive Symptomatology; BAI, Beck Anxiety Inventory; MET-min/wk, metabolic equivalent of number of calories in minutes per week; IQR, interquartile range; T/S ration, telomere sequention ratio; CRP, C-Reactive protein; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-alpha; AUCg, area under the curve with respect to the ground; AUCi, area under the curve with respect to the increase; BPM, beates per minute; PEP, Pre-ejection period ; RSA, Respiratory Sinus Arrhythmia.

Associations between physiological stress markers and physical function

Table 6.2 shows the associations between physiological stress markers and physical function with adjustment for all covariates. Higher CRP (B = -0.21, $p < .001$) was associated with lower hand grip strength. Higher AUCg (B = 0.06, $p = .047$) was associated with higher hand grip strength. Higher CRP (B = -2.07, $p = .002$), higher TNF-α (B = -3.35, $p = .022$), and higher evening cortisol (B = -2.22, $p < .001$) were associated with poorer lung function. Additional analyses including only complete cases confirmed above results (data not shown).

Table 6.2. Associations between physiological stress markers and physical function (*N* = 2860)

	Hand grip strength		Lung function	
	B (SE)	*p*-value	B (SE)	*p*-value
Inflammation				
CRP	-0.21 (0.06)	**.001**	-2.07 (0.66)	**.002**
IL-6	-0.15 (0.11)	.18	-1.38 (1.23)	.26
TNF-α	-0.12 (0.13)	.36	-3.25 (1.42)	**.022**
HPA-axis				
AUCg	0.06 (0.03)	**.047**	-0.57 (0.31)	.066
AUCi	0.02 (0.03)	.57	0.13 (0.33)	.70
Evening cortisol	0.01 (0.06)	.88	-2.22 (0.59)	**< .001**
Autonomic nervous system				
Heart rate	-0.01 (0.02)	.37	-0.33 (0.18)	.065
PEP	-0.003 (0.01)	.68	-0.15 (0.10)	.11
RSA	-0.004 (0.01)	.60	0.01 (0.08)	.92

Based on linear regression analyses. Each line presents a single analysis. B (SE) is based on imputated physiological stress markers. Analyses were adjusted for sex, age, education, BMI, somatic diseases, use of heart medication, anti-inflammatory medication and lung medication, physical activity, smoking, alcohol use. CRP, C-reactive protein; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor; AUCg, Area Under the Curve with respect to the Ground; AUCi, Area Under the Curve with respect to the Increase; PEP, Pre-ejection period; RSA, Aggregated respiration rate.

Figure 6.1 graphically illustrates the associations between the cumulative index of inflammation, HPA-axis and autonomic nervous system with hand grip strength and lung function with adjustment for all covariates. A high number of inflammation markers in the high risk quartile was found to be associated with poorer hand grip strength and lung function (resp. *p* for linear trend < .001 and .002). A high number of HPA-axis makers in high risk quartiles was found to be associated with lung function (*p* for linear trend = .01) but not with hand grip strength. A high number of ANS markers in high risk quartiles was not associated with hand grip strength or lung function.

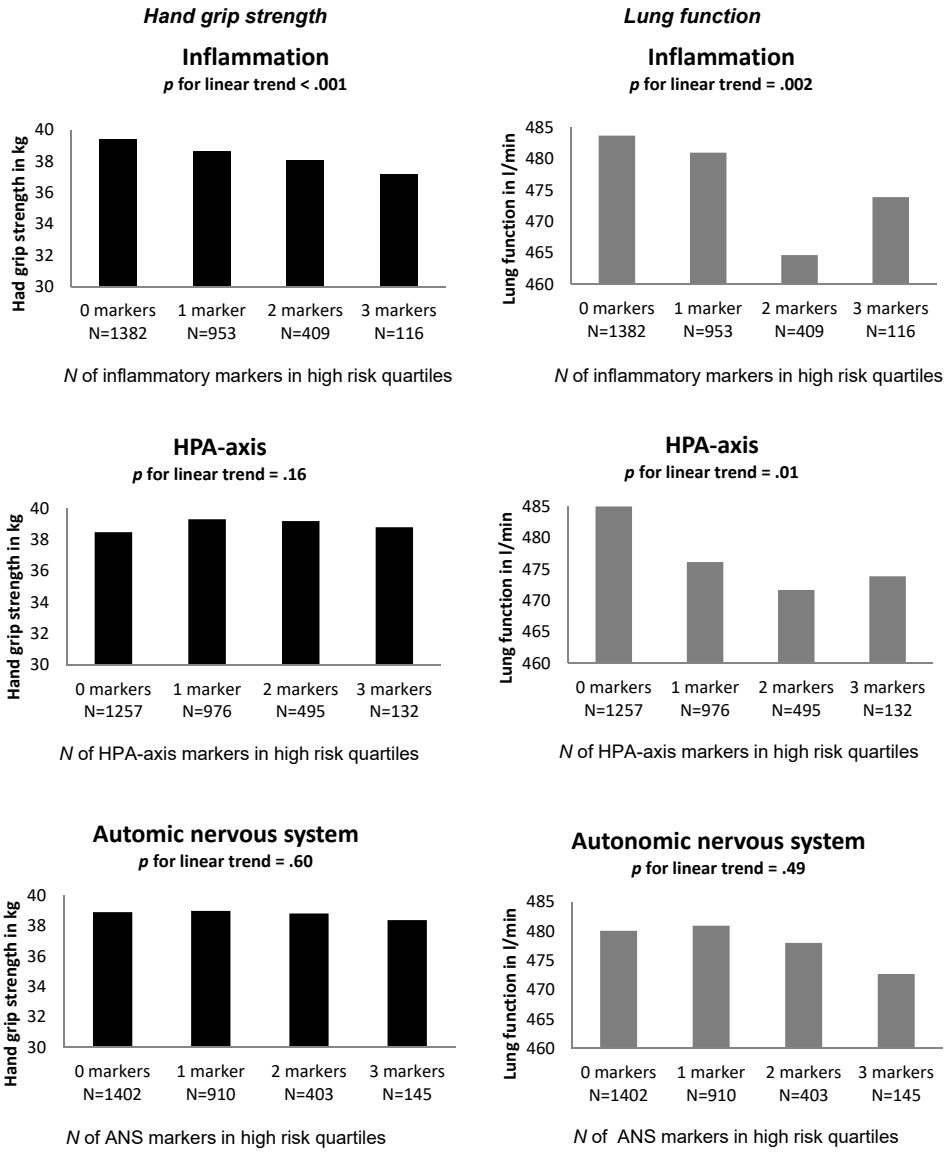

Figure 6.1. Associations between physiological cumulative index scores and physical function.
Based on ANCOVAs with adjustment for sex, age, education, BMI, somatic diseases, use of lung medication (only for lung function), physical activity, smoking and alcohol use.

Interaction terms for stress marker*sex were added but were not significant, suggesting that there do not seem to be large no sex differences exist in the association between physiological stress markers and physical function. One exception (out of 24 interaction terms) was found; the interaction term of PEP*sex for hand grip strength (p = .04) was

statistically significant: stratified analyses showed that the association between PEP and hand grip strength had a different direction for men (B = -0.02, p = .244) than for women (B = 0.01, p = .441) but neither were statistically significant.

The relationship between depressive and anxiety disorders and physical function with adjustment for physiological stress markers

Table 6.3 shows the associations between depressive and anxiety disorders and physical function, and these results were in line with previous analyses [2]. In men, no significant associations were found between current depression and/or anxiety disorders and physical function. In women, strong associations between lower hand grip strength (B = -1.13, p = .001) and lower lung function (B = -12.82, p < .001) in currently depressed or anxious women were found compared to women without current depressive and anxiety disorders. Analyses with depression symptom severity as outcome confirmed these results, illustrating a dose-response association between depression and poorer physical function in women only.

Table 6.3. Associations between depression/ anxiety and physical function with and without adjustment for physiological stress (*N* = 2860)

	Hand grip strength				Lung function			
	Men		Women		Men		Women	
	B (SE)	*p*-value	B (SE)	*p*-value	B (SE)	*p*-value	B (SE)	*p*-value
Model 1 [a]								
Current depression/ anxiety [b]	0.32 (0.63)	.61	-1.13 (0.34)	**.001**	8.96 (6.69)	.18	-12.82 (3.64)	**< .001**
IDS score	-0.004 (0.02)	.86	-0.04 (0.01)	**.006**	0.03 (0.24)	.90	-0.52 (0.14)	**< .001**
Model 1 + adjustment for physiological stress [c]								
Current depression/ anxiety [b]	0.39 (0.63)	.54	-1.17 (0.34)	**.001**	10.94 (6.70)	.10	-12.77 (3.64)	**< .001**
IDS score	-0.001 (0.02)	.95	-0.04 (0.01)	**.004**	0.12 (0.24)	.63	-0.52 (0.14)	**< .001**

Based on linear regression analyses. Each line presents a single analysis. B (SE) is based on imputed physiological stress markers. Bold indicates significance level of .05 was used.

[a] Model 1 = adjusted for age, education, BMI, somatic diseases, use of heart medication, anti-inflammatory medication and lung medication, physical activity, smoking and alcohol.

[b] No current diagnoses is the reference group.

[c] Model 1 + additional adjustment for cumulative inflammation index, cumulative HPA-axis index and cumulative ANS index. Cumulative indexes were based on imputed physiological stress data.

In order to examine the extent to which stress markers explained the associations between depressive and/or anxiety disorders and physical function we additionally adjusted for the cumulative indexes of inflammation, HPA-axis and ANS activity in subsequent models (Table 6.3). These results suggest that the relationship between depressive and/or anxiety disorders and poorer physical function in women was not dependent on dysregulations of physiological stress markers as taking the latter into account did not change the relationship between depressive and/or anxiety disorders and poorer physical function.

4. DISCUSSION

This study examined whether physiological stress markers are associated with objective physical function in a large cohort. The results clearly show that higher levels of inflammatory markers, indicative of chronic systemic inflammation, were associated with both poorer hand grip strength and poorer lung function. Furthermore, higher levels of cortisol, indicative of hyperactivity of the HPA-axis, were associated with poorer lung function. The observed association between depressive and anxiety disorders and poorer physical function in women could not be explained by physiological stress markers, since adjustment for these markers did not alter the estimates of the association between depression, anxiety and physical function.

The finding that higher inflammation levels were associated with poorer physical function is consistent with the literature [11, 12, 39, 40]. However, these studies mostly included older persons while this study included middle-aged persons. Our findings suggest that deterioration of bodily function due to higher inflammation levels holds also in younger populations. The link between inflammation and poorer physical function was to be expected since the literature shows evidence that inflammatory markers contribute to muscle wasting and/or dysfunction [39, 41- 43]. Our study included several inflammation markers and, as the literature suggests, by putting these markers together in the analysis as cumulative indices, an efficient network of inflammation is more likely captured [32].

Poorer lung function was associated with higher cortisol levels which implicates a lack of diurnal decline and hyperactivity of HPA-axis. Hyperactivity of the HPA-axis could lead to worse somatic health, more disability and also to worse physical performance as observed in older samples in the meta-analysis by Gardner et al. [15]. Our findings are consistent with the findings of Peeters et al. [44] and Kumari et al. [45] who both

found poorer physical performance in older persons with hypercortisolism. In contrast and against our expectations, a higher morning cortisol level (AUCg) was associated with higher hand grip strength. One other study observed something similar. Gardner et al. [46] found that higher baseline morning cortisol predicted faster walking speed 20 years later in middle-aged men and those with higher night-time cortisol levels and a smaller diurnal-drop had slower walking speed after 20 years. This study implicates that maintenance of good circadian regulation of HPA activity is associated with better physical performance in later life. In contrast, Peeters et al. [44] found that higher cortisol was associated with greater loss of grip strength after 4 years. These mixed findings call for more longitudinal research to understand the relationship between HPA-axis and objective physical function.

While dysregulations of the immune-inflammatory and HPA-axis systems were associated with poorer physical function, ANS markers however were not associated with objective physical function. The literature shows some evidence of lower heart rate variability in those with poorer hand grip strength which could be due to a poorer lifestyle [16]. However, Koopman et al. [47] included Ghanaian older persons from rural areas who are probably not comparable to our sample.

Our results show that the association between poorer physical function and current depressive and anxiety disorders in women remained present after adjustment for inflammation markers, HPA-axis markers and markers of the autonomic nervous system. Thus, the link between depression, anxiety and poorer physical function does not seem to be explained by higher activation of these physiological stress systems. This could be due to the use of static measures of physiological stress systems limited to a limited frame (single blood sample for inflammation, a few hours for ANS measures and repeated measures within a day for cortisol sampling). Using reactivity measures of physiological stress when people undergo (experimental) stress exposure may show different associations with depression, anxiety and objective physical function, but such measures were not available in our study. Other possible underlying mechanisms are poorer lifestyle and somatic health status, but adjustment for these mechanisms did not impact much on our associations. Despite our study using objective physical function measures, a lower motivation of participants with a depressive or anxiety disorder to do performance tasks could play a role. Furthermore, our study adjusted for somatic health status, however, only the number of chronic diseases was included and not the severity of the disease. It could be that higher severity of somatic diseases could be accompanied with poorer physical function. However, these speculations should be tested in future research.

Some limitations of this study should be noted. Causality is difficult to infer in our study due to the cross-sectional design. Longitudinal analyses in which physiological stress will be measured over time can help further to disentangle ordering of associations and to examine e.g. whether stress system dysfunction predicts subsequent change in physical function or whether physical function impacts on change in stress system dysfunction over time. This helps to determine to what extent there is directionality in the association between stress system dysfunction and physical function. Thirty percent of the sample had missing salivary cortisol data, however, multiple imputation was performed to impute missing data in an effort to overcome bias and imputed and non-imputed analyses showed similar results. The used physiological stress markers were rather static measures collected during a limited time frame and do not capture reactivity during a stress exposure assessment which may have different associations with objective physical function, depression and anxiety. Finally, the measures of physical function used in this study are simple physiological measures and do definitely not capture the overall fitness and health of our participants in fullness. For instance, peak expiratory flow, is not as well validated as FEV1 and FVC measured with spirometry, to characterize lung function capacity. Also other more dynamic measurements, such as a sit-up-and-go test or a 6-min walk test could provide more extensive information about physical functioning in daily life. Nevertheless, the chosen hand grip strength and peak flow measures in our study are practical and general physiologic health status indicators that can be obtained in a standardized manner in large cohorts, have no ceiling effects in younger populations, and have shown to be predictive of subsequent health outcomes such as disease onset, hospitalization and mortality in large-scale studies [34, 48].

This study also had some important strengths. First, we have a well-characterized, large sample of persons with depression or anxiety and healthy controls. The NESDA patient sample is large and generally representative for persons with depressive and/or anxiety disorders since persons with depression and anxiety were recruited in various settings with different stages of psychopathology. Second, we had the unique possibility to study various indicators of three different physiological stress systems simultaneously in relation to objectively measured physical function, while being able to control for important covariates.

To conclude, higher levels of dysregulated physiological stress systems were associated with poorer objective physical function. More precisely, higher inflammation levels were associated with both poorer hand grip strength and lung function and higher cortisol levels were associated with poorer lung function. Furthermore, after

adjustment for physiological stress, the association between depressive and anxiety disorders and poorer physical function in women remained significant, which suggests other underlying mechanisms play a role in that association. While some physiological stress markers are cross-sectionally linked to physical function, future research should shed more light on the longitudinal association of these indicators.

Disclosure summary

B.W.J.H.P. has received (non-related) research funding from Janssen Research & Development, LLC, and Boehringer Ingelheim. All other authors declare that they have no conflicts of interest.

Contributors

B.W.J.H. Penninx and J.H. Smit contributed to the conception and design of the study, and interpretation of the data. B.A. Lever-van Milligen undertook the analyses and together with F Lamers interpreted the results. B.A. Lever-van Milligen made the first draft of the article, and B.W.J.H. Penninx, J.H. Smit and F. Lamers contributed to revising the article critically for important intellectual content. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

All authors declare that they have no conflicts of interest. Study sponsors had no further role in study design; in the collection, analyses and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Acknowledgements

The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (ZonMw, grant number 10-000-1002) and financial contributions by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Leiden University Medical Center, Leiden University, GGZ Rivierduinen, University Medical Center Groningen, University of Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Rob Giel Onderzoekscentrum). Assaying of basal inflammatory markers was supported by a VICI grant (NWO Grant No. 91811602) to BWP.

Abbreviations

ANS, autonomic nervous system; AUCg, area under the curve with respect to the ground; AUCi, area under the curve with respect to the increase; BMI, body mass index; CAR, cortisol awakening response; CIDI, composite international diagnostic instrument; CRP, c-reactive protein; DSM-IV, diagnostic statistical manual of mental disorders-fourth edition; HPA, hypothalamus-pituitary-adrenal; HR, heart rate; IDS-SR30, Inventory of Depressive Symptomatology 30-item; IL-6, interleukin-6; IPAQ, International Physical Activity Questionnaire; MET, Metabolic Equivalent of Task; MDD, major depressive disorder; NESDA, Netherlands study of depression and anxiety; PEP, pre-ejection period; RSA, respiratory sinus arrhythmia; SD, standard deviation; TNF-α, tumor necrosis factor; VU-AMS, vrije universiteit ambulantory monitoring system.

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CHAPTER 7

The impact of depression and anxiety treatment on biological aging and metabolic stress: study protocol of the MOod Treatment with Antidepressants or Running (MOTAR) study

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Published in BMC Psychiatry 2019: 19; 425.

ABSTRACT

Background: Depressive and anxiety disorders have shown to be associated to premature or advanced biological aging and consequently to adversely impact somatic health. Treatments with antidepressant medication or running therapy are both found to be effective for many but not all patients with mood and anxiety disorders. These interventions may, however, work through different pathophysiological mechanisms and could differ in their impact on biological aging and somatic health. This study protocol describes the design of an unique intervention study that examines whether both treatments are similarly effective in reducing or reversing biological aging (primary outcome), psychiatric status, metabolic stress and neurobiological indicators (secondary outcomes).

Methods: The MOod Treatment with Antidepressants or Running (MOTAR) study will recruit a total of 160 patients with a current major depressive and/or anxiety disorder in a mental health care setting. Patients will receive a 16-week treatment with either antidepressant medication or running therapy (3 times/week). Patients will undergo the treatment of their preference and a subsample will be randomized (1:1) to overcome preference bias. An additional no-disease-no-treatment group of 60 healthy controls without lifetime psychopathology, will be included as comparison group for primary and secondary outcomes at baseline. Assessments are done at week 0 for patients and controls, and at week 16 and week 52 for patients only, including written questionnaires, a psychiatric and medical examination, blood, urine and saliva collection and a cycle ergometer test, to gather information about biological aging (telomere length and telomerase activity), mental health (depression and anxiety disorder characteristics), general fitness, metabolic stress-related biomarkers (inflammation, metabolic syndrome, cortisol) and genetic determinants. In addition, neurobiological alterations in brain processes will be assessed using structural and functional Magnetic Resonance Imaging (MRI) in a subsample of at least 25 patients per treatment arm and in all controls.

Discussion: This intervention study aims to provide a better understanding of the impact of antidepressant medication and running therapy on biological aging, metabolic stress and neurobiological indicators in patients with depressive and anxiety disorders in order to guide a more personalized medicine treatment.

Trial registration: Trialregister.nl Number of identification: NTR3460, May 2012. https://www.trialregister.nl/trial/3313

Key words: depression, anxiety, treatment, antidepressant, SSRI, running therapy, aging, telomere length, telomerase activity, inflammation, metabolic syndrome, cortisol, fMRI.

1. BACKGROUND

Depressive and anxiety disorders are common comorbid conditions with a large impact on public health [1, 2]. Meta-analyses show that persons with depressive and anxiety disorders have increased risks for the onset of cardiovascular diseases, diabetes, stroke, obesity [3], and advanced physical [3, 4] and cognitive decline [5]. In other words, depressive and anxiety disorders need to be considered as an important risk factor for a multitude of aging-related conditions. Dysregulation of physiological stress systems such as inflammation, hyperactivity of the HPA-axis and metabolic dysregulation [6, 7] have been suggested to partly underlie these associations. Additionally, persons with depressive and anxiety disorders are found to be subject to advanced biological aging. Furthermore, these physiological stress systems may also play a role in recovery mechanisms of depression and anxiety disorders.

Two treatment regimens for depressive and anxiety disorders that have shown to be effective are antidepressants and running therapy [8-11]. It is, however, unclear whether they could beneficially affect biological aging and physiological stress-systems dysregulations. Well-designed studies looking into the underlying physiological pathways of both treatments are lacking. It has been suggested that these interventions may work through different pathophysiological mechanisms. Despite their comparable effectiveness on mental health outcomes [8], running therapy may have a more beneficial impact on somatic health indicators including biological aging [12]. This intervention study examines and compares the impact of antidepressant medication and running therapy on biological aging, metabolic stress and neurobiological abnormalities related to depression and anxiety.

Depressive and anxiety disorders and biological aging

In line with their negative impact on a multitude of aging-related somatic conditions, depression and anxiety disorders have found to be related to more advanced biological aging. This is for instance evidenced by shorter telomeres found in depression and/or anxious patients as compared to healthy controls [13-16]. Telomere length (TL), a relatively well-studied marker of cellular age, integrates the cumulative lifetime burden of genetic and environmental factors dependent on chronological age [17], and predicts several aging-related diseases and early mortality [18]. Telomeres are tandem repeated DNA sequences that form protective caps at chromosome ends [19] which can be elongated by telomerase enzymes. High telomerase activity has protective functions for aging and cell death and lower telomerase activity is linked to aging-related

disease factors [20-22]. Some studies suggest that telomerase activity is elevated in the presence of a depression diagnosis [23], possibly as an attempt to compensate for the loss of TL. However, another study found decreased telomerase activity in a chronically stressed sample [24], leaving it unclear whether increased activity of the enzyme is a sign of improved health or rather a compensatory mechanism. The extent to which depression and anxiety treatment impacts the telomere/ telomerase system has not been extensively examined [25].

Depressive and anxiety disorders, metabolic stress and neurobiological abnormalities

In various studies and meta-analyses, depressive and anxiety disorders have been linked to physiological alterations of central bodily stress systems: systemic inflammation [7, 26-27] and oxidative stress [6], hyperactivity of the hypothalamus-pituitary adrenal (HPA) axis [28], a dysregulated autonomic tone [29, 30] accompanied with metabolic syndrome dysregulations [31]. Metabolic and physiological stress system dysregulations could contribute to the process of advanced biological aging as they have shown to affect TL and the telomere maintenance system [32-34].

Physiological stress systems also impact the structural and functional integrity of the brain, such as hippocampal volume, prefrontal cortex (PFC) morphology, and activity of the amygdala, insula and anterior cingulate cortex (ACC) [35-38], albeit inconsistently [39]. These are key brain regions implicated in depression and anxiety as there is converging evidence for widespread but subtle structural alterations in prefrontal regions such as the ACC, dorsomedial and orbitofrontal cortex, posterior cingulate cortex, insula, and the hippocampus [40-45]. There is also some evidence for rostral ACC, amygdala and medial PFC hyperactivation during emotional processing, while dorsal regions may be hypoactive in people with depression or anxiety disorders [46-49], although findings have been inconsistent across studies [50].

Depressive and anxiety disorder treatment and physiological changes

Commonly prescribed selective serotonin re-uptake inhibitors (SSRI) have shown to be effective in depression and anxiety treatment [9, 51]. Some -although limited- evidence exists suggesting that SSRI treatment results in decreased cortisol [52], inflammatory [53] and antioxidant [54] levels. A recent review suggested a role for telomerase activity mediating the beneficial effects of antidepressants medication [55], possibly by promoting cell survival and/or function both in the brain and in the periphery.

Only a few studies examined the association between antidepressant treatment and the telomere system and found shorter leukocyte telomere length (LTL) in patients who did not respond to antidepressants compared to those who did respond [56, 57]. Sample sizes of above-mentioned studies were relatively small, thus associations between antidepressant response and telomere length/telomerase activity remain to be extensively explored.

A similarly effective intervention is running therapy [10, 58, 59]. Running therapy works through the direct impact of aerobic exercise on opioid [60, 61], monoaminergic mechanisms [62] and regional cerebral blood flow [63]. The impact of running therapy has also been shown to reduce oxidative stress [64], inflammation [65-67], and cortisol [68]. Exercise has also shown to have beneficial impact on TL in a cancer population with higher telomerase activity emerging after three months of exercise, which was paralleled by decreases in psychological distress [69], a finding confirmed in other research [12, 70-72]. Two studies comparing running therapy and SSRI treatment confirmed a similar effectiveness for depression [8, 73] and anxiety disorders [74]. Nevertheless, these interventions probably work through different pathophysiological mechanisms and may have different impact on biological aging.

Objective

This intervention study examines and compares the impact of antidepressant medication and running therapy on biological aging (primary outcome) and psychiatric status, metabolic stress and neurobiological abnormalities relevant for depression and anxiety disorders (secondary outcomes). This study also examines to what extent treatment-induced improvement in psychiatric status parallels with improvement of biological aging, metabolic stress and neurobiological abnormalities. Furthermore, this study compares the pre- and posttreatment outcomes to the physiological stress parameters of the no-disease-no-treatment control group.

2. METHODS

Study design

The MOod Treatment with Antidepressant or Running (MOTAR) study is a 16-week intervention study with two treatment arms: 1) antidepressant medication and 2) running therapy (see Figure 7.1). In total, 160 patients with a depressive and/or anxiety

disorder receive antidepressants or running therapy. Depressive and anxiety disorders are highly comorbid [75], also over time [76, 77], their underlying pathophysiology is largely comparable and both disorders are treated with similar treatments [10, 51, 74, 78]. A randomised controlled trial is the preferred method to compare two interventions, but also comes with limitations: quite some patients do not agree with random treatment assignment, and therefore, studies may result in selective inclusion of subjects which hampers the generalizability of results. Consequently, we decided to conduct a pragmatic study (resembling a partially randomised preference patients design (PRPP) [79]. First, patients without strong preference for treatment allocation are randomly allocated (1:1) to either antidepressant medication or running therapy. The SPSS random generator (SPSS, version 20.0) is used to randomise these participants. Subsequently, persons who were not willing to be randomised but are willing to participate in the study, were allocated to their preferred intervention. In order to be certain that no age differences arise, randomization is stratified by age in two groups (cut off 40 years). Further, in a subset of at least 50 subjects (25 from both treatment conditions) neuroimaging (Magnetic Resonance Imaging (MRI) data will be collected. A no-disease-no-treatment-control group (*N* = 60) will be examined to compare health, physiological and neurobiological indicators between persons with and without depression and anxiety disorders at baseline, and allows checks on whether improvements over time after treatment completely restores health and physiological levels to those of healthy controls.

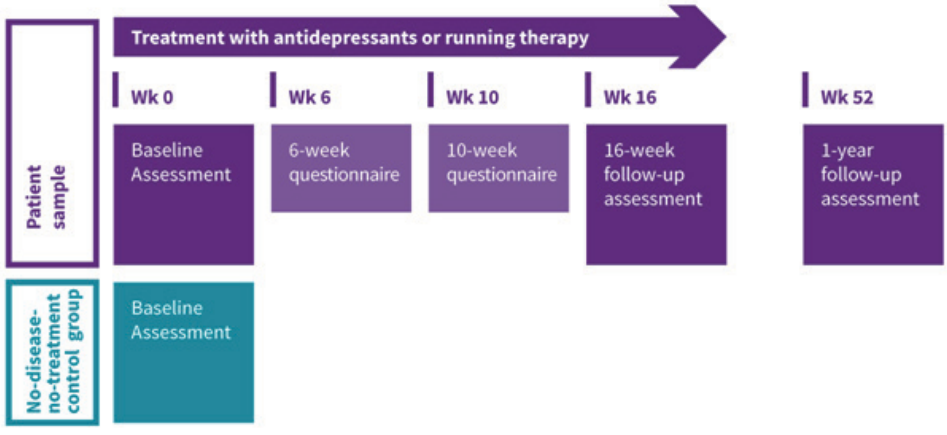

Figure 7.1. MOTAR flowchart.

Recruitment and study settings

Between 2012 and 2019, patients are recruited when (newly) enrolled at GGZ inGeest (mental health organization in the surroundings of Amsterdam, The Netherlands) with depressive and/or anxiety disorders. Patients receive information about the study during the intake and are asked for their participation. During a telephone screening, in- and exclusion criteria are checked and when consent is given, patients undergo a baseline assessment before starting their treatment. All patients are also asked to participate in the MRI study substudy.

The no-disease-no-treatment-control group is recruited through advertisements in the area and through the website www.motar.nl. Persons receive information about the study and are asked for their participation. Patients and controls are matched on the basis of age, sex and educational level. In- and exclusion criteria are checked and after given consent, the healthy persons only undergo a baseline and neuroimaging assessment.

Eligibility criteria

Inclusion criteria of the patient sample include: having a current depressive disorder (major depressive disorder) or anxiety disorder (social phobia, generalized anxiety disorder, panic disorder with or without agoraphobia) as ascertained by the Diagnostic and Statistical Manual of Mental Disorders – Fourth edition (DSM-IV) algorithms with the CIDI (Composite International Diagnostic Interview) [80] and being aged between 18 and 70 years. Exclusion criteria are: 1) use of antidepressants in last two weeks, 2) current use of other psychotropic medication, except for the use of benzodiazepines with stable usage, 3) regular exercising more than once a week, 4) primary severe, clinically diagnosed psychiatric diagnosis other than a depressive or anxiety disorder, 5) evidence of acute suicidal risk (based on clinical view), 6) medical contra-indications to running therapy or antidepressants (e.g. serious heart problems) as confirmed by the patient's physician, and 7) being pregnant.

Inclusion criteria of the no-disease-no-treatment-control group are having a negative lifetime history of psychiatric disorders as checked with the CIDI and being aged between 18 and 70 years. Exclusion criteria are: 1) participation in regular (> 1/week) exercise and 2) medical contra-indications to running therapy or antidepressants (e.g. serious heart problems) as confirmed by a physician.

Additional exclusion criteria for the MRI sub-study are major internal or neurological disorders, pregnancy and known contra-indications for MRI investigations, such as the presence of metal objects (e.g. pacemaker, arteriovenous clips) or claustrophobia.

Consent procedure, baseline and follow-up assessments

Informed consent approved by the Medical Ethical Committee VU University Medical Centre has to be signed before starting the baseline assessment. During a 4-h face-to-face baseline assessment a wide range of data will be collected, including demographic information, a diagnostic psychiatric interview, a medical examination, a cycle ergometer test, collection of saliva, urine, and blood and various self-reported clinical questionnaires. At week 6 and week 10 depression and anxiety symptom severity will be assessed by self-report questionnaires. At week 16 and week 52, the assessments will be repeated in the patient sample (see Figure 7.1). For each face to face assessment, the patient will receive a gift voucher of €50. MRI measurements consist of a clinical interview and a neuroimaging session with a total duration of approximately 2.5 h. For each MRI measurement, the patient will receive a gift voucher of €25. The control group will undergo a baseline and neuroimaging assessment, but no follow-up assessments. The control participants will receive a gift voucher of €50. Table 7.1 gives an overview of the data collection.

Intervention

Participants will undergo an intervention of 16 weeks since this period has shown to be sufficient to decrease depressive and anxiety symptoms and to impact on physiological stress after antidepressant therapy [81] or running therapy [70, 82].

Antidepressant medication

Patients will receive standardized treatment with escitalopram, a selective serotonin reuptake inhibitor (SSRI) which has documented efficacy, a rather favorable side effect profile, is recommended as first-step treatment in both the General Practitioner (NHG Standardized depressive disorder and anxiety disorder (in Dutch)) and Psychiatry treatment guidelines (Multidisciplinary guidelines depression and anxiety (in Dutch)), and is one of the most commonly prescribed antidepressants [81, 83]. An initial dosage of 10 mg per day of escitalopram is used. Medication management is provided by a psychiatrist who meets each patient at study onset and at weeks 2, 6, 10 and 16. At these meetings, the psychiatrist evaluates treatment response and side effects,

Table 7.1. Collected information on central (mental) health outcomes in MOTAR

	Instrument	Method	Week 0	Week 6	Week 10	Week 16	Week 52
Primary outcomes							
Biological aging: telomere length, telomerase activity	Fasting blood samples	Blood	X	-	-	X	X
Secondary outcomes							
Biological and general health indicators							
Biomarkers (inflammation, metabolic syndrome)	Fasting blood samples	Blood	X	-	-	X	X
Gene-expression (RNA)	Fasting blood samples	Blood	X	-	-	X	X
HPA-axis (cortisol)	2 days of 6 saliva samples	Saliva	X	-	-	X	X
Oxidative stress	Urine sample	Urine	X	-	-	X	X
Autonomic nervous system	Electro + impedance cardiography, heart rate variability [88]	ME	X	-	-	X	X
Blood pressure	Systolic and diastolic BP	ME	X	-	-	X	X
Body composition	Weight, height, waist+ hip circumfereence	ME	X	-	-	X	X
Physical condition	Astrand sub max test [89]	ME	X		-	X	X
Muscle strength	Hand grip strength [88]	ME	X	-	-	X	X
Lung function	Peak expiratory flow [89]	ME	X	-	-	X	X
Pain	Chronic graded pain scale [90]	Int	X	-	-	X	X
Somatization	Short somatization questionnaire [91]	SR	X	-	-	X	X
Disability severity	WHO-DAS II [92]	SR	X	-	-	X	X

Table 7.1 continues on next page.

Table 7.1. ***Continued***

	Instrument	Method	Week 0	Week 6	Week 10	Week 16	Week 52
Depressive and anxiety disorders							
Presence of MDD	CIDI: MDD [78]	Int	X	-	-	X	X
Presence of anxiety dis	CIDI: SocPhob, Agora, GAD, PA [78]	Int	X	-	-	X	X
Course of symptoms	Life-chart [93]	Int	X	-	-	X	X
Severity of depression	Inventory of depressive symptoms [94]	SR	X	X	X	X	X
Severity of anxiety	Beck anxiety index [95] and Fear questionnaire [96]	SR	X	X	X	X	X
Sleep	Insomnia Rating Scale [97]	Int	X	-	-	X	X
Descriptive variables, potential confounding covariates and potential mediating variables							
Age, gender, ethnicity	Standard questions	Int	X	-	-	-	-
Socio-economic status	Education, income, occupation	Int	X	-	-	-	-
Physical activity	SQUASH questionnaire [98]	SR	X	-	-	X	X
Smoking	Past + current smoking questions	SR	X	-	-	-	X
Medication use	Drug container observation	Int	X	-	-	X	X
Regular alcohol intake	AUDIT questionnaire [99]	SR	X	-	-	-	X
Somatic diseases	Presence + symptoms of disease	Int	X	-	-	X	X
Health care	Perceived need of care [100]	Int	X	-	-	X	X
Work and disability	Tic-P questionnaire [101]	Int	X	-	-	X	X
Personality	NEO-FFI questionnaire [102]	SR	X	-	-	X	X
Locus of control	Pearlin & Schooler mastery scale [103]	SR	X	-	-	X	X
Depression vulnerability	LEIDS-R questionnaire [104]	SR	X	-	-	X	X
Anxiety vulnerability	Anxiety senstivity index [105]	SR	X	-	-	X	X
Experimental cognitive task	Implicit association test (IAT) [106]	CT	X	-		X	X
Experimental memory task	Digit Span (WAIS) [107]	Int	X	-	-	X	X
Important neg + pos life events	Brugha questionnaire [108]	Int	X	-	-	X	X
Childhood Trauma	Youth Trauma questionnaire [109]	SR	X	-	-	-	-
Familiy history	Familiy history inventory	Int	X	-	-	-	-

Table 7.1. ***Continued***

	Instrument	Method	Week 0	Week 6	Week 10	Week 16	Week 52
Neuroimaging assessment (subsample)							
Verbal episodic memory	15-words test [110]	MRI	X	-	-	X	X
Task-related brain activity	Emotional face matching paradigm and N-back paradigm [111]	MRI	X	-	-	X	X
Brain network connectivity	Resting state MRI images	MRI	X	-	-	X	X
Process indicators (intervention adherence)							
Exercise intervention group: Exercise participation and heart rate will be administrated during each session..							
Antidepressant intervention group	Side effect medication questionnaire	Int	-	X	X	X	-
	Adherence (pill count)	Int	-	X	X	X	-

SR, self-report; Int, interview; Blood, data collection via fasting blood sample; CT, computer task; ME, medical examination.

and titrates dosage (to a maximum of 20 mg) according to the multidisciplinary depression/anxiety guidelines until a clinically effective dosage is achieved. Following the medication protocol, if the initial SSRI is poorly tolerated, the psychiatrist can switch prescription to another SSRI drug (sertraline, dosage of 50 mg to a maximum of 150 mg). Adherence to treatment is evaluated by a patient's diary and administration log by the psychiatrist. After 16 weeks of treatment, a research assessment will take place and further treatment is conducted following clinical guidelines.

Running therapy

Therapy consists of three 45-minute outdoor running sessions per week, in line with the public health recommendations by CDC/American College of Sports Medicine [84] and its earlier successful effects on depression and anxiety [74, 85]. Patients will be gradually assigned individual training ranges equivalent to 70-85% of their heart rate reserve, calculated from the heart rate achieved during a cycle ergometer test with the formula of Karvonen [86]. This intensity level was confirmed to be effective in decreasing depressive symptoms [87]. During the screening phase and during baseline assessment, so before formal inclusion to the study, potential physical and/or somatic problems and use of medication are administrated. When serious somatic conditions are signalled, the person's own physician will be contacted and consulted in order to discuss potential study participation. Furthermore, at the beginning of the running intervention, the running therapist discusses experience of exercise in the past, and will provide information about food, moisture balance, fatigue, injuries, sleep and recovery. The running therapy intervention was conducted at a medical institution (GGZ inGeest) where there is always a physician approachable. Running sessions will be organized and supervised by qualified staff, starting with a 10-minute warming-up exercise period followed by 30 minutes of jogging at an intensity that maintains heart rate within the assigned training range (starting in the first 4 weeks at 50-70% of heart rate reserve and in the subsequent 12 weeks at 70-85% of heart rate reserve), finishing with 5 minutes of cooling-down exercises. During the running sessions, all subjects wear a heart rate monitor. Heart rate will be confirmed three times per session to ensure that patients are exercising within the prescribed exercise training ranges. Data of the heart rate monitor will be uploaded after sessions and used to encourage study compliance. Patients are stimulated to participate in all three organized group sessions, but if strongly preferred, home-based individual running is allowed once per week. The trainer monitors training attendance. The size of the running group is on average 5 or 6 patients. Both interventions were conducted using evidence-based

clinical guidelines (https://www.nhg.org/sites/default/files/content/nhg_org/ uploads/ multidisciplinaire_richtlijn_depressie_3e_revisie_2013.pdf). Adverse events in both treatment programs will be signalled and reported the medical ethical committee. After 16 weeks of treatment, a research assessment will take place and further treatment is conducted following clinical insights by the responsible clinician.

Outcomes

Primary outcomes

The primary outcome of this trial is the change in biological aging, measured through TL and telomerase activity before the start and at the end of the intervention. TL has been shown to be correlated to functioning of multiple physiological stress systems such as the immune-inflammatory system, the hypothalamus-pituitary-adrenal (HPA)-axis and the autonomic nervous system (ANS) [33, 34] and therefore picks up potential improvement in various underlying mechanisms. In addition, TL has been shown to be predictive of various somatic health outcomes including mortality. TL has earlier been used in studies examining the effects of lifestyle interventions [72, 87, 88] and has shown sensitive to change, even at rather short term, interventions were linked to less shortening of TL. In addition to explore the underlying telomere system dynamics, we also will measure telomerase activity, as was done in Wolkowitz et al. [23]. TL will be measured from purified DNA samples from peripheral blood mononuclear cells that were stored frozen at -80 °C using a quantitative polymerase chain reaction (qPCR)-based assay. Telomerase enzymatic activity will be measured by the Telomerase Repeat Amplification Protocol (TRAP149) using the commercial TRAPeze kit (Chemicon, Upstate/CHEMICON, Temecula, CA, USA) [23]. Less shortening of TL after treatment will be seen as reverse of biological aging.

Secondary outcomes

Biological and general health indicators: Biomarkers of physiological health will be gathered through fasting blood samples, 24-h urine, and six saliva samples were taken at one day covering morning awakening response (at awakening and at 30, 45 and 60 min later), afternoon (at 6 pm) and evening levels (at 10 pm) to e.g. examine inflammatory markers, cortisol levels, metabolic syndrome abnormalities, DNA and oxidative stress. Activity of the autonomic nervous system will be measured using the ambulatory monitoring system (VU-ams) of which reliability and recording methodology have been described previously [90]. Furthermore, blood pressure,

fitness (using bicycle ergometer with the Astrand method [91]), hand grip strength (by Jamar hand grip meter) [92] and lung function (using Mini Wright peak flow meter) [93] will be tested. The chronic graded pain scale [94] will be taken to evaluate pain, somatization will be assessed with the short somatization scale [95] and disability severity will be gathered using the WHODAS II [96].

Depressive and anxiety disorders: The presence of depressive disorders (Major Depressive Disorder) and anxiety disorders (social phobia, generalized anxiety disorder, panic disorder and agoraphobia) will be established using the CIDI. The CIDI is a valid and reliable instrument to assess depressive and anxiety disorders [80] and will be administered by specially trained research staff. The type and number of depressive and anxiety disorders will be compared across the intervention groups and, if necessary, these clinical characteristics will be considered as covariates in the main analyses. Fluctuation of depression and anxiety during follow-up will be examined using the Lifechart method [97]. Severity of depression is measured using the 30-item Inventory of Depressive Symptomatology (IDS-SR30) [98]. Severity of anxiety is measured with the 21-item Beck Anxiety Inventory (BAI) [99]. For both scales higher scores mean higher symptom severity. Phobia symptoms will be measured with the Fear Questionnaire [100]. Sleep duration and quality will be examined with the Insomnia Rating Scale [101]. Psychotropic medication use was assessed during the interview at baseline, 16 and 52 weeks by inspection of the participant's medication containers. It contained lifetime history of use as well as use during the study and was classified using the World Health Organization Anatomic Therapeutic Chemical (ATC) classification (World Health Organization Centre for Drug Statistics Methodology, 2010).

Descriptive variables, potential confounding covariates and potential mediating variables: Lifestyle indicators, (change in) health care status and utilization, personality and cognitive vulnerability, and personal history are also considered as mediating variables. The SQUASH questionnaire [102] will be taken to examine daily-life physical activities. Questions of smoking and drug use will be asked during the interview and the Audit questionnaire [103] will be used to measure regular alcohol intake. A chronic disease inventory and the Perceived Need for Care Questionnaire will be used to assess (changes in) health and health care use [104]. Loss of productivity at work and health care utilization will be gathered with the TIC-P [105]. Personality and cognitive vulnerability traits will be measured using the NEO-FFI questionnaire [106], personal mastery questionnaire [107], the Leids-R questionnaire [108], and the Anxiety Sensitivity Index (ASI) [109]. The Implicit association test (IAT) [110] will be used as experimental cognitive emotional task and the Digit Span (WAIS) [111] as

an experimental memory task to assess working memory. Personal history contains assessment of important negative life events with the Brugha questionnaire [112], childhood trauma with the childhood trauma questionnaire [113], and family history of psychiatric disorders will be gathered by specific questions.

Neuroimaging assessment: In a subsample of the patients and in the healthy controls a neuroimaging assessment will be taken using the 3T Philips Intera MR system. The 15-words test, a Dutch version of the Rey's auditory verbal learning test [114] will be performed outside the scanner to assess verbal episodic memory.

Anatomical T1-weighted and diffusion tensor imaging (DTI) scans will be obtained to assess grey and white matter structure. An emotional face matching paradigm [115] and N-back paradigm [116] will be employed to examine task-related brain activity. Finally, brain network connectivity will be examined during rest by acquiring resting state fMRI images.

Sample size

Published running therapy and antidepressant intervention studies in non-psychiatric groups have yielded effect sizes for changes in biological aging ranging from 0.5 [74] to 1.2 [83]. When using the minimum effect size found (0.5), 80% power and $p = .05$, we need 63 subjects per group. Considering a dropout of 20%, $N = 76$ patients per group are needed to illustrate significant antidepressant and running therapy effects on biological aging in a patient group. That is why we strive for 80 patients per group, and 160 total.

As described by Thirion, functional MRI analyses require a minimum of 25 subjects per group for adequate statistical power [117]. In addition, we aimed to include 60 healthy controls to allow additional comparisons in outcomes between controls and patients.

Organisation, and quality insurance and data management

Compliance with antidepressant medication or running therapy is assessed using patient's and therapeutic logs. Patients who withdraw from the intervention will be asked reason(s) for drop out and they will be motivated to continue the measurements with the purpose to minimize loss of follow-up data and to make the intention to treat analysis and per-protocol analysis possible.

Research data will be collected by a coded participant number. Interviews will be conducted by computer and questionnaires by paper and will be entered into the system by the research assistant. An administrative database will be used to ensure timely assessments. The data manager will make back-ups for the monitoring of overall progress and data quality.

Statistical analysis plan

Missing data will be inspected and handled via full information maximum likelihood. Mixed model regression analyses will be conducted to estimate the effect size of both interventions on biological aging and psychiatric status, metabolic stress and neurobiological abnormalities. Per protocol analyses within intervention groups will be conducted to evaluate whether change of biological aging and metabolic stress is a function of protocol adherence. The two intervention groups will be compared using mixed models or generalized estimating equations (GEE) to assess the longitudinal change of biological aging, physiological and metabolic stress and psychiatric symptoms. These models will also compare physiological and clinical effects of those who are willing and not willing to be randomised to check the impact of a patients' preferred or allocated intervention. Furthermore, pre- and posttreatment outcomes to physiological stress parameters will be compared to the no-disease-no-treatment control group using regression analyses.

Trial status

The MOTAR study was approved by the Medical Ethics Committee of the VU University Medical Center Amsterdam and registered with the Netherlands Trial Register under NTR3460. Recruitment commenced in September 2012 and is ongoing.

3. DISCUSSION

A wide range of treatment programs for depressive and anxiety disorders are available but it remains largely unknown whether the impact of these programs on biological aging, metabolic stress and neurobiological abnormalities are comparable. Treatment with antidepressant medication or running therapy have both shown to be effective in depression and anxiety, but a well-designed comparative study of these treatment strategies and their impact on physiological and neurobiological processes is currently lacking. As the number and type of clinician contacts between groups are not similar,

this could be underlying clinical improvement. However, the interventions in this trial were developed in line with current guideline standards and therefore are as much as possible reflective of regular clinical care treatments.

This intervention study is designed to examine and compare the impact of antidepressant medication and running therapy on changes of both mental and physiological health, including biological aging, metabolic stress and neurobiological function and whether these pre- and posttreatment outcomes are comparable with persons without a psychiatric status. It is expected that this study provides more detailed information about underlying biological mechanisms of depression and anxiety treatment effects. Having insight in the favourable physiological stress effects of these treatment regimens could probably also be helpful in increasing the effectiveness of personalised medicine.

Abbreviations

ACC; Anterior cingulate cortex, Agora; Agoraphobia, ASI; Anxiety ensitivity index; BAI, Beck's anxiety index; BP, blood pressure; CDC, center for disease control; CIDI, composite international diagnostic interview; CT, computer task; DSM-IV, diagnostic and statistical manual of mental disorders fourth edition; DTI, diffusion tensor imaging; GAD, generalised anxiety disorder; HPA, hypothalamus-pituitary adrenal; IAT, implicit association task; IDS-SR, inventory of depressive symptomatology; LTL, leukocyte telomere length; MDD, major depressive disorder; ME, medical examination; MOTAR, mood treatment with antidepressants or running; MRI, magnetic resonance imaging, NEO-FFI, neuroticism- extraversion-openness five-factor inventory; NHG, nederlands huisartsen genootschap; PA, panic disorder; PFC, prefrontal cortex; qPCR, quantitative polymerase chain reaction; SocPhob, social phobia; SR, self-report; SSRI, selective serotonin re-uptake inhibiters; SPSS, statistical package for social sciences; SQUASH, short questionnaire to assess health enhancing physical activity; TIC-P, treatment inventory of costs in patients; TL, telomere length; TRAP, telomerase repeat amplification protocol; VU-ams, VU university ambulatory monitoring system; WAIS, Wechsler adult intelligence scale; WHODAS, world health organisation disability assessment schedule.

Author's contributions

BP designed and got funding for the study; all authors helped conducting the study; BL coordinated the recruitment of patients and the data collection. BL and JV drafted the first manuscript; all other authors commented on the manuscript; all authors read and approved the last version of the manuscript.

Funding

The MOTAR study was funded by NWO VICI grant number 91811602 of B.W.J.H. Penninx. NWO had no role in the design of the study, the collection, analysis and interpretation of the data, or in the preparation, review, or approval of the manuscript.

Availability of data and materials

MOTAR-data can be requested through the submission of an analysis plan. Instructions can be found on the website www.motar.nl

Ethics approval and consent to participate

Ethical and professional guidelines will be followed at all times, in line with Good Clinical Practice guidelines. Institutional review board approval has been obtained from the Medical Ethics Committee of VU Medical Centre Amsterdam, the Netherlands (May 23, 2012, VUmc METC registration number: 2012-064). All participants gave written informed consent prior to baseline assessment. The MOTAR study was registered in the Trial register of The Netherlands: Trialregister.nl, Number of identification: NTR3460.

Consent for publication

Not applicable.

Competing interests

BP has received (non-related) funding from Jansen Research and Boehringer Ingelheim. All other authors declare that they have no conflicts of interest.

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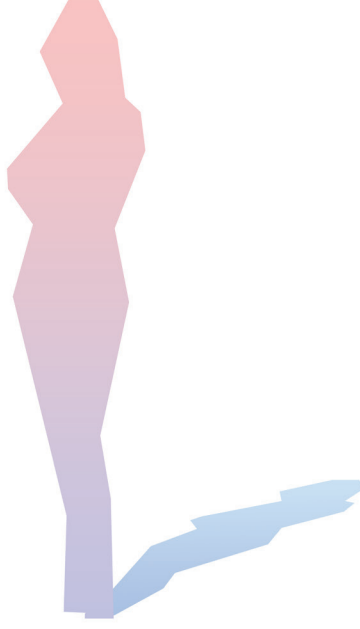

CHAPTER 8

Summary and general discussion

1. SUMMARY OF THE MAIN FINDINGS

The main aim of this dissertation was to examine the relationship between depressive and anxiety disorders and objective physical function. Physical function is a broad concept, that ranges from objective measures of physical functions through measures of self-reported disability in life. In this dissertation, I focused primarily on two general indicators of objective physical functions that have shown valid to measure and predictive of general poor health status and subsequent disease outcomes: hand grip strength (measured with a Jamar hand held dynamometer) and lung function (measured with spirometry). The first aim was to investigate cross-sectional associations between depressive and anxiety disorders and objective physical function measures of hand grip strength and lung function (Chapter 3) with an extension to hemoglobin level (Chapter 2). The second aim was to examine the link between depressive and anxiety disorders and objective physical function over time (Chapter 4 and 5). The final, and third, aim was to provide insight into underlying mechanisms of the association between depression, anxiety and objective physical function (Chapter 6). To conclude with a clinical focus, the design of the Mood Treatment with Antidepressants or Running therapy (MOTAR) study is described in Chapter 7.

In *Chapter 2*, we explored the cross-sectional association between depressive and anxiety disorders and hemoglobin level. Low levels of hemoglobin, also called anemia, can be seen as a general biological indicator of poorer health status [1]. Two thousand nine hundred and twenty persons from the Netherlands Study of Depression and Anxiety were included in this study. Higher hemoglobin levels were found in those with current depressive and/or anxiety disorders compared to healthy controls after adjustment for socio-demographics variables. In addition, both higher and lower hemoglobin levels were found in persons with higher depression and anxiety severity. However, after additional adjustment for disease indicators and lifestyle factors, associations were no longer statistically significant. We concluded that an independent association between depressive and/or anxiety disorders and increased severity scores with hemoglobin levels or anemia status could not consistently be confirmed in this large-scale study.

Chapter 3 investigated the cross-sectional association between depressive and anxiety disorders and objective physical function as indicated by lung function and hand grip strength. Persons with current depressive and/ or anxiety disorders (N = 1629) and healthy controls without lifetime diagnoses (N = 629) were included (N = 2258). Women with depressive or anxiety disorders, especially those with a late age of onset (≥ 40 years), had significantly poorer physical function – both lower grip strength and lung

function – compared to healthy controls. Focusing at the patients with a depressive and/or anxiety disorder, poorer lung function was more often present among the women using antidepressants (vs no antidepressant use), those with higher symptom severity (vs lower symptom severity), and those with depression compared to anxiety disorder. In contrast, in men, depressive or anxiety disorder was associated with better lung function than controls, but was not associated with hand grip strength.

Furthermore, in *Chapter 4*, we assessed whether poor physical function at baseline was a predictor for the persistence of depressive and anxiety disorders two years later. The study sample consisted of 1206 persons with current depressive and anxiety disorders at baseline. Lower hand grip strength predicted the persistence of depressive and/or anxiety disorders at 2-year follow-up. Poorer lung function was associated with the persistence of depressive disorders but not with persistence of anxiety disorders. This was not differential in depressed men and women.

Chapter 5 describes the six-year trajectory of physical function in depressed and anxious patients. During six years, hand grip strength and lung function were assessed in 2480 participants. Although there were no differences in the rate of decline over time, women with current depressive and/or anxiety disorders at baseline had poorer hand grip strength and poorer lung function compared to healthy women during the entire 6-year follow-up. Associations with depression and anxiety severity measures confirmed dose-response relationships with objective physical function. In men, stronger 6-year decline of lung function was found in those with current disorders and even in those with remitted disorders compared to healthy men. So, depression and anxiety were associated with consistently poorer hand grip strength and lung function in women and a stronger decline of lung function in men over 6 years of time, implicating their long-lasting impact on physical functioning.

In *Chapter 6*, we determined whether physiological stress systems (immune-inflammatory system, HPA-axis, and the autonomic nervous system) were associated with objective physical function, and partly explain the earlier described associations between depression/anxiety and poorer objective physical functioning. Baseline data of 2860 persons of the NESDA study was used. The results show that poorer objective physical function was associated with higher levels of inflammation and HPA-axis markers. However, the observed association between poorer physical function and depressive and/or anxiety disorders in women (Chapter 3) hardly changed and remained significant after adjustment for physiological stress markers, which may suggest that other pathways than those studied here are involved.

In *Chapter 7* the design of the Mood Treatment with Antidepressants or Running therapy study (MOTAR) is described. MOTAR's goal is to examine and compare the impact of a medication versus a lifestyle intervention on mental health, but also on biological processes and somatic and physical function. It is an intervention study for patients with depressive or anxiety disorders in which they receive antidepressants (Selective Serotoninergic Reuptake Inhibitors, SSRIs) or running therapy (3 times a week) during 16 weeks. Before and after treatment, research assessments were taken including a psychiatric diagnostic interview, blood samples (including e.g. physiological stress markers), hemoglobin level, hand grip strength, lung function and various other variables. *N* = 160 patients are included in the study and 50 patients are included in the MRI sub study. Furthermore, 60 healthy controls are included to compare primary and secondary outcomes at baseline.

2. DISCUSSION OF MAIN FINDINGS

In this section, the main findings per aim are discussed and compared to other literature. Table 8.1 gives an overview of the main integrated findings.

Table 8.1. Summary of the findings: link between depressive and anxiety disorders and objective physical function

	Link with depressive and anxiety disorders (baseline)		Link with depressive and anxiety disorders at various waves over time		Predictor of persistence of depressive and anxiety disorders		Link with physiological stress systems (baseline)	
	♂	♀	♂	♀	♂	♀	♂	♀
Hemoglobin level	x	x	N.E.	N.E.	N.E.	N.E.	N.E.	N.E.
Hand grip strength	x	-	x	-	-	-	-*	-*
Lung function	+	-	-	-	-	-	-*	-*

Positive (+) or negative (-) significant association between psychiatric status and hand grip strength or lung function. x = no significant association. N.E.= not examined.
*= lower hand grip strength was associated with inflammation and lower lung function was associated with inflammation and HPA-axis. Physiological stress markers did not impact on the association between physical function and depressive and anxiety disorders.

2.1 Depressive and anxiety disorders and poorer objective physical function

Hemoglobin level

In Chapter 2, we showed that the association between depression, anxiety and low hemoglobin level disappeared after adjustment for health and lifestyle indicators. Since the publication of this study, the literature provides more studies on this topic. In 2020, a meta-analysis of observational studies examining the association between anemia and adult depression by Lee and colleagues [2] was published. This is the first large meta-analysis performed on this topic and included 14 studies examining a total of 10764 participants, including our study. The most important conclusion of this meta-analysis was that anemia was associated with a moderately increased risk of depression in adults (OR = 1.43 (95% CI = 1.23-1.65)). This is higher than the non-significant OR found in our study (OR = 1.02 (95% CI = 0.69-1.51)). All included papers in the meta-analysis were adjusted for health and lifestyle variables, so a lack of adjustment could not explain the contrast of findings in this meta-analysis and our study. It is not easy to completely explain the difference in our findings with that of the meta-analysis, as we have depressed persons according to the stricter DSM-criteria whereas most other studies only focus on self-report depression symptoms. The difference in findings may be explained by the higher mean age (60 years) of the sample in the meta-analysis compared to our study (mean age of 42 years) since higher age is associated with higher prevalence of anemia. Therefore, maybe at older age, there is more power to examine the impact of anemia, and also at higher age hemoglobin levels may be a stronger health indicator. The authors of this meta-analyses suggest that having chronic somatic diseases or having nutritional problems are vulnerability factors for both anemia and depression, which could explain the found association between depression and low hemoglobin level. That somatic diseases play an important role in the association between low hemoglobin level and depression and anxiety was also observed in our study; the association between low hemoglobin level and depression/anxiety disappeared after adjustment for health and lifestyle indicators, including somatic diseases.

Our study was the first examining hemoglobin levels in anxious persons, finding higher anxiety severity in those with anemia compared to those with higher hemoglobin levels. However, these results were not significant. Recently, a large Taiwanese study has been published examining the psychiatric comorbidity, including anxiety disorders as well, of an iron-deficiency anemia (IDA) group compared to a non-IDA group [3].

The sample consisted of almost 60000 cases without a psychiatric history with a mean age of 49 years. The IDA group had a subsequent increased risk of psychiatric disorders, including depression and anxiety disorders, compared to the non-IDA group after adjustment of sociodemographic and somatic comorbidity during 13 years of follow-up. The sample size could play a role in the different results of our study and this large Taiwanese study, as well as their longitudinal design.

Earlier research was mostly focused on low hemoglobin level in relation to depression and anxiety. In our research, however, we also showed an association between high hemoglobin level and depressive and anxiety disorders. After adjustment for lifestyle and health factors, this relationship became non-significant. Especially smoking seems to be an important factor explaining this association. It has been shown that active smokers have higher hemoglobin levels and that these higher levels are reversible by quitting smoking in persons without somatic diseases [4]. Smoking leads to the production of more red blood cells due to the disastrous effects of carbon monoxide of cigarettes, which hinder oxygen uptake. The increased production of red blood cells compensates these effects and leads to increased hemoglobin level. So, the higher hemoglobin levels in depressed or anxious persons could be largely explained by their higher smoking patterns as compared to healthy controls.

In all, since our conducted study on hemoglobin and depressive and anxiety disorders in 2014, there have been several new initiatives to examine the extent to which low (or high) hemoglobin is linked to depressive and anxiety disorders. In contrast to our results, there are some indications for more anemia among those with depressive or anxiety disorders, which seems independent of lifestyle and sociodemographic covariates. Understanding this association requires further research.

Hand grip strength and lung function

Poorer objective physical function, both hand grip strength and lung function, was found in depressed women compared to healthy women (Chapter 3), which is in line with findings from other studies [5–9]. Following this, depressed and anxious women are more likely to be physically disabled and have higher mortality rates compared to healthy women [10, 11]. These findings of poorer objective physical function in depressed and anxious persons were confirmed in Chapter 4 and 5 describing longitudinal results (see Table 8.1). In Chapter 4 we showed that both hand grip strength and lung function predicted the persistence of depressive and/or anxiety disorders after two years of follow-up. In Chapter 5 we showed that during six years

of follow-up, physical function remained poorer over time in women with depressive and anxiety disorders compared to healthy control women. However, physical function did not decrease faster over time in current and remitted depressive and anxious women than healthy women. These findings have been found before in the literature on older persons, but our research adds to this knowledge by showing that poorer physical function is already found in younger, middle-aged women. So, impairment of physical function seems to start early in life when persons have affective disorders.

The association between objective physical function and depressive and anxiety disorders in men shows a different pattern than that found in women. Our cross-sectional results show higher lung function in depressed and anxious men compared to healthy men (Chapter 3) while hand grip strength was comparable for both groups. Our longitudinal results show that both hand grip strength and lung function predicted the persistence of depressive and/or anxiety disorders after two years of follow-up in men (Chapter 4) and show that men with depressive and anxiety disorders had higher decline of lung function over time during six years of follow-up compared to healthy men while again no differences were found in hand grip strength (Chapter 5). Consequently, the findings of hand grip strength and lung function are not as consistent in men and were therefore weaker and different compared to the findings in women.

Thus, the association between depression, anxiety and poorer physical function was most consistently present in women, but inconsistent in men. A partial plausible explanation could be a sex-differential pathophysiology of depression and anxiety, potentially partly because of hormonal differences across sex [12]. Indeed, sex hormone differences are quite large, and testosterone is known to have a promoting impact on physical function, such as through direct promotion of muscle growth and strength [13]. As confirmed by our findings, men have higher muscle strength and lung function as compared to women. Maybe at a relative young adult age, the stronger physical function in men prevents a potential impact of mental health conditions to be visible on more objective assessments of physical function.

Although sex-differential hormonal influences may provide an explanation, questions remain about the observed sex differences. Is there truly no relationship between hand grip strength and psychiatric status in men? Are the performance measurements that we used not accurately enough to show differences? Did we perhaps face a ceiling effect in men? Or are there simply no differences in men in objective physical function between those men with and without depressive or anxiety disorders? The literature cannot provide consistent information about this point, as there are hardly

any studies that examined these physical impairments in psychiatric populations. At least it is important to indicate that our physical performance and depression/anxiety associations did not show evidence for age moderation in men. This indicates that even in the oldest men in our cohort, where ceiling effects of physical assessments are less likely to exist, we could not confirm associations with depressive and/or anxiety disorders either.

As we are not aware of other longitudinal research among psychiatric adult patients that examined the longitudinal decline of physical performance, it is difficult to compare our findings to other studies. However, if we take a step to the older population, contrasting longitudinal results are found in the associations between depression, anxiety and physical function. Both stronger as well as comparable decline of objectively measured physical function was found in depressed compared to non-depressed older persons during follow-up [14–16]. Further research is needed to confirm the change of physical function over time in depressed and anxious adult patients.

The link between lung function and hand grip strength is strong (Pearson's correlation coefficient = 0.59, $p < .001$). A large amount of oxygen provides the muscles to deliver force and thus increased lung capacity facilitates performing activities. Poor lung function could have impact on muscle strength as well. On the other hand, poor muscle strength could limit good lung function as well. Overall poor muscle strength may indicate un underlying inadequate strength to help spreading the lungs to get large lung volume which is needed during the performance of activities [17]. Also, both assessments – lung function and hand grip strength – are general indicators of overall general health status. So even if they are not directly impacting on each other, they could be correlated as they both reflect a similar underlying general health and physical function status. In line with this, a recent study showed that lung function and hand grip strength do not share genetic background but may have shared environmental factors such as living conditions [18]. More specifically, the heritability of hand grip strength and lung function are approximately 52% and 55% [18–20] which means that the other 50% is determined by environmental factors which could be partly comparable for hand grip strength and lung function.

Conclusion 1: Hemoglobin levels and presence of anemia were cross-sectionally not associated with depressive and anxiety disorders. However, objective physical function as measured with hand grip strength or lung function, was consistently poorer in depressed and anxious middle-aged women as compared to non-depressed/anxious women, both at baseline as well as during six years of follow-up. In men, associations were less consistent: depressive or anxiety disorders were inconsistently linked to higher baseline and stronger decline in lung function over time, and not linked to hand grip strength. Finally, poorer physical function predicted a more chronic subsequent depression and anxiety disorders course in female and male patients.

2.2 Underlying mechanisms of the relation between depressive and anxiety disorders and objective physical function

What mechanisms could explain the findings of poorer physical function in depressed and anxious patients? Physical performance requires, amongst others, a cooperation of muscles, nerves and skeletal structures [21]. Dysfunction of one of these three systems can lead to limitations in physical performance. Muscles are important for physical performance and for having optimal health during lifetime. Muscles are involved in and affected by different metabolic pathways, such as the insulin and glucose exchange and fatty acids [21]. Metabolic disturbances in muscles could therefore be involved in the presence of metabolic syndrome and obesity which are found to be associated with depression and anxiety disorders as well [22–24]. An increase of body fat could lead to higher inflammation levels with a secretion of cytokines. Elevated cytokines may lower skeletal muscle mass and decrease physical performance as they interact with hormones such as insulin, testosterone and BDNF [25, 26]. The muscle system is controlled by the nervous system. For instance, planning and control of physical movements lays in the pre-frontal cortex which is also involved in emotional facets, e.g. depression and anxiety. Last but not least, skeletal structures form the basic fundament for performances. Any change in skeletal structure will impair physical performances and could be caused by the presence of osteoporosis in the elderly, birth defect or an accident. The different systems are influenced by lifestyle, biological and psychosocial factors as already mentioned in the introduction of this dissertation [21]. Multiple facets mentioned above are linked to depression and anxiety as well which could contribute to the presence of the link between poorer physical function and depression and anxiety.

This dissertation shows evidence for poorer physical function in depressed and anxious patients, especially in women. We adjusted for a priori chosen important factors which may have impact on the relationship between depression, anxiety and objective physical function. These factors included health and lifestyle factors and previous research showed those factors to be associated with depression/ anxiety and physical function. However, adjustment for health and lifestyle factors did not impact the relationship between objective physical function and depressive and anxiety disorders as was shown in Chapter 3, 4 and 5. These health and lifestyle factors only impacted on the association between hemoglobin levels and depressive and anxiety disorders. This association disappeared after adjustment for health and lifestyle factors.

Our results demonstrate that physiological stress is associated to objective physical function (Chapter 6). By jointly analysing markers of three physiological stress systems (immune-inflammatory system, HPA-axis, and autonomic nervous system), we can evaluate the joint effects of the three systems. This is welcome because of the inter-connections between the three stress systems. A focus on all three stress systems gives a more complete picture of the relationship between the physiological stress markers and its link with objective physical function. Despite the relationship between physiological stress and objective physical function, physiological stress indicators covering the HPA-axis, inflammation and autonomic nervous system functioning were not found to be an important underlying mechanism of the relationship between objective physical function and depression/anxiety.

Conclusion 2: Physiological markers indicating higher activity of stress systems (immune system and HPA-axis, but not the autonomic nervous system) were associated with poorer objective physical function. However, these stress systems did not play a further explanatory role in the association between objective physical function and depressive and anxiety disorders.

3. METHODOLOGICAL CONSIDERATIONS

Design

The NESDA study is an ongoing longitudinal prospective cohort study with a large sample size. We used six years of data which provided information about the course of mental and physical function. The wide range of assessments, including mental

health, physical health, sociodemographic, environmental and biological factors, gives researchers the opportunity to examine the predictors of the long-term course and consequences of depression and anxiety disorders.

The presence of depressive and/or anxiety disorders is thoroughly diagnosed using the CIDI, a diagnostic instrument based on the DSM-IV, and depressive and anxious symptoms are measured with severity scales during all assessments. Using the NESDA data, diagnostic information about almost 3000 persons could be used for research into physical function and disability.

In longitudinal studies, attrition is often present. Although the attrition in NESDA is relatively low (24.3% after six years), it was more present in those with a – more severe – psychiatric disorder, which may have biased the results, most likely through underestimation [27]. Consequently, the associations between depressive and/or anxiety disorders and physical function are probably stronger due to higher attrition rates of those with a psychiatric disorder.

The NESDA sample consisted of persons with a large variation of depressive and/or anxiety symptoms since the recruitment took place in the community, at general practitioners and at mental health care facilities, added with respondents without a lifetime psychiatric disorder. This gave us the opportunity to examine physical function in all stages of severity of depression and anxiety. However, 95% of the included persons had a Caucasian ancestry [27] which impaired the generalizability of the results.

Assessment of variables of interest

Objective physical function

Hemoglobin level, hand grip strength and lung function were most important variables of interest in this dissertation. These measures were available for the complete NESDA sample at baseline and – for hand grip strength and lung function – also at follow-up assessments. Hemoglobin level is just one example to measure somatic health [1] and is an indicator of general poorer health, underlying specific (lung) problems or vitamin deficiency. In this dissertation, the hemoglobin marker is a bit of an outlier, as it is not directly reflective of physical function. Nevertheless, it is a biological marker that could be relevant in clinical care as it has been linked to mortality and subsequent disability.

Hand grip strength and lung function were used as more general, objective physical function measures in this dissertation. Hand grip strength is the most widely reported

and recommended objective performance-based measurement [8]. It gives a good indication of overall bodily muscle strength and it has an important role in the evaluation of functionality. Lung function, measured with peak expiratory flow, is used to detect changes in the ventilatory performance [28]. Including both instruments in the analyses a broad range of functioning was considered. The measurement of hand grip strength and lung function are both highly reliable and are simple to do [8, 29]. These instruments are informative for older persons since they have shown to predict disability and mortality in older persons [30–33]. However, whether similar associations are also present in younger adults is less clear, as these measures are not often included in young-age studies.

There are other interesting physical performance measures that are used in the literature and provide information about a more dynamic process of physical function, for example the 6-meter walk test or sit-up-and-go test that give a very good indication of physical functioning [34]. These measures are often used in older samples, but may be less suitable for younger samples because of possible ceiling effects [8]. To measure physical performance in a younger sample, the 12-minute Cooper test of physical fitness may be a good measure. However, due to space, time, budget and potentially lack of motivation of the participants, it was not feasible to include this test in the NESDA study. Physical function measures such as hand grip strength and lung function are more feasible to do during a research assessment including a wide range of questionnaires and biological measures. However, our results still showed that there are possible ceiling effects in men for hand grip strength.

In this dissertation, hand grip strength has been measured with the Jamar strength dynamometer. This is a reliable and valid meter and has often been used in research. It represents the strength of the complete body strength. Other measures that gives an indication of bodily strength in an adult sample are pinch strength measurements [35, 36] and leg strength measurement [37]. Pinch strength measurement reaches comparable results of physical function compared to hand grip strength. However, pinch strength has mostly been used in clinical settings and has not shown to be linked to physical disabilities. To conduct leg strength measures, large equipment is needed which is less feasible in large cohort research.

In this dissertation, lung function has been measured with PEF (peak expiratory flow) using the Wright peak flow meter. This is a reliable and valid peak flow meter [29] and has often been used by general practitioners. However, PEF is not as reliable as other spirometry methods are such as FVC (forced vital capacity; volume that is delivered

during an expiration made as forcefully and completely as possible starting from full inspiration) and FEV1 (forced expiratory volume; volume delivered in the first second of an FVC manoeuvre) [38], which are the most important measures of spirometry. Spirometers measuring FEV1 or FVC give more accurate information about the lung capacity and are often used in studies among patients with COPD or asthma. However, in a large psychiatric, and not COPD or asthma, cohort in which lung function is only a small part of the assessment, the Wright peak flow measurement is less-time consuming, not dependent on trained supervisors, easy to perform and less costly [39].

4. CLINICAL IMPLICATIONS

Depressive and anxiety disorders are associated with poorer objective physical function. Following this, patients with depressive or anxiety disorders are more likely to experience both mental and physical disability, with a large impact on the health care system. Since objective physical function measures are indicators of physical disability, we may carefully take a look at the possibility of using physical function measures as informative measures in mental health care. Early detection of physical problems is needed [40] to prevent severe disability problems later on. Hand grip strength and lung function are suitable measures for a screening of physical function. In the older population, hand grip strength is part of a frailty screening together with measures as weight loss and cognition. Further research is needed to explore whether it is helpful to use objective physical function measures in the mental health setting in younger populations with depressive and anxiety disorders as well, with the aim of guiding clinicians in making the choice for a treatment program [41]. However, we have to be careful with too early recommendations, as generally the effect sizes in our studies were not huge and we did observe different associations across gender. Consequently, currently our findings cannot suggest quick implementation of such measures.

In the last years, a large group of depressive and/or anxiety patients has been treated with antidepressants or running therapy within the MOTAR study. The pre- and posttreatment assessments of the MOTAR study will be analysed and published in the upcoming year. We expect that our findings (Chapter 6) of the link between physiological stress and poorer objective function will be replicated in this intervention study. Some studies have indicated a similar impact on depression and anxiety parameters for both interventions, but such studies have so far been mainly conduced in milder cases [42]. We hypothesize that physical function will be influenced positively after 16 weeks of therapy, potentially more in the running therapy intervention than

in medication intervention. So, running therapy may have an additional advantage in restoring physical function better than other standard depression/anxiety treatments. However, this is something that needs to be proven first in empirical studies. Such future interventions studies should not only measure the symptom recovery of depression and anxiety, but also focus on underlying pathophysiology in which we have close attention for physical function. Such studies are still scarce.

5. RECOMMENDATIONS FOR FUTURE RESEARCH

Our research shows that those with depression and/or anxiety have poorer physical function compared to healthy controls, especially in women. However, further examining the course of depressive and/or anxiety disorders and physical function is needed to understand the longitudinal consequences of poorer physical in relation to mental functioning. Increasing knowledge about the link between physical function and psychiatric status could provide insight in the distribution of predictors and consequences.

A possible predictor of deterioration, which was not examined is this dissertation, could be personality traits since they play an important role in the course of depressive and anxiety disorders. Depressive and anxiety disorders often parallels with higher neuroticism, lower extraversion, and maybe also lower agreeableness, conscientiousness and openness to experience [43]. Personality traits, like neuroticism and extraversion, have also been associated with poorer health and more cognitive decline [44, 45]. Whether personality traits were associated with having poorer physical function in a depressed and/or anxious population remained rather unclear.

Physical function decreases with increasing age. However, our research shows that, especially in women, also in a younger sample lower levels of physical function were found in those who are depressed or anxious. However, since these associations were not found in men maybe due to ceiling effects of hand grip strength in men, further research is needed including a wide age range with older and younger persons to confirm poorer physical function in an adult sample with depressive and/or anxiety disorders. Furthermore, further research should also include instruments that measure enough variation between younger and older persons and should focus on potential sex differences. Finally, it remains important to better understand the relevant explanations for the poorer objective physical function seen in persons with depressive/anxiety disorders.

Poorer physical function in middle-aged persons plays a role in the degree of disabilities at later age [46]. The literature confirmed this by showing that elderly persons with a depressive and/or anxiety disorder have a higher risk for disabilities at older age compared to elderly without psychiatric disorders [47]. This indicates that it is clearly important to pay attention to restoration of physical health and function during psychiatric treatments. However, unfortunately, it remains largely unclear whether broader treatments e.g. focused on both mental and physical function could decrease the risk for future disabilities at older age. Future research should focus on the effects of treatment programs that evaluate not just mental improvement but also physical function restoration as both may be equally important in preventing disability at later age.

6. CONCLUSION: IS THERE AN INTERPLAY BETWEEN OBJECTIVE PHYSICAL FUNCTION AND DEPRESSIVE AND ANXIETY DISORDERS?

This dissertation examined associations between objective physical function and depressive and anxiety disorders. Overall, we provided evidence of poorer objective physical function (handgrip strength and lung function) in those with depressive and anxiety disorders compared to those who are healthy, both cross-sectionally and longitudinally, and especially in women. Furthermore, we showed that higher physiological stress levels are associated with poorer objective physical function but do not explain the association between objective physical function and depressive and anxiety disorders. As physical and mental health are related, interventions to improve both physical and mental health should be paired in the future in both research and in mental health care.

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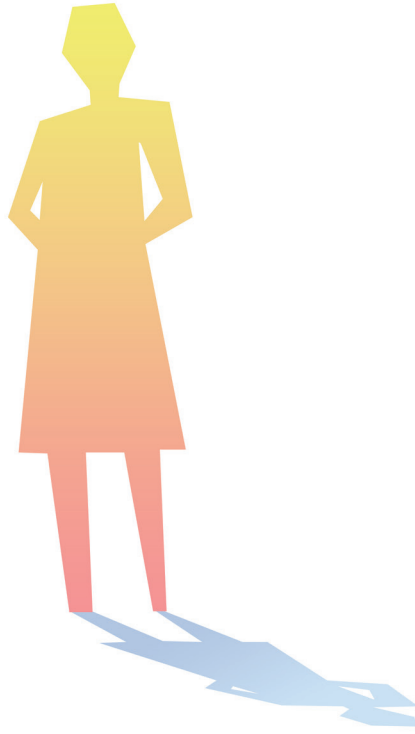

CHAPTER 9

Samenvatting (Summary in Dutch)

Depressieve en angststoornissen

Depressieve en angststoornissen zijn veel voorkomende psychiatrische aandoeningen. Ongeveer 20% van de bevolking krijgt ooit in zijn leven te maken met een depressie of angststoornis. Deze stoornissen komen vaak samen voor, komen bij vrouwen bijna twee keer zo vaak voor als bij mannen en hebben een grote impact op het dagelijks leven. De stoornissen worden geclassificeerd en gediagnosticeerd op basis van de criteria van de Diagnostic and Statistical Manual of Mental Disorders (DSM; vierde editie in dit proefschrift). De meest voorkomende depressieve en angststoornissen zijn depressie, dysthymie, sociale fobie, gegeneraliseerde angststoornis en paniekstoornis met en zonder agorafobie.

Depressie wordt gekenmerkt door een sombere stemming en/of verlies van interesse in bijna alle activiteiten gedurende het grootste deel van de dag, bijna elke dag en voor tenminste twee achtereenvolgende weken. Daarnaast is er vaak sprake van verlies of toename in gewicht en/of eetlust, slaapproblemen, psychomotorische onrust, concentratieproblemen, vermoeidheid, schuldgevoelens of waardeloos voelen en/of gedachten aan de dood. Dysthymie is een mildere vorm van depressie maar met een langere duur. Personen met een dysthymie hebben een aanhoudende sombere stemming voor tenminste twee jaar. De sociale fobie gaat gepaard met een aanhoudende angst voor situaties waarin veel aandacht op de desbetreffende persoon is gericht (bijvoorbeeld bij het geven van een presentatie). Iets doen in het bijzijn van anderen brengt angst met zich mee omdat men meent beschaamd of vernederd te worden wat weer kan leiden tot vermijding van deze situaties. De gegeneraliseerde angststoornis is een stoornis waarbij mensen zich, gedurende een periode van tenminste zes maanden, irreëel zorgen maken over alledaagse dingen. Hierbij treden meestal ook somatische klachten op zoals onrust, vermoeidheid, concentratieproblemen en verhoogde spierspanning. De paniekstoornis kenmerkt zich door plotseling onverwacht optredende paniekaanvallen die gepaard gaan met extreme angst en vermijding tot gevolg kunnen hebben (agorafobie). Hierop volgen perioden van aanhoudende angst voor het opnieuw krijgen van een aanval, de angst om gek te worden en van een verandering in het gedrag.

De Wereldgezondheidsorganisatie (WHO) geeft aan dat depressieve en angststoornissen belangrijke oorzaken zijn van beperkingen wereldwijd en dat depressie en angst een grote bijdrage leveren aan de algehele ziektelast. Depressieve en angststoornissen gaan samen met een toename van beperkingen, somatische klachten, mortaliteit, problemen op het werk en gebruik van de gezondheidszorg. Een onderliggende oorzaak hiervan

kan een verminderd fysiek functioneren zijn. De samenhang tussen een verminderd fysiek functioneren en het hebben van een depressieve en/of angststoornis is echter nog onvoldoende onderzocht in een volwassen groep in de leeftijdscategorie 18 tot 65 jaar. Het vergroten van deze kennis kan helpen bij de preventie en behandeling van mensen met depressieve en angststoornissen.

Fysiek functioneren

Het niveau van functioneringsproblemen van mensen heeft de WHO vastgelegd in het ICF (International Classification of Function, Disability and Health). Er zijn drie verschillende niveaus van het functioneren in het dagelijkse leven vastgesteld: het functioneren van het lichaam (hoe goed functioneren bijvoorbeeld de gewrichten, het hart en de hersenen), de activiteiten die een persoon zelf kan uitvoeren en de deelname van iemand in de maatschappij. Een verstoring op één van deze drie kan leiden tot een beperking in het dagelijkse leven. Hierbij speelt de interactie van gezondheid, persoonlijke en omgevingsfactoren een belangrijke rol. Dit proefschrift richt zich op één van de onderdelen van de beperkingen, namelijk het functioneren van het lichaam (fysiek functioneren).

Het fysiek functioneren wordt gedefinieerd als de mogelijkheid om te kunnen bewegen om basale activiteiten uit te voeren die de basis vormen voor onafhankelijkheid waardoor complexe activiteiten kunnen worden uitgevoerd. Een voorwaarde hiervoor is het hebben van een optimale mobiliteit zoals spierkracht en uithoudingsvermogen. Het fysiek functioneren neemt toe tot ongeveer de leeftijd van 30 à 40 jaar waarna het fysiek functioneren afneemt. Lichamelijke activiteit heeft een positief effect op het fysiek functioneren terwijl een leefstijl met een gebrek aan beweging en chronische ziekten een negatief effect hebben.

Het fysiek functioneren is al eerder onderzocht in relatie tot depressie en angst. Echter werd hierbij voorheen gebruik gemaakt van zelf-gerapporteerde vragenlijsten waarbij het invullen beïnvloed kan worden door de gevoelens van de deelnemer. Door objectieve maten voor het meten van het fysiek functioneren te gebruiken, worden deze gevoelens zo goed als uitgesloten en kan het werkelijk fysiek functioneren getoetst worden. Veel objectieve maten zijn ontwikkeld voor gebruik bij ouderen (60+) maar zijn mogelijk niet sensitief genoeg voor een groep van middelbare leeftijd. Twee objectieve maten die wel goed lijken aan te sluiten bij een volwassen populatie zijn de handspierkrachtmeting en longfunctietest. Deze meetinstrumenten zijn betrouwbaar en valide gebleken in volwassen populaties en zijn voorspellers voor

beperkingen in het dagelijkse leven en mortaliteit. De *handspierkrachtmeting* is één van de meest gebruikte en aanbevolen objectieve prestatiegerichte meetinstrumenten. Dit instrument geeft een goede indicatie voor de spierkracht in het gehele lichaam en speelt een belangrijke rol in de evaluatie van functionaliteit. Handspierkracht is gemeten in dit onderzoek met een Jamar handspierkrachtmeter. *Longfunctietesten* worden gebruikt om de longinhoud te meten. Een goede longinhoud is noodzakelijk voor het uitvoeren van dagelijkse activiteiten. Longfunctie is in dit onderzoek gemeten met de Wright peak flow meter. Dit instrument meet de maximale uitblaascapaciteit na een maximale inhaling.

Naast handspierkracht en longfunctie is er in één hoofdstuk in dit proefschrift gekeken naar het hemoglobine gehalte in relatie tot depressie en angst. Er zijn veel verschillende mogelijkheden om een indicatie van de lichamelijke algehele gezondheid te meten. Eén voorbeeld hiervan is het *hemoglobine gehalte*. Hemoglobine is een molecuul in de rode bloedcellen dat zuurstof vervoert door het lichaam. Afwijkende waarden van hemoglobine kunnen een indicatie zijn van onderliggende gezondheidsproblematiek.

De samenhang tussen depressie, angst en objectief gemeten fysiek functioneren

Het is relevant om de samenhang tussen depressie, angst en het objectief fysiek functioneren te onderzoeken om verschillende redenen. Ten eerste is het van belang om te onderzoeken in hoeverre objectief gemeten fysiek functioneren daadwerkelijk verminderd is bij mensen met een depressieve en/of angststoornis in vergelijking met mensen zonder psychische klachten. Ten tweede is het belangrijk om het natuurlijke beloop van deze relatie te bepalen om te weten of een verminderd fysiek functioneren de oorzaak of juist een gevolg is van de psychische klachten. Ten derde kan het detecteren van een verminderd fysiek functioneren tijdens een depressie of angststoornis helpen om tijdens de behandeling de focus te leggen op beweging en andere lifestyle interventies om beperkingen te voorkomen. Dit proefschrift draagt bij aan dit onderzoeksveld door het onderzoeken van de samenhang tussen depressie, angst en objectief gemeten fysiek functioneren.

Potentiële onderliggende mechanismes die het verminderd fysiek functioneren verbinden met depressieve en angststoornissen

Tijdens de verdieping in de relatie tussen depressie, angst en het fysiek functioneren rijst de vraag op welke mechanismen potentieel onderliggend zijn aan deze relatie. De literatuur laat zien dat een ongezonde leefstijl (zoals weinig beweging, roken en alcoholgebruik), slechter zelfmanagement en naleving van de behandeling gerelateerd zijn aan depressieve en angststoornissen en ook effect hebben op lichamelijke beperkingen. Een ander potentieel onderliggend mechanisme zou dysregulatie van fysiologische stress systemen (zoals het immuunsysteem, het stresshormoon cortisol en het autonome zenuwstelsel) kunnen zijn omdat deze systemen een verband hebben met depressieve en angststoornissen en er enig bewijs is dat deze systemen ook een verband hebben met het fysiek functioneren. Dit is echter nog niet eerder onderzocht.

Doelen van dit proefschrift

De belangrijkste onderzoeksvraag van dit proefschrift is of er een relatie is tussen het objectief fysiek functioneren en depressieve en angststoornissen in een volwassen populatie. Deze vraag is opgedeeld in drie deelvragen. De eerste vraag richt zich op de cross-sectionele samenhang tussen het objectief fysiek functioneren en depressie en angst. De relatie tussen handspierkracht, longfunctie, hemoglobine en depressie en angst is onderzocht. De tweede vraag richt zich op de longitudinale samenhang tussen objectief fysiek functioneren en depressie en angst. Het fysiek functioneren (handspierkracht en longfunctie) is als voorspeller voor de persistentie van depressie en angst na twee jaar bekeken. Ook het zesjarig beloop van het fysiek functioneren werd onderzocht bij mensen met en zonder depressieve en angststoornissen. De derde vraag richt zich op potentiële onderliggende mechanismen van het mogelijk aanwezige verband tussen het fysiek functioneren en depressie en angst. Hierbij werd onderzocht of fysiologische stress systemen gerelateerd zijn aan het fysiek functioneren en of deze stress systemen een verklaring kunnen geven voor het verband tussen het fysiek functioneren en depressie en angst.

Studiepopulatie in dit proefschrift

Alle studies in dit proefschrift zijn gebaseerd op gegevens van de Nederlandse Studie Depressie en Angst (NESDA). NESDA is een groot psychiatrisch cohortonderzoek gericht op het beloop en gevolgen van depressieve en angststoornissen. NESDA heeft 2981 deelnemers geïncludeerd tussen de 18 en 65 jaar. De deelnemers zijn geworven

in de algemene bevolking (19%), eerste lijn zorg (54%) en in instellingen voor de geestelijke gezondheidszorg (27%) voor het verkrijgen van een cohort van mensen met verschillende stadia van depressie en angst. Op de basismeting hadden 1700 deelnemers een huidige depressieve en/of angststoornis, 626 deelnemers hadden een herstelde depressie of angststoornis en 655 deelnemers hadden nooit in hun leven een psychiatrische stoornis gehad (gezonde controles). De basismeting vond plaats tussen 2004 en 2007 en het grootste gedeelte van de deelnemers is opnieuw gemeten na twee, vier, zes en negen jaar.

Belangrijkste bevindingen van dit proefschrift

Het hoofddoel van dit proefschrift was om de relatie tussen depressieve en angststoornissen en objectief fysiek functioneren te onderzoeken. Hieruit volgde drie subdoelen; het eerste doel van dit proefschrift was om de samenhang tussen depressieve en angststoornissen en het objectief functioneren op één moment te onderzoeken. In **hoofdstuk 2** vonden we in een groep van 2920 mensen een hoger hemoglobine level bij de mensen met een huidige depressie of angststoornis in vergelijking met de gezonde controles. Hiernaast vonden we dat een hogere ernst van depressie of angst samenhing met zowel een hoger als een lager hemoglobine gehalte. Echter bleek dat er een grote invloed van gezondheid en leefstijl factoren was op de samenhang tussen depressie, angst en hemoglobine; de verschillen tussen de groepen verdwenen na correctie voor deze factoren. Deze bevindingen impliceren dat wij niet kunnen bevestigen dat er een onafhankelijke relatie is tussen depressie, angst en hemoglobine level. In **hoofdstuk 3** onderzochten we de samenhang tussen depressieve en angststoornissen en het objectief fysiek functioneren bij 1629 mensen met een depressie of angststoornis en 629 gezonde controles. Deze studie laat zien dat vrouwen met een depressieve of angststoornis een verminderd fysiek functioneren hebben, zowel een lagere handspierkracht als een lagere longfunctie, in vergelijking met vergelijkbare vrouwen zonder stoornis. Het verminderd objectief functioneren kwam nog sterker naar voren bij de vrouwen waarbij de depressie of angststoornis op latere leeftijd ontstond. Ook bleek dat mannen met een depressie of angststoornis een vergelijkbare handspierkracht en een betere longfunctie hadden dan de mannen zonder psychische klachten.

Het tweede doel was om de relatie tussen depressieve en angststoornissen en het objectief functioneren over de tijd te onderzoeken. In **hoofdstuk 4** vonden we in een groep van 1206 mensen met een huidige depressieve of angststoornis dat

verminderde handspierkracht een voorspeller is voor de persistentie van depressie en angst na twee jaar. Een verminderde longfunctie voorspelde de persistentie van de depressieve stoornis na twee jaar, maar niet van persistentie van de angststoornis. **Hoofdstuk 5** beschrijft het zesjarig traject van objectief functioneren van 2480 mensen met en zonder een depressie of angststoornis. Er zijn geen verschillen in de mate van achteruitgang van fysiek functioneren gevonden tussen de groepen. Echter bleek dat vrouwen met een huidige depressie en/of angststoornis een verminderd fysiek functioneren hadden in vergelijking met gezonde vrouwen gedurende het gehele zesjarige traject. Bij mannen met een depressie en/of angststoornis is een sterkere achteruitgang van longfunctie gevonden gedurende zes jaar in vergelijking met gezonde mannen. Depressie en angst zijn geassocieerd met een consistent verminderde handspierkracht bij vrouwen en een verminderde longfunctie bij vrouwen en mannen gedurende het zesjarig traject wat de langdurige impact van depressie en angst op het fysiek functioneren impliceert.

Het derde, en laatste, doel was om inzicht te krijgen in de onderliggende mechanismen in de samenhang tussen depressie, angst en het objectief functioneren. In **hoofdstuk 6** is bij 2860 mensen onderzocht of fysiologische stress systemen (het immuunsysteem, het stresshormoon cortisol en het autonome zenuwstelsel) zijn geassocieerd met het objectief fysiek functioneren. Het verminderd objectief functioneren bleek inderdaad samen te hangen met hogere levels van markers van het immuunsysteem en cortisol, maar niet met het autonome zenuwstelsel. De fysiologische stress systemen konden de samenhang tussen depressie, angst en het fysiek functioneren echter niet verklaren wat suggereert dat andere onderliggende mechanismen hierbij een rol spelen.

Naast het onderzoeken van de vraag of er een relatie is tussen depressie, angst en het objectief gemeten fysiek functioneren, heeft het onderzoeksteam de afgelopen jaren ook gewerkt aan de uitvoer van een interventiestudie op dit terrein. In **hoofdstuk 7** staat het protocol van de MOTAR (MOod Treatment with Antidepressants or Running) studie beschreven. Deze unieke interventie studie onderzoekt of antidepressiva en runningtherapie vergelijkbaar zijn als behandeling voor het verminderen van depressieve en angstsymptomen en of beide interventies een vergelijkbaar effect hebben op biologische veroudering en metabole stress. Deze resultaten worden geanalyseerd en in de toekomst gepubliceerd.

Conclusie

Dit proefschrift bevestigt dat er aanwijzingen zijn voor een verminderd objectief fysiek functioneren bij mensen met een depressieve en/of angststoornis in vergelijking met mensen zonder deze stoornissen. Deze bevindingen zijn gevonden bij vergelijkingen op één moment en over de tijd en lijken in het bijzonder bij vrouwen aanwezig. Ook lijken er aanwijzingen te zijn voor een relatie tussen fysiologische stress systemen en het fysiek functioneren, maar deze stress systemen verklaren niet de samenhang tussen depressie, angst en het verminderd fysiek functioneren. Deze bevindingen pleiten er voor om onderzoek in de toekomst te richten op voorspellers en consequenties van een verminderd fysiek functioneren bij mensen met een depressieve en/of angststoornis en om interventies aan te bieden aan patiënten met deze klachten die ingrijpen op zowel het mentaal als fysiek functioneren.

CHAPTER 10

Dankwoord (Acknowledgements)
About the author
Dissertation series

Zet elke dag een stapje meer
Al is hij nog zo klein
Uiteindelijk kom je een keer
Precies waar je wil zijn

- Martin Gijzemijter -

DANKWOORD (ACKNOWLEDGEMENTS)

Graag wil ik de mensen die mij geholpen hebben bij het schrijven van mijn proefschrift in het zonnetje zetten. Het maken van dit proefschrift heeft een behoorlijke tijd geduurd en ik voel me hierin gesteund door velen. Mijn promotieonderzoek verliep niet via een regulier traject maar door het sprokkelen van uren en dagen her en der tussen mijn andere werkzaamheden door. Het schrijven was voor mij een behoorlijke kluif, een enorme uitdaging en een prachtige verdieping. Uiteindelijk ligt er een proefschrift waar ik trots op ben.

Als eerste wil ik de deelnemers van de NESDA en MOTAR studies hartelijk bedanken. Alle uren die zij besteedden om vrijwillig geïnterviewd en onderzocht te worden zijn heel waardevol voor ons als onderzoekers en hopelijk ook voor de deelnemers zelf.

Ik ben enorm blij met mijn promotieteam bestaande uit Brenda, Jan en Femke. Jullie hebben zo ontzettend veel kennis van de wetenschap in de psychiatrie. Brenda, jouw geweldige helikopterview geeft veel richting aan de doelen van de artikelen en proefschriften van al jouw promovendi en ook aan die van mij. Je geeft vaak in korte tijd feedback die het manuscript altijd beter en indrukwekkender maakt. Jouw expertise op het gebied van psychiatrische epidemiologie is immens en dat bewonder ik. Ik voel me vereerd dat ik onder jouw begeleiding mocht promoveren. Jan, jouw methodologische kennis over de uitvoer van onderzoek is specialistisch en kenmerkend. Met jouw pragmatische blik heb jij vaak een verduidelijking gegeven aan de opzet en logica van mijn artikelen. Ik ben heel dankbaar voor wat jij als grondlegger van onze afdeling tot stand hebt gebracht. Wat fijn om met jou samen te werken. Femke, jij was er altijd op elk moment om mijn vreemde vragen te beantwoorden, om mee te sparren over de juiste vervolgstappen en analyses. Heel fijn dat jij zo laagdrempelig benaderbaar bent. Dank voor je geweldige ondersteuning en begeleiding de afgelopen jaren. Dank ook aan Nicole voor jouw hulp bij het schrijven van twee papers in dit proefschrift. Ik heb veel gehad aan jouw kritische blik die jij subtiel wist om te buigen in een prettige verwoording en concrete verbeteringen.

Het werken op de onderzoeksafdeling vind ik na zoveel jaar nog steeds fantastisch. Als net afgestudeerde startte ik als onderzoeksassistent en kwam ik in aanraking met het NESDA onderzoek. Vele interviews mocht ik afnemen waarbij ik indrukwekkende en soms ook zorgwekkende verhalen van de deelnemers aanhoorde. De inhoud van het interview was steeds hetzelfde maar elk gesprek verliep anders en dat maakte het afnemen van de interviews heel interessant. Reen, dank voor je vertrouwen in

mij om het coördineren van verschillende projecten aan mij over te laten. Zo spijtig dat je er niet meer bent.

Dank aan de collega's met wie ik samen heb gewerkt om MOTAR een succes te laten worden. Josine, Dora, Catharine, Brenda, Neeltje, Anneke, Ton, Patricia, Lianne, Laura, Laura, Denise, Rianne, Judy en vele stagiaires. Het was me een genoegen om deze mooie uitdagende klus met jullie te klaren en om de deelnemers te rekruteren, te interviewen, te laten behandelen en weer terug te zien.

Lieve MTOL-collega's Melany, Tim, Gerard en Merijn, wat geweldig om met jullie de infrastructuur van onze afdeling te vormen. De samenwerking met jullie brengt veel plezier in mijn werk. Onze samenwerking leidt tot zo'n mooie uitvoer van vele projecten wat de kwaliteit van de projecten ten goede komt. Het is een voorrecht om in zo'n sterk en gezellig team te mogen werken.

Dank lieve onderzoeksassistenten die ik, naast mijn promotieonderzoek, als Hoofd Veldwerk Onderzoek mocht aansturen en coachen. Ik beleef veel plezier aan het leidinggeven aan jullie en leer veel van jullie. Leuk om te zien hoe jullie in de loop van de tijd steeds meer ervaren worden in de uitvoer van het veldwerk. Dank voor de fijne samenwerking Alanur, Anna, Camille, Claire, Elise, Elles, Emiel, Esther, Eva, Floor, Hanneke, Inge, Judy, Kim, Krista, Laura, Lena, Linda, Liza, Lotte, Maaike, Marieke, Marja, Marlies, Martine, Mary, Michelle, Milou, Misha, Nancy, Natasja, Nel, Nina, Rachel, Rebekka, Rianne, Rik, Rochelle, Roxanne, Saskia, Simone, Siri, Sophie, Suzanne en Suzanne. In de loop van de jaren heb ik een aantal stagiaires mogen begeleiden bij het schrijven van hun scriptie. Ik ben steeds onder de indruk geweest van jullie talent en snelle ontwikkeling. Het was voor mij heel leerzaam en leuk om jullie te begeleiden Anne, Daisy, Eline, Erik, Esra, Funda, Judith, Lisa, Merel, Sanne en Suzanne.

Lieve paranimfen Merijn en Heleen, ontzettend fijn dat jullie deze speciale rol op jullie willen nemen. Ik heb jullie graag aan mijn zijde als ik de verdediging van dit proefschrift aan ga. Merijn, al heel wat jaren werken wij samen maar de laatste jaren toch het meest intensief. Allebei stoeien we met onze tijd om naast onze 'gewone' baan een proefschrift te schrijven en ook jij promoveert bijna, succes met de laatste loodjes! Je bent een fijne vent met hart voor de zaak en oog voor iedereen. 'Even bijpraten' doen we graag en houden we erin! Heleen, steeds vaker merken we dat we veel dingen hetzelfde aanpakken en er hetzelfde over denken. Je bent een hele fijne zus waar ik altijd kan aankloppen. Super leuk om jou en jouw gezin zo vaak te zien en met elkaar te genieten van het leven. Dank voor de leuke belevenissen die vaak eindigen in een slappe lach.

Lieve pap, mam, Joost, Liesbeth, Michiel, Heleen, Robin, Tannie, Thijs, Sophie, Floor, Iris, Lanah, Elsa en Jonne, wat fijn dat jullie als familie altijd zo dichtbij zijn. Super om jullie zo vaak te zien en om samen leuke dingen te doen. Een stabiele basis heb ik van huis uit meegekregen. Dit heeft mij kracht gegeven om op mezelf te vertrouwen en het leven altijd van de positieve kant te bekijken. Dank lieve vriendinnen voor de gezellige momenten om samen wijntjes te drinken, te eten, prachtige gesprekken te voeren, te wandelen, hard te lopen en de kinderen groot te zien worden. Ik geniet met volle teugen.

Auke, wat is het leven met jou ontzettend fijn. Jij brengt liefde, humor en rust in mijn leven. Samen kunnen we de wereld aan. We genieten intens van onze prachtige kinderen. Lieve Jurre, Stef en Meike, dank dat jullie er zijn. Het is heerlijk om met jullie het leven te delen en jullie groot te zien worden. Jullie zijn nu al zulke unieke mensjes met eigen ideeën en gedachten. Jullie maken ons leven compleet. Ik houd van jullie.

ABOUT THE AUTHOR

Bianca Lever-van Milligen was born on June 3rd, 1982 in Alphen aan den Rijn, the Netherlands. She graduated from high school in 2000 at the Groene Hart Lyceum. She received her bachelor's degree in Oefentherapie Cesar at the Hogeschool van Utrecht in (2003), followed by a master's degree in Bewegingswetenschappen at the Vrije Universiteit in Amsterdam with a focus on psychiatry in (2006). For her thesis, she examined the relationship between the self-received motor competence and motor performance in children. During her master, she worked as Oefentherapeut Cesar in multiple practices. After graduating, she worked part-time as Oefentherapeut Cesar in Oefentherapie Practice in Alphen aan den Rijn which she continued to do until 2012. She combined this with a position as research assistant at GGZ inGeest/ department of Psychiatry of VU medical center in Amsterdam as of September 2006. As research assistant, she took part in the data collection of NESDA and many other studies. In March 2009, Bianca started coordinating the fieldwork of a large cohort of patients with obsessive compulsive disorders (NOCDA study), and in 2010 she started to work as part-time junior researcher on the topic of objective physical function and depression and anxiety with the NESDA study which resulted in a PhD trajectory. She was involved in setting up and conducting an intervention study for patients with depressive and anxiety disorders to examine the effects of antidepressants and running therapy on psychiatric and biological function (the Mood Treatment with Antidepressants or Running (MOTAR) study) starting in 2012. In 2015, Bianca was promoted to Head of research fieldwork at GGZ inGeest/department of Psychiatry of Amsterdam University Medical Center in Amsterdam. In this role, she manages the team of research assistants, gives advice on fieldwork logistics for new research projects and coordinates multiple studies.

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