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The handle http://hdl.handle.net/1887/20090 holds various files of this Leiden University dissertation.

Author: Reedt Dortland, Arianne Klaartje Beraldine van
Title: Metabolic risk factors in depressive and anxiety disorders
Issue Date: 2012-11-06

Metabolic risk factors in depressive and anxiety disorders

Arianne Klaartje Beraldine van Reedt Dortland

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 organizations (VU University Medical Centre, GGZ inGeest, Arkin, Leiden University Medical Centre, GGZ Rivierduinen, University Medical Centre Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Scientific Institute for Quality of Health Care [IQ Healthcare], Netherlands Institute for Health Services Research [NIVEL] and Netherlands Institute of Mental Health and Addiction [Trimbos]). Data analyses were supported by a Netherlands Organisation for Scientific Research (NWO) grant (VIDI 917.66.320) to prof.dr. B.W.J.H. Penninx.

Financial support by the Dutch Heart Foundation and by the J.E. Jurriaanse Foundation for the publication of this thesis is gratefully acknowledged. Further financial support for the printing of this thesis was kindly provided by Gijs Lauret, Lundbeck B.V. and Servier Nederland Farma B.V.

Cover image: Elena Ray
Cover design: Mirjam van Emden & Arianne van Reedt Dortland
Editing: Arianne van Reedt Dortland
Printed by: Uitgeverij BOXPress, 's-Hertogenbosch
ISBN: 978 90 8891 489 8

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Metabolic risk factors in depressive and anxiety disorders

Proefschrift

ter verkrijging van

de graad van Doctor aan de Universiteit Leiden

op gezag van de Rector Magnificus Prof. Mr. P.F. van der Heijden,

volgens besluit van het College voor Promoties

ter verdediging op dinsdag 6 november 2012

klokke 11.15 uur

door

Arianne Klaartje Beraldine van Reedt Dortland
geboren te Utrecht
op 10 februari 1981

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Er is iets meer waard dan een geleerde te zijn.
Dat is een mens te zijn.

Jules Gabriel Compayré (1843-1913), bron onvindbaar

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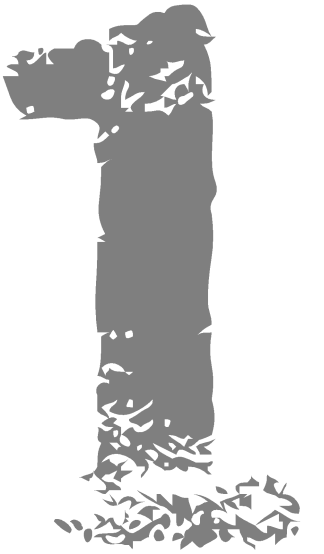
General introduction



Depressive and anxiety disorders as well as cardiovascular disease (CVD) are leading contributors to the worldwide burden of disease. Substantial evidence implies an association between these syndromes,[1-8] but the mechanisms underlying this link are still unknown. Metabolic risk factors for CVD might connect depressive and anxiety disorders to CVD. The relation of depressive and anxiety disorders to metabolic risk is a relatively new topic of research, and only a few studies have addressed it. By means of this thesis we aim to expand this innovative area of research. We thoroughly investigate the association of depressive and anxiety disorders with metabolic risk factors. Moreover, the contribution of biological stress system alterations and lifestyle to metabolic risk in depression and anxiety is examined. Also, we take a broader perspective by exploring whether personality traits and childhood trauma are associated with adverse metabolic risk factors. This knowledge may help to develop and extend personalized prevention and treatment programs. In this introduction, we present background information and the general aim and outline of the thesis.

1.1 DEPRESSIVE AND ANXIETY DISORDERS

1.1.1 Diagnostic criteria

A major depressive disorder (MDD) is characterized by the presence of five or more MDD symptoms for at least a two week period, of which minimally a depressed mood and/or a diminished interest or pleasure in nearly all activities should be manifested. Further MDD symptoms include weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, inability to concentrate take decisions, and recurrent thoughts about death or suicide. A diagnosis of MDD is only applicable if symptoms cause significant distress or impairment in everyday functioning.

Combinations of depressive and anxiety symptoms differ between individuals. For example, some depressed people report weight loss and severe feelings of guilt as core symptoms, while others mainly present with weight gain and hypersomnia. As a result of this heterogeneity of depressive symptoms, MDD subtypes have been formulated. MDD subtypes include MDD with melancholic features and MDD with atypical features. These subtypes are seen as particular forms of MDD and are observed in a subset of all patients with MDD. An MDD with melancholic features presents with anhedonia, worse symptoms in the morning, early morning awakenings, psychomotor agitation or retardation, weight loss and severe feelings of guilt. An MDD with atypical features is characterized by mood reactivity (i.e., mood brightening in response to positive events), weight gain, hypersomnia, leaden paralysis (i.e., heavy limbs) and interpersonal rejection sensitivity. A mild but chronic (> 2 years) depressive disorder is called dysthymia.

Anxiety disorders comprise situational (e.g., social phobia, and panic disorder with or without agoraphobia) and generalized anxiety

disorders (GAD), among others. Social phobia refers to a marked and persistent fear of certain social or performance situations in which one fears doing something that is embarrassing or humiliating. A panic disorder is characterized by recurrent unexpected panic attacks. It may be accompanied by agoraphobia. Agoraphobia is defined as a form of anxiety experienced in situations from which escape might be difficult or embarrassing, or in which help may not be available in case of panic. Typical agoraphobic situations are being outside, in a crowd or standing in line, and traveling by bus, train or car. GAD is an excessive anxiety and worry about various every day situations for at least 6 months.

1.1.2 Epidemiology, burden & co-morbidity

Depressive and anxiety disorders are very common. They both affect around 19 percent of the Dutch population during their lifetime, and respectively 4 to 10 percent during the preceding month.[9] The impact of depressive and anxiety disorders on public health is substantial and increasing. According to the World Health Organisation (WHO), depressive disorders currently rank fourth among the leading causes of disease burden, and they are even estimated to rank second in the World and first in high-income countries by the year 2030.[10] This increased disease burden is due to two processes. First, the risk of depression increases with age and the progressive ageing process will therefore raise prevalence rates. Simultaneously, the advancing control of physical illnesses will proportionally increase the burden of depression. As a consequence of their negative effects on individual and public health, depressive and anxiety disorders have a significant impact on the economy. The costs of such mental disorders are comparable to those of physical illnesses, mainly due to loss of production.[11]

Depressive and anxiety disorders often occur simultaneously. Co-morbidity rates of over 60 percent have been reported.[12, 13] This interrelatedness poses the question whether they actually are distinct disorders. Because depressive and anxiety disorders both are highly prevalent and show substantial overlap, it is important to study depressive and anxiety disorders in concert in relation to metabolic risk.

1.1.3 Depression and anxiety severity

The severity of depressive and anxiety symptoms varies per person: some people show more and more severe symptoms of depression or anxiety than others. Since diagnoses are dichotomous classifications, a diagnosis of a depressive or anxiety disorder offers limited information on the amount of difficulties an individual person experiences. Severity scales both for symptoms of depression and anxiety have been developed to account for this variation in the severity of symptoms.[133, 171] Severity scales assess the number of symptoms as well as give weights for each symptom. Some people score rather high on such a severity scale while they fall short of the diagnostic criteria for a depressive or anxiety disorder. Severity

scales recognize this group of people who is being overlooked by use of standard diagnostic criteria. Despite its importance, so far only some studies have investigated depression severity in relation to metabolic risk factors, and even a smaller number of studies has reported on the severity of anxiety. Therefore, the inclusion of severity measures for depressive and anxiety symptoms importantly adds to research on metabolic risk.

1.1.4 Depression and anxiety dimensions

Although variation in the general severity of symptoms among people is explored by severity scales, the use of severity scales is still only an indicative method to assess symptoms of depression or anxiety. Some people with severe symptoms of depression feel especially guilty, while others for instance mainly have lost interest in things they normally enjoy. Severity scales do not account for this heterogeneity in the type of symptoms. Moreover, as outlined earlier, depressive and anxiety disorders do not seem to be discrete syndromes, as they often co-exist. To tackle these issues of heterogeneity and co-morbidity, distinct and shared dimensions of depression and anxiety symptoms can be examined.[14,15] For this purpose the 'tripartite model' by Clark and Watson[14] can be used. This model includes negative affect, positive affect and somatic arousal dimensions. Negative affect covers aversive emotional states such as anger and guilt. This dimension is associated with both depression and anxiety. Positive affect represents positive emotional states such as feeling active, excited, delighted, enthusiastic and interested. A lack of positive affect is associated with depressive moods. The somatic arousal dimension embodies symptoms of physiological hyperarousal, such as trembling, shaking, dizziness and sweating. Somatic arousal is thought to be distinctive for anxious moods, and for panic in particular.[14] Every single person scores low, high, or somewhere in between upon all three dimensions. These dimensions are useful for research on depressive and anxiety disorders as they take account of the heterogeneity and co-morbidity of these syndromes. Despite their additive value depression and anxiety dimensions have not yet been studied in relation to metabolic risk.

1.2 METABOLIC RISK FACTORS FOR CVD

Globally, CVD is the leading cause of death and an important source of disease burden. The WHO expects that CVD will still be the second cause of disease burden by the year 2030, right after depression.[10] Mounting evidence indicates that depressive and anxiety disorders are related to an increased risk of CVD. Meta-analyses among patients with CVD but also in the general population indicate that depression increases the risk of CVD twofold.[1-6] Anxiety is associated with an almost 40 percent increased risk of CVD.[7,8] Various hypotheses attempt to explain the high co-morbidity of depression and anxiety with CVD. One of these hypotheses suggests that metabolic factors may be linking mechanisms.[18] Such metabolic factors as might be related to depressive and anxiety disorders, which also increase

risk of CVD, include dyslipidemia, (abdominal) obesity, hypertension and hyperglycemia. The metabolic syndrome is a constellation of these metabolic risk factors. As these metabolic risk factors collectively predict over half of CVD cases,[16,17] they are core targets in general CVD prevention and treatment.[18] If related to symptoms of depression or anxiety, they might also be promising targets for CVD management in depressive and anxiety disorders. Hence it is important to thoroughly study the relationship of metabolic risk factors with depression and anxiety.

1.2.1 Dyslipidemia

A major metabolic risk factor for CVD is dyslipidemia. Dyslipidemia stands for an aggregation of serum lipid/lipoprotein abnormalities like elevated low-density lipoprotein (LDL) cholesterol or triglycerides, and reduced high-density lipoprotein (HDL) cholesterol.[19] Cholesterol is an essential lipid in cell membranes as well as for the synthesis of steroid hormones and bile acids. It is produced by the liver, replenished by our diet, and influenced by factors such as smoking, physical activity and certain kinds of medication. Triglycerides are derived from dietary fats and from other energy sources like carbohydrates that are converted into triglycerides if not used immediately after consumption. LDL and HDL are lipoproteins that bind to lipids like cholesterol and triglycerides and thereby enable lipids to be transported within the water-based blood stream. LDL bound cholesterol and triglycerides foster plaque build-up on the artery wall and as a result a hardening of the arteries (i.e., atherosclerosis). Consequently, increased serum levels of LDL cholesterol or triglyceride adversely affect CVD risk. HDL removes cholesterol from the blood stream and artery walls and transports it back to the liver for re-use. High HDL cholesterol levels therefore diminish the development of atherosclerosis.

Findings regarding dyslipidemia in depression were not entirely consistent. The majority of studies reported that depression was associated with dyslipidemia.[20-33] However, some studies found that depression related to favourable lipid or lipoprotein levels,[34-41] while others reported absent associations.[45-54] Relatively few studies on lipids in relation to anxiety have been carried out. These studies predominantly reported that anxiety was not associated with lipid levels at all,[26,29,47] although one study reported an association of anxiety with unfavourable lipid values[20] and another study[40] found a favourable association.

1.2.2 (Abdominal) obesity

Another main metabolic risk factor for CVD is obesity. Two of the most commonly used obesity measures are waist circumference (WC) and body mass index (BMI). WC represents both subcutaneous (i.e., beneath the skin) and intra-abdominal (i.e., around the organs of the belly) fat cells in the abdomen. The main function of fat cells is lipid storage. Besides, intra-abdominal fat cells are metabolically active and so induce insulin resistance and free fatty acid (i.e., a breakdown product of triglycerides)

production. Through these processes, WC could be directly associated with an increased CVD risk. BMI (i.e., weight (kg)/height (m)^2) is an approximation of overall body fat.[42]

Most studies on depression and obesity have reported that depression was associated with a higher WC[20,23-28,43-46] or BMI,[30,45,56,57] although some studies did not objectify any association of depression with WC[24,25,32,33,45,49] or BMI.[22,24,43,44,47] The small number of studies on anxiety and obesity all reported no association between anxiety and WC[23,26,29,47] or BMI.[23,44]

1.2.3 Hypertension

Hypertension (i.e., high blood pressure) points to an elevated pressure in the arteries. Blood pressure is subdivided into systolic and diastolic pressures. Systolic blood pressure is the arterial pressure during a heart beat. Diastolic pressure is the pressure between heart beats. When the systolic or diastolic blood pressure exceeds the accepted normal values, it is classified as hypertension. Persistent hypertension is an important risk factor for CVD, as it puts a continual strain on the heart and arteries.

Most studies on blood pressure in relation to depression did not find any association,[22-26, 28-30, 43-49] although two studies reported an association of depression with higher blood pressure,[24, 30] and one found an association with lower blood pressure.[20] Most studies on anxiety reported no association with blood pressure,[23, 26, 44, 46] although one study found that anxiety was related to a lower blood pressure.[20]

1.2.4 Hyperglycemia

High blood glucose levels (i.e., hyperglycemia) detrimentally affect the cardiovascular system as well. Glucose is a simple sugar that is derived from dietary carbohydrates and from bodily stored glucose. Glucose has various important functions in the body, among which energy supply. A higher than usual (fasting) glucose level is a sign of insulin resistance and of (pre)diabetes mellitus (DM). Normally insulin, a hormone produced by the pancreas, causes glucose to be stored in body cells when blood glucose levels increase after a meal. If body cells such as fat cells do not respond properly to insulin, and thus are 'insulin resistant', glucose builds up in the blood stream and therefore blood glucose levels rise. High blood glucose levels (i.e., hyperglycemia) cause high glucose levels inside body cells and consequently tissue damage, especially renal, retinal and neuronal but also microvascular damage. Moreover, hyperglycemia induces vascular inflammation.

Most former studies reported no association of depression[20,21,23-30,44,46,49] or anxiety[20,23,26,44,46] with glucose levels. Some studies did however find an association of depression with high glucose levels.[25,46,48]

1.2.5 The metabolic syndrome

A clustering of several of the abovementioned metabolic risk factors is referred to as the metabolic syndrome, which was originally described as 'Syndrome X' by Reaven in 1988.[50] These metabolic risk factors are interrelated and therefore tend to co-occur. For example, excess body fat (particularly abdominal obesity) is thought to promote the development of insulin resistance and therefore of high blood glucose levels. And as insulin not only catalyzes storage of glucose but also that of lipids out of the blood stream into fat cells, insulin resistant fat cells impair lipid intake and therefore cause dyslipidemia. High blood glucose probably also raises blood pressure through increased blood volume and suppression of vasolidation. Moreover, because the heart has to work harder to distribute an adequate amount of blood throughout the body, (abdominal) obesity is thought to increase blood pressure too. High blood pressure causes damage to the inside of blood vessels. This damage allows plaques (among others consisting of triglycerides) to build up. Obesity stimulates this build-up through promotion of dyslipidemia such as increased triglyceride levels. To be precise, adipose tissue secretes inflammatory cytokines, which arouse the release of lipids into the bloodstream to provide energy for host defense. In addition, lipids can be deployed to bind to inflammogens in order to block their cytotoxic effects.[51] The accumulation of plaques on blood vessel walls narrows or even blocks them (i.e., atherosclerosis). The decreased circumference of the arteries forces the heart to work harder to be able to deliver blood to body cells, which further increases blood pressure. These were illustrations of the complex interplay between metabolic risk factors.

The metabolic syndrome predisposes a person to type 2 DM[52] and CVD, and strongly predicts CVD mortality.[53] Several definitions of the metabolic syndrome have been proposed,[20,22,62-65] of which the latest definition is the revised one of the National Cholesterol Education Program—Third Adult Treatment Panel (NCEP-ATPIII).[17] According to this definition, the metabolic syndrome is diagnosed when three or more of the following criteria are met:

1. Abdominal obesity: waist circumference > 102 cm in men or > 88 cm in women
2. Elevated triglycerides: ≥ 1.7 mmol/L (150 mg/dL), or medication for elevated triglycerides
3. Reduced high-density lipoprotein (HDL) cholesterol: ≤ 1.03 mmol/L (40 mg/dL) in men or ≤ 1.3 mmol/L (50 mg/dL) in women, or medication for reduced HDL cholesterol
4. Hypertension: blood pressure ≥ 130/85 mm Hg, or medication for hypertension
5. Hyperglycemia: fasting glucose ≥ 5.6 mmol/L (100 mg/dL), or medication for elevated glucose

The metabolic syndrome is very common. It affects 6.7 percent of the American population aged 20-29, rising to 43.5 percent of the 60-69 old.[54] The prevalence of the metabolic syndrome in the Netherlands is estimated around 14 percent in adults,[55] and rises to 36.5% for people aged over 65.[56] Its incidence raises, mainly through increasing obesity rates.[57]

Although metabolic risk factors included in the metabolic syndrome more often co-occur than chance would dictate, the value of the metabolic syndrome concept as such is subject of substantial debate.[70,71] One of the issues for discussion is that metabolic syndrome risk factor combinations are heterogeneous: they vary considerably between individuals.[17] For example, some people have high blood pressure, elevated glucose and a high waist circumference, while others have high blood pressure, high waist circumference and dyslipidemia. All those people meet the criteria for metabolic syndrome, but in different ways. A second issue is that probably no single underlying pathophysiological mechanism underlies the metabolic syndrome. Moreover, whether the whole of the metabolic syndrome is greater than the sum of its parts in the determination of CVD or DM risk is still uncertain. As a result of these doubts, it is important to study not only the (heterogeneous) metabolic syndrome, but also its separate components. However, until recently many studies focused on the metabolic syndrome as a whole but not on separate metabolic risk factors in relation to depression or anxiety. These studies yielded inconsistent results. Most studies found that depression increased the risk of the metabolic syndrome,[23-32,45,46,49,50,72-74] while others did not find any association.[33,47,48]

In accordance with the definitions of the metabolic syndrome, various former studies included individual metabolic risk factors as dichotomous variables (for instance WC below or above 102 cm for men). However, these risk factors are better studied as continuous variables. Dichotomization of continuous variables results in a loss of information as individual differences in metabolic values are not being considered.

1.3 METABOLIC RISK IN DEPRESSIVE AND ANXIETY DISORDERS

People with depressive or anxiety disorders are at increased risk of CVD as compared to people without these psychiatric syndromes. As mentioned, people with depressive disorders have a two times higher risk of cardiovascular morbidity and mortality,[1-6] while people with anxiety disorders have an increased CVD risk of almost 40 percent.[7,8] There is growing interest in the question whether people with a depressive or anxiety disorder are also prone to metabolic risk factors like the metabolic syndrome. As metabolic risk factors substantially contribute to the development of CVD, these could link depressive and anxiety disorders to CVD. Moreover, since metabolic risk factors are relatively easy to identify and treat, these could be profitable targets to improve cardiac health among depressed and anxious people. Thereby, improvement of metabolic risk factors among people with depression or anxiety could contribute to a reduction of general CVD prevalence. Hence, it is of interest to study whether depressive and anxiety disorders are related to metabolic risk factors.

The majority of former studies focused on depressive and anxiety disorders on the one hand and on the metabolic syndrome on the other hand. It is however important to additionally explore associations of depression and anxiety severity and dimensions with separate continuous metabolic risk factors, as such associations reflect more subtle individual differences. These associations have been less frequently addressed in previous research.

1.3.1 Antidepressant use and metabolic risk factors

Antidepressant medicines are used to alleviate depressive and anxiety disorders. The two most commonly prescribed antidepressants are tricyclic antidepressants (TCAs) and selective serotonin re-uptake inhibitors (SSRIs). There are signs that TCAs induce CVD related side effects. Antihistaminergic[58,59] and inflammatory[60] side effects are thought to promote obesity and consequent dyslipidemia. TCA use is also thought to provoke hyperglycemia,[61] and hypertension[62] through agonism of the α1 adrenergic receptor.[63] To a lesser extent, SSRIs tend to induce obesity and thereby dyslipidemia in some patients as well. Antidepressants are a central part of the treatment of depressive and anxiety disorders and therefore commonly prescribed: in 2009, 5.8 percent of the Dutch population received antidepressants (i.e., 954.000 of 16.439.659 insured residents).[64,65] Given their side effects and their common use, antidepressant use among depressed and also among anxious people might cause them to be at higher risk of metabolic adversities and thereby of CVD. However, it has not yet been exhaustively studied whether antidepressant use relates to metabolic risk and if antidepressant use contributes to metabolic risk in depression and anxiety. We therefore intend to increase our understanding in this area.

1.4 CONTRIBUTORS TO METABOLIC RISK IN DEPRESSION AND ANXIETY

When an increased metabolic risk among people with symptoms of depression or anxiety is verified, it would be valuable to study what factors contribute to this relationship. Thus far, such explanatory factors have not been extensively explored and so the nature of metabolic risk in depressive and anxiety disorders remains unclear. We intend to provide insight into these explanatory factors. Multiple factors may contribute to metabolic risk in depressive and anxiety disorders. In this thesis, we focus on the impact of biological stress systems and lifestyle.

1.4.1 Biological stress systems

1.4.1.1 The hypothalamic-pituitary-adrenal (HPA) axis

The hypothalamus, pituitary and adrenals shape the HPA axis, which is the main neuroendocrine system involved in our response to stress. In reaction to stress, the paraventricular nucleus of the hypothalamus secretes vasopressin and corticotrophin-releasing hormone, which stimulate the pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH then arouses secretion of the glucocorticoid 'stress hormone' cortisol by the adrenal glands. Cortisol in turn suppresses hormone secretion by the hypothalamus and the pituitary gland in a negative feedback cycle. Cortisol enables us to react adequately to stress through the mobilization of stored energy by releasing stored glucose and cholesterol into the bloodstream.[66] However, prolonged stress causes HPA axis exhaustion. HPA axis dysfunction is thought to underlie hyperglycemia, abdominal obesity and dyslipidemia,[84-86] but also depressive and anxiety disorders.[67-69] Therefore, HPA axis alteration might be related to increased risk of CVD among depressed and anxious people. Consequently, we study the possible role of the HPA axis in metabolic risk related to depression and anxiety.

1.4.1.2 The autonomic nervous system (ANS)

The ANS is the neural part of our stress system and consists of the counteracting parasympathetic and sympathetic nervous systems (PNS, SNS). The PNS mediates calm, vegetative activities; the SNS kicks in at times of stress and causes our blood pressure to rise. Consequently, chronic stress causes hypertension. Hypertension causes damage to the blood vessels, on which mobilized cholesterol aggregates,[70] causing atherosclerosis, as explained above. SNS predominance is also a characteristic of obesity.[71] Chronic stress during depression or anxiety is suggested to cause reduced PNS and increased SNS activity[92,93] and consequently unfavorable alterations of metabolic risk factors. Given this possible role of the ANS in depressive and anxiety disorders as well as in metabolic risk, we believe it is desirable to study the role of the ANS in

metabolic risk among people with symptoms of depression or anxiety. This has not yet been investigated.

1.4.1.3 Inflammation

The immune system defends our body against infectious agents. Not only physical injury, but also psychological stressors activate the immune system and thus the release of inflammatory factors[66] like C-reactive protein (CRP), interleukin(IL)-6 and tumor necrosis factor-alpha (TNF-α). Inflammation stimulates lipid release into the blood stream to fuel host defense and to block cytotoxic effects of inflammogens by binding to them.[51] Adipose tissue cells release inflammatory markers themselves, and thereby further stimulate dyslipidemia. Depressed[72] and anxious[73] people appear to have higher levels of inflammation. Given these complex and bi-directional associations between inflammation, metabolic risk factors and depressive and anxiety disorders, inflammation might well be an important link between the latter two entities. This was not previously examined. Therefore, we study the role of inflammation in the association of metabolic risk with depression and anxiety.

1.4.2 Lifestyle

In general, people with depression and to a lesser degree those with anxiety disorders more often drink higher amounts of *alcohol*,[74] more often *smoke*, and display *lower physical activity*[97] than those without psychopathology. These lifestyle tendencies lead to unfavorable alterations of metabolic risk factors.[19,75] They could therefore cause people with symptoms of depression and anxiety to have adverse levels of metabolic risk factors. As the role of lifestyle in metabolic risk among people with symptoms of depression or anxiety has not yet been studied extensively, we take lifestyle into account as a possible explanatory factor.

1.5 METABOLIC RISK IN RELATION TO PERSONALITY TRAITS AND CHILDHOOD TRAUMA

Factors other than symptoms of depression and anxiety might affect metabolic risk as well. It is for instance conceivable that personality and the experience of trauma during infancy influence levels of metabolic risk factors. Since personality and childhood trauma might be bi-directionally related, it is important to study them in tandem in relation to metabolic risk.

1.5.1 Personality traits

The most commonly used description of personality traits is the Big Five model, which classifies extraversion, openness, agreeableness, neuroticism and conscientiousness. Lower levels of conscientiousness[99-102] and openness,[76,77] and higher levels of neuroticism[102] are related to CVD and general morbidity and mortality. This might be because certain personality traits are associated with (unhealthy) lifestyles,[78] for instance through seeking external stimulation and social events, vulnerability to depression[79] and relatively poor self-discipline.[80,81] These trends affect metabolic risk factors and thereby risk of CVD. Until now, research on personality and metabolic risk has been equivocal and therefore this subject matter deserves further examination.

1.5.2 Childhood trauma

Childhood trauma (i.e., emotional neglect and psychological, physical or sexual abuse) may also detrimentally affect metabolic risk. Emotional neglect, and sexual or physical abuse during infancy increase risk of CVD in adult women.[108] People who experienced trauma in infancy generally have a lower socio-economic status and also more often display unhealthy lifestyles and eating disorders in later life. They also are at increased risk of psychopathology[82-84] and are thought to show adverse (early) adaptation of their biological stress systems.[112-114] Such mechanisms might cause childhood trauma to be related to adverse levels of metabolic risk factors and consequently to an increased risk of CVD. Previous research indicates that various kinds of childhood trauma are related to (abdominal) obesity.[85-90] Studies on metabolic risk factors other than obesity in relation to childhood trauma have not been reported. Consequently, the inclusion of a wider range of metabolic risk factors in this area of research is innovative.

No previous studies have investigated both personality and childhood trauma in relation to metabolic risk. But since personality and childhood trauma are likely to be intertwined, it is enlightening to study them simultaneously in their associations with metabolic risk. Over 20 percent of the variance in (traumatic) life events is due to genetic influences,[91] and this is largely mediated by personality.[92] Personality shapes one's personal environment and thus protects against or facilitates the experience of trauma.[92] Also, personality affects the appraisal of

potentially traumatic events.[93] And vice versa, trauma affects ones perceptions and beliefs, and therefore shapes personality development.[94]

Although the main focus of this thesis is on symptoms of depression and anxiety, personality and childhood trauma are additionally studied as possible correlates of metabolic risk. This will broaden our insights into characteristics that make people prone to metabolic adversities and consequently to CVD.

1.6 THE NETHERLANDS STUDY OF DEPRESSION AND ANXIETY (NESDA)

For this thesis, we used baseline and 2-year follow-up NESDA data. NESDA is an ongoing longitudinal cohort study which was created to describe the long-term course and consequences of depressive and anxiety disorders. Furthermore, it integrates biological and psychosocial research paradigms within an epidemiological approach to examine (interactions between) predictors of the long-term course and consequences of these disorders. NESDA includes 2981 participants aged 18 to 65 years, who were recruited from the general population, general practices, and mental health organisations in the Netherlands. The NESDA sample contains people with a current or remitted depression and/or anxiety disorder, people at increased risk because of family history or subtreshold symptoms of depression or anxiety, and healthy controls without depressive or anxiety disorders in their history. Assessments comprise a face-to-face interview, written questionnaires and biological measurements. NESDA is described in detail elsewhere.[95,96]

1.7 GENERAL AIM OF THE THESIS

The general aim of this thesis is to identify which characteristics of depression and anxiety make people prone to unfavorable metabolic risk factor levels. More specifically, it is the intention to discover whether depressive and anxiety disorders, their degree of severity or different dimensions are associated with adverse levels of metabolic risk factors. Up until now, these associations have remained unclear. Severity scales for depression and anxiety have not been systematically applied and their various dimensions have not been studied at all in this research field. Moreover, so far the focus has been mainly on the metabolic syndrome as a whole instead of on separate metabolic risk factors. Therefore, the relative importance of separate metabolic adversities in their association with symptoms of depression and anxiety will also be extensively discussed. And because the temporal association of depression and anxiety with metabolic risk is still uncertain, the association of depressive and anxiety symptoms with metabolic risk factors will be addressed longitudinally as well. The question whether antidepressant use affects metabolic risk factors will also be examined. In addition, the contribution of biological stress systems and unhealthy lifestyles to metabolic risk in depression and anxiety will be explored. Furthermore, the relationship of

personality traits and childhood trauma with metabolic risk factors will be studied. These objectives are shown schematically in Figure 1.

The knowledge that will be obtained by this thesis could be important for clinical practice. It will increase our understanding of what characteristics make people with symptoms of depression or anxiety vulnerable to an unfavorable metabolic profile and thus to developing CVD. This awareness may contribute to future guidelines for prevention and treatment of metabolic risk. Once characteristics that predispose people with depressive or anxiety disorders to increased metabolic risk have been established, people with these characteristics might be routinely screened for the presence of metabolic adversities. Subsequently, modification of contributors to these associations might reduce their metabolic risk.

1.8 THESIS OUTLINE

The numbers in Figure 1 refer to the thesis chapters. Chapters 2 through 4 comprise research on cross-sectional associations of metabolic risk factors with symptoms of depression and anxiety. In **chapter 2** we describe the risk of the metabolic syndrome and its components among people with pure MDD, pure anxiety or co-morbid MDD and anxiety, as compared to people without such disorders (i.e., controls). Next, we address the question whether severity of depression or anxiety is associated with the metabolic syndrome or its components. Finally, we examine whether antidepressant use independently increases metabolic syndrome (component) risk. In **chapter 3**, total, LDL and HDL cholesterol and triglycerides are compared between people with current MDD, those with remitted MDD, and controls. We also examine the importance of the severity of depression, the presence of atypical or melancholic MDD subtypes, co-morbid anxiety disorder or dysthymia, and suicide attempt in history. In **chapter 4** we discuss how symptom dimensions (i.e., negative affect, positive affect and somatic arousal) relate to the metabolic syndrome and its components.

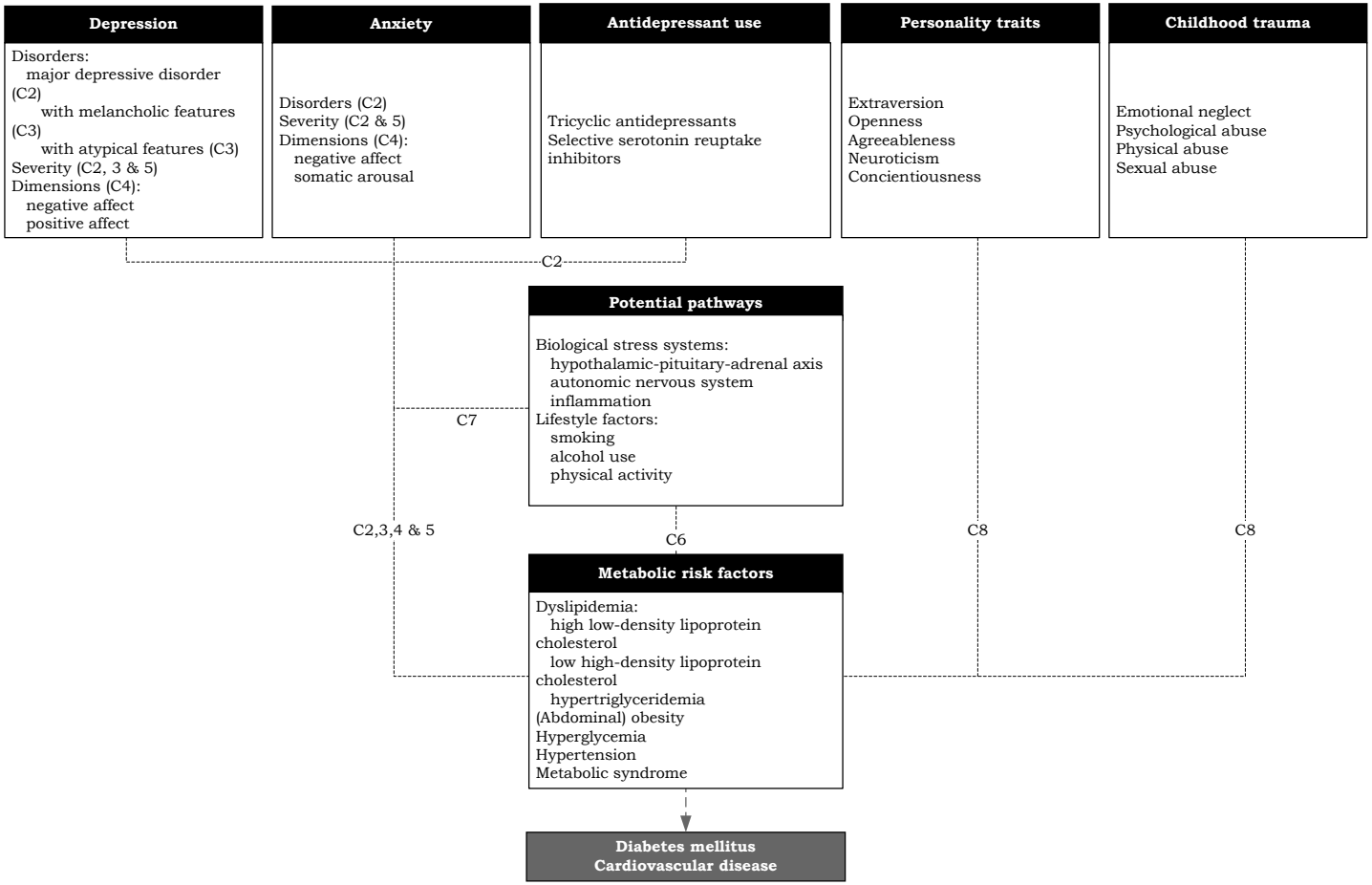
In **chapter 5**, longitudinal associations of symptoms of depression and anxiety with metabolic risk factors are described. We address the question whether baseline depression or anxiety severity predicts a change in metabolic values over a 2-year follow-up period, and whether changes in severity of depression or anxiety coincide with changes in metabolic risk factors.

Chapter 6 and 7 include studies regarding possible contributors to metabolic adversities among depressed and anxious people. **Chapter 6** shows general associations of the biological stress systems ANS and HPA axis with the metabolic syndrome. In **chapter 7**, we address the impact of biological stress system alterations and lifestyle on associations of metabolic risk factors with severity of depression and anxiety, and with antidepressant use.

Chapter 8 outlines whether personality or childhood trauma are correlates of metabolic risk factors. In **chapter 9**, the main results of

chapter 2 through 8 will be summarized and discussed within the framework of contemporary scientific knowledge. Furthermore, directions for future research and for clinical practice will be addressed.

Figure 1. Schematic thesis outline
C represents chapter number



Metabolic syndrome abnormalities are associated with severity of anxiety and depression and with tricyclic antidepressant use

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Acta Psychiatrica Scandinavica 2010, 122 (1): 30-39

ABSTRACT

Introduction
The metabolic syndrome predisposes to cardiovascular disease and diabetes mellitus. There might also be an association between the metabolic syndrome and anxiety and depression, but its nature is unclear. We aimed to investigate whether diagnosis, symptom severity and antidepressant use are associated with the metabolic syndrome.

Methods
We addressed the odds for the metabolic syndrome and its components among 1217 depressed and/or anxious subjects and 629 controls, and their associations with symptom severity and antidepressant use.

Results
Symptom severity was positively associated with prevalence of the metabolic syndrome (adjusted odds ratio [OR] = 2.21 for very severe depression: 95% confidence interval [CI]: 1.06–4.64, $p = .04$), which could be attributed to abdominal obesity and dyslipidemia. Tricyclic antidepressant (TCA) use also increased odds for the metabolic syndrome (OR = 2.30, 95% CI: 1.21–4.36, $p = .01$), independent of depression severity.

Conclusion
The most severely depressed people and TCA users more often have the metabolic syndrome, which is driven by abdominal adiposity and dyslipidemia.

2.1 INTRODUCTION

The metabolic syndrome is defined as a cluster of metabolic abnormalities, including abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hypertension and hyperglycemia. The metabolic syndrome thereby predisposes to cardiovascular disease (CVD) and diabetes mellitus.[17,97] Mapping risk factors for the metabolic syndrome is important given the high global risk and burden of CVD and diabetes,[98] plus the increasing prevalence of obesity and the metabolic syndrome worldwide.[99] There is a growing interest in whether anxious or depressed people are at higher risk for the metabolic syndrome, since depression as well as anxiety show high co-morbidity with CVD.[100,101]

In most studies investigating the link between depressive symptoms and the metabolic syndrome,[23,24,26-29,32,46-49,73,74,132-140] a positive association was reported,[24,26-29,32,46,48,49,73,74,132-137,139,140] while some described none.[20,44,45,102,103] Only few studies focused on the association between anxiety and the metabolic syndrome,[20,23,44,49,103-105] of which only two confirmed a positive association,[103,104] and others did not confirm a link. In studies considering the metabolic syndrome and its components, mainly abdominal obesity,[23,24,26-29,46-48,134,138] hypertriglyceridemia [23,24,26,27,133,134,140,142] and a low HDL cholesterol[20,21,25,26,32,102,106,107] were found to be associated with depressive symptoms, while associations with hypertension[23,24,138] or hyperglycemia[24,47,73,138,140] have rarely been reported. In the few studies on anxiety and metabolic syndrome components,[23,26,47,137] only an association with hypertriglyceridemia[137] and high blood pressure[20] was found. This raises the question whether anxiety or depression are risk factors for several individual metabolic syndrome components, rather than for the whole metabolic syndrome cluster.

It is not only important to study whether metabolic syndrome prevalence differs among DSM-IV diagnoses groups, but also simultaneously its association with symptom severity, as this latter approach focuses on a separate psychopathological aspect, namely dimensionality of disease. Vogelzangs et al.[28] for example, reported an association of the metabolic syndrome with depression severity, while no association was present with the dichotomous depression classification. Another point of interest is whether antidepressant use influences the odds for having the metabolic syndrome. Previous studies have scarcely addressed this topic. Nevertheless, the use of TCAs is known to induce side effects like hypertension,[62] hyperglycemia,[78] and weight gain,[75,76] which may consequently promote dyslipidemia.[143] To a lesser extent, the commonly prescribed selective serotonin re-uptake inhibitors (SSRIs) also tend to induce weight gain[59] and thereby dyslipidemia[143] in some patients, but they do not cause hyperglycemia.[61]

The present study is the first to analyze clinical anxiety and depression diagnoses, as well as symptom severity and antidepressant use, as potential predictors of the metabolic syndrome. We also aimed to

elucidate which of the individual metabolic syndrome components are most strongly associated with these predictors.

2.2 METHODS

Subjects

Subjects participated in the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA), an 8-year longitudinal cohort study including 2981 persons aged 18–65 years. Subjects were recruited from community, primary care, and mental health care in the Netherlands. The baseline assessment comprised of a face-to-face interview, written questionnaires, and biological measurements. The study design is described in detail elsewhere.[95] The study protocol was approved by the Ethical Review Board of each participating center, and all subjects signed informed consent at the baseline assessment.

For the current analyses, four study groups were constructed, i.e., subjects with an anxiety disorder within the past 6 months but no lifetime major depressive disorder (MDD) (i.e., 'current pure anxiety', n=276), subjects with an MDD within the past 6 months but no lifetime anxiety disorder (i.e., 'current pure MDD', n=272), subjects with both MDD and anxiety disorder within the past 6 months (i.e., 'current anxiety and MDD', n=731), and those who never had a MDD or anxiety disorder (i.e., 'controls', n=652), resulting in a preliminary sample size of 1931. Then, 84 subjects with missing values on metabolic syndrome components or on anxiety or depression severity (see below) were excluded, resulting in the current sample of 1846 subjects (i.e., n=266 current pure anxiety, n=261 current pure MDD, n=690 current anxiety and MDD, and n=629 controls).

Indicators of psychopathology

The presence of an anxiety disorder (i.e., panic disorder with or without agoraphobia, social phobia or generalized anxiety disorder) or MDD within the past 6 months was diagnosed according to the fourth edition of the Diagnostic and Statistical Manual for mental disorders (DSM-IV) criteria using the Composite International Diagnostic Interview (CIDI).[108]

Anxiety severity was assessed by the 21-item self-report Beck Anxiety Inventory (BAI) ranging from 0 to 63. Beck Anxiety Inventory total scores were subdivided into four severity groups, i.e., normal (total score 0–9), mild (10–18), moderate (19–29), and severe (30–63), as described before.[109] Depression severity was assessed by the 30-item Inventory of Depressive Symptoms self-report (IDS-SR) ranging from 0 to 84. IDS-SR total scores were, as before,[110] subdivided into five severity groups, i.e., low (total score 0–13), mild (14–25), moderate (26–38), severe (39–48), and very severe (49–84).

Antidepressant medication use within the past month, as registered by observation of drug containers brought in, was subdivided into selective serotonin re-uptake inhibitors (SSRI, ATC code N06AB), tricyclic antidepressants (TCA, ATC code N06AA) and other antidepressants (mainly

consisting of serotonergic and noradrenergic working antidepressants N06AF and N06AX). Subjects who used more than one kind of antidepressant (n=15) were classified according to the category with the strongest assumed metabolic side effects (TCAs > SSRIs > other).

The metabolic syndrome

The metabolic syndrome was defined according to the American Heart Association & National Heart, Lung and Blood Institute's update of the National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III) definition.[17] It requires the presence of three or more of the following criteria: i) abdominal obesity, i.e., waist circumference ≥ 102 cm in men and ≥ 88 cm in women; ii) hypertriglyceridemia, i.e., elevated triglyceride level (≥ 1.70 mmol/L) or drug treatment for elevated triglycerides; iii) low high-density lipoprotein (HDL) cholesterol (< 1.03 mmol/L in men and < 1.30 mmol/L in women) or drug treatment for reduced HDL cholesterol; iv) hypertension, i.e., elevated blood pressure (≥ 130/85 mmHg) or use of antihypertensive medication and v) hyperglycemia, i.e., elevated fasting glucose level (≥ 5.6 mmol/L) or use of antidiabetic medication.

Waist circumference was measured with a measuring tape at the central point between the lowest front rib and the highest front point of the pelvis, upon light clothing. Triglyceride, HDL cholesterol and glucose levels were determined using routine standardized laboratory methods after a mean of 11:16 h (SD = 1:50 h) overnight fast. Systolic and diastolic blood pressure were measured twice during supine rest on the right arm by the OMRON M4 IntelliSense (HEM-752A; Omron Healthcare, Inc., Bannockburn, IL, USA), and were averaged over the two measurements. ATC coded[111] use of HDL increasing or triglyceride lowering (ATC codes C10AB, C10AD, C10BA01), antihypertensive (ATC codes C02, C03, C07, C08, C09) or antidiabetic medication (ATC code A10) within the past month was registered by observation of drug containers brought in.

In line with previous research,[137,148] the number of metabolic syndrome components was used as an indicator of severity of metabolic abnormalities.

Covariates

Sociodemographic variables included age, sex (male/female) and years of education. Oral contraceptive use (no/yes) was identified through self-report. Clinic site (five sites) was added as a covariate as well. We also included lifestyle characteristics previously associated with anxiety, depression and the metabolic syndrome: smoking status (never/former/current) and alcohol use (<1/1–2/>2 drinks per day) were assessed by standardized questionnaires; physical activity was assessed using the International Physical Activity Questionnaire,[112] and expressed in 1000 metabolic equivalent of task (MET)-minutes in the past week. MET reflects the ratio of the associated metabolic rate for specific activities

divided by the resting metabolic rate, multiplied by the minutes performed activity. Prevalent medicated CVD or diabetes mellitus were assessed by standardized questionnaires.

Statistical analyses

Characteristics of DSM-IV diagnosis groups were compared by Kruskal–Wallis test (Monte Carlo method with 95% confidence intervals) for (non-normally distributed) quantitative variables, and by x^2 statistics for categorical variables. To evaluate which group differences accounted for significant overall *p* values, post hoc tests were done by Mann–Whitney U-tests with Bonferroni correction. Mann–Whitney U-tests were performed only between controls and the three psychopathology groups (and not between all groups) to reduce the type I error rate. Multivariate logistic regression analyses were conducted to assess the association between DSM-IV diagnosis (controls [i.e., reference group]/current pure anxiety/current pure MDD/current anxiety and MDD), anxiety (BAI) or depression severity (IDS-SR) group or antidepressant use group (none [i.e., reference group]/SSRI/TCA/other; all independent variables) and the presence of the metabolic syndrome (absent [i.e., reference group]/present; dependent variable). We adjusted for basic covariates (i.e., age, sex, years of education, clinic site and oral contraceptive use) in model 1, and additionally for lifestyle-related covariates (i.e., smoking status, alcohol use, and physical activity) in model 2. Since sex differences in the association between anxiety, depression and the metabolic syndrome have been observed before,[21, 43, 105] sex × DSM-IV diagnosis/anxiety severity/depression severity interaction terms were examined in model 2. Furthermore, CVD / diabetes × DSM-IV diagnosis / anxiety severity / depression severity interaction terms were tested within model 2. Differences in the mean number of prevalent metabolic components per DSM-IV diagnosis group, anxiety or depression severity group, and per antidepressant use group were assessed by x^2 statistics (using linear-by-linear tests for anxiety and depression severity). In multivariate logistic regression analyses, the associations were assessed between DSM-IV diagnosis, anxiety or depression severity or antidepressant use group (independent variables) and the presence of each single component of the metabolic syndrome (absent [i.e., reference group]/present; dependent variables). In analyses on symptom severity or antidepressant use, only those subjects with psychopathology were included. Statistical significance was inferred at $p < 0.05$. All statistical analyses were undertaken with SPSS 16.0 (IBM company, Chicago, Illinois, USA).

2.3 RESULTS

Table 1 shows the characteristics of the DSM-IV diagnosis groups. The mean age of the sample was 41.1 years (SD 13.2) and 35.5% were male.

Table 1. Characteristics according to DSM-IV diagnosis in 1846 subjects

Characteristics	Controls	Current pure anxiety	Current pure MDD	Current anxiety and MDD	*p* *
n	629	266	261	690	
Age	43.0 (27.0-55.0)	42.0 (29.8-53.0)	41.0 (30.0-51.0)	42.0 (31.0-51.0)	.58
Sex (% men)	38.3	38.0	39.1	30.6	.009
Years of education	12.0[a] (10.0-15.0)	11.0[b] (10.0-15.0)	11.0[b] (10.0-15.0)	11.0[b] (9.0-15.0)	<.001
Oral contraceptive use (%)	18.9	16.2	20.7	19.7	.55
Smoking status (%)					<.001
Never	36.7	25.6	26.8	27.0	
Former	36.2	31.6	31.0	26.1	
Current	27.0	42.9	42.1	47.0	
Alcohol use (%)					.009
<1 glasses/day	57.6	60.9	65.9	67.5	
1-2 glasses/day	23.7	23.7	18.8	17.2	
> 2 glasses/day	18.8	15.4	15.3	15.2	
Physical activity (in 1000 MET-minutes last week)	3.2[a] (1.6-4.9)	2.8[a] (1.4-4.8)	2.9[a] (1.2-4.6)	2.7[b] (1.2-4.8)	.02
Antidepressant use (%)					
Selective serotonin re-uptake inhibitors	0.6	14.7	24.9	32.9	<.001
Tricyclic antidepressants	0.2	2.6	3.1	4.9	<.001
Other antidepressants	0.2	4.5	9.6	12.3	<.001
Anxiety severity (BAI; %)					<.001
Normal	87.9	32.3	46.0	15.9	
Mild	10.5	35.3	32.6	29.1	
Moderate	1.4	24.4	17.6	32.6	
Severe	0.2	7.9	3.8	22.3	
Depression severity (IDS-SR; %)					<.001
None	80.3	21.8	9.6	4.2	
Mild	16.4	43.6	30.3	17.8	
Moderate	2.9	26.7	40.2	40.6	
Severe	0.5	6.4	15.7	24.8	
Very severe	0.0	1.5	4.2	12.6	

Table 1. Continued

Characteristics	Controls	Current pure anxiety	Current pure MDD	Current anxiety and MDD	*p**
n	629	266	261	690	
Metabolic syndrome (%)	19.4	22.2	21.8	22.5	.56
Abdominal obesity (≥ 88/102 cm, %)	28.6	29.3	32.6	36.7	.01
Hypertriglyceridemia (≥ 1.7 mmol/L, %)	18.6	21.8	21.5	21.3	.68
Low HDL-cholesterol (< 1.03/1.3 mmol/L, %)	11.1	14.3	15.7	15.9	.18
Triglyceride lowering or HDL cholesterol increasing medication use (%)	0.3	0.4	0.4	0.1	.88
Hypertension (≥ 130/85 mmHg, %)	61.9	57.5	54.8	57.0	.15
Antihypertensive medication use, %)	14.5	15.8	11.9	14.1	.63
Hyperglycemia (≥ 5.6 mmol/L, %)	21.3	23.4	21.5	21.3	.90
Antidiabetic medication use (%)	3.7	2.6	3.1	3.6	.85

Abbreviations: BAI, Beck Anxiety Inventory; HDL, high-density lipoprotein; DSM-IV, Diagnostic and Statistical Manual of mental disorders – fourth edition; IDS-SR, Inventory of Depressive Symptoms self-report; MDD, major depressive disorder; MET, metabolic equivalent of task.

Medians (interquartile ranges) or percentages are given, when appropriate.

**: p* by Kruskal-Wallis test for quantitative variables or x^2 statistics for categorical variables.

[abc]: Superscript letters that differ from the superscript letter of the control group indicate that the post hoc *p* values of those groups differ significantly ($p<0.05$ by Mann-Whitney test after Bonferroni correction).

Control subjects had more years of education, tended to use more alcohol and to smoke less than the anxiety or MDD groups. The prevalence of abdominal obesity tended to be higher among depressed or anxious subjects. There were no statistically significant differences in the prevalence of the metabolic syndrome or its components between diagnosis groups.

As shown in Table 2, no statistically significant associations between diagnosis group and the metabolic syndrome were found. Although the moderate and severe anxiety groups were associated with the presence of the metabolic syndrome in unadjusted analyses, no statistically significant associations were found in models 1 and 2. The odds for presence of the metabolic syndrome increased with increasing levels of depression severity, which was statistically significant for very severe depression as compared to the reference group (OR = 2.21, 95% CI: 1.06–4.64, $p = .04$ in model 2). Additional adjustment for antidepressant use did not alter these results (OR = 2.18, 95% CI: 1.04–4.60, $p = .04$). Prevalence of the metabolic syndrome was also significantly increased in TCA users as compared to the group not using antidepressants (OR = 2.30, 95% CI: 1.21–4.36, $p = .01$ in model 2), which was not affected by additional adjustment for depression severity (OR = 2.18, 95% CI: 1.15–4.15, $p = .02$). In Table 2, repeated analyses of model 2 including sex × DSM-IV diagnosis/anxiety severity/depression severity interaction terms, showed no statistically significant interaction (all $p > 0.6$). This suggests that associations do not significantly differ for men or women. CVD/diabetes × DSM-IV diagnosis/anxiety severity/depression severity interaction terms were also non-significant (all $p > 0.20$), suggesting similar associations among subjects with or without CVD or diabetes. Figure 1 shows that the mean number of metabolic syndrome components did not differ between DSM-IV diagnosis groups. The number of metabolic syndrome components increased over increased severity of both anxiety ($p < 0.001$) and depression ($p < 0.001$). Moreover, antidepressant use, and TCA use in particular, was associated with a higher mean number of metabolic syndrome components.

Table 3 shows the odds for the presence of each single metabolic syndrome component across DSM-IV diagnoses, anxiety or depression severity and antidepressant use groups in model 2. The unadjusted higher odds for having abdominal obesity in co-morbid current MDD and anxiety (OR = 1.44, 95% CI: 1.15–1.82, $p = .002$), as compared to controls, was no longer statistically significant in model 2. Nevertheless, the odds for abdominal obesity increased with increasing severity of anxiety symptoms. However, its association with low HDL cholesterol in model 1 (OR = 1.88, 95% CI: 1.14–3.10, $p = .01$) was reduced in model 2. In model 1, very severe depression was associated with abdominal obesity (OR = 2.37, 95% CI: 1.27–4.41, $p = .007$) and hypertriglyceridemia (OR = 2.11, 95% CI: 1.05–4.24, $p = .04$), but only the association with abdominal obesity

Table 2. The associations between DSM-IV diagnosis, severity, antidepressant use and the presence of the metabolic syndrome

		Crude			**Model 1**			**Model 2**		
	n	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
DSM-IV diagnosis										
Controls*	629	1.00			1.00			1.00		
Current pure anxiety	266	1.18	0.83-1.68	.34	1.10	0.75-1.60	.64	1.04	0.71-1.54	.83
Current pure MDD	261	1.16	0.82-1.65	.41	1.19	0.81-1.75	.37	1.12	0.76-1.66	.57
Current anxiety and MDD	690	1.20	0.92-1.57	.17	1.14	0.85-1.53	.39	1.08	0.80-1.46	.62
Anxiety severity (BAI)°										
Normal*	316	1.00			1.00			1.00		
Mild	380	1.21	0.82-1.77	.34	1.11	0.73-1.67	.63	1.09	0.72-1.66	.68
Moderate	336	1.68	1.15-2.46	.007	1.38	0.92-2.07	.12	1.37	0.90-2.07	.14
Severe	185	1.81	1.17-2.79	.008	1.46	0.91-2.33	.12	1.38	0.85-2.23	.19
Depression severity (IDS-SR)°										
None*	112	1.00			1.00			1.00		
Mild	318	1.51	0.83-2.74	.17	1.21	0.64-2.29	.55	1.24	0.65-2.35	.52
Moderate	456	1.44	0.81-2.56	.22	1.11	0.60-2.06	.74	1.09	0.58-2.04	.79
Severe	229	2.48	1.36-4.53	.003	1.65	0.87-3.14	.13	1.51	0.78-2.91	.22
Very severe	102	3.27	1.68-6.38	<.001	2.55	1.24-5.25	.01	2.21	1.06-4.64	.04
Antidepressant use°										
None*	730	1.00			1.00			1.00		
SSRI	328	1.35	0.99-1.84	.06	1.30	0.93-1.82	.13	1.22	0.87-1.72	.25
TCA	49	3.35	1.85-6.05	<.001	2.56	1.36-4.82	.004	2.30	1.21-4.36	.01
Other	110	1.21	0.75-1.96	.44	0.97	0.59-1.61	.92	0.97	0.58-1.63	.91

Abbreviations: BAI, Beck Anxiety Inventory; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of mental disorders– fourth edition; IDS-SR, Inventory of Depressive Symptoms self-report; MDD, major depressive disorder; OR, odds ratio by multivariate logistic regression analysis; SSRI, selective serotonin re-uptake inhibitor; TCA, tricyclic antidepressant.
Model 1: adjusted for age, sex, years of education, clinic site and oral contraceptive use.
Model 2: additionally adjusted for smoking status, alcohol use and physical activity.
*: Reference group to the subsequent groups.
°: Controls (n=629) were excluded from these analyses.

Table 3. The association between DSM-IV diagnosis, severity, antidepressant use and the presence of individual metabolic syndrome components

		Abdominal obesity			Hypertriglyceridemia			Low HDL cholesterol		
	n	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Model 2										
DSM-IV diagnosis										
Controls*	629	1.00			1.00			1.00		
Current pure anxiety	266	0.96	0.68-1.35	.80	1.10	0.76-1.61	.61	1.06	0.68-1.64	.81
Current pure MDD	261	1.23	0.88-1.72	.22	1.07	0.73-1.57	.72	1.12	0.73-1.72	.61
Current MDD and anxiety	690	1.28	0.99-1.66	.06	1.08	0.80-1.45	.62	1.00	0.71-1.40	.98
Anxiety severity (BAI)°										
Normal*	316	1.00			1.00			1.00		
Mild	380	1.16	0.82-1.66	.41	1.07	0.71-1.61	.75	1.12	0.70-1.79	.64
Moderate	336	1.40	0.97-2.00	.07	1.43	0.96-2.14	.08	1.47	0.92-2.33	.11
Severe	185	1.74	1.14-2.65	.01	1.33	0.83-2.13	.24	1.57	0.94-2.64	.09
Depression severity (IDS-SR)°										
Low*	112	1.00			1.00			1.00		
Mild	318	0.92	0.54-1.57	.76	1.06	0.57-1.94	.86	1.26	0.62-2.53	.52
Moderate	456	0.96	0.57-1.60	.87	1.09	0.61-1.97	.77	0.99	0.50-1.97	.98
Severe	229	1.52	0.88-2.63	.13	1.37	0.73-2.57	.32	1.34	0.65-2.75	.43
Very severe	102	2.30	1.22-4.34	.01	1.72	0.85-3.52	.14	1.20	0.53-2.67	.67
Antidepressant use°										
None*	730	1.00			1.00			1.00		
SSRI	328	1.12	0.83-1.51	.45	1.27	0.91-1.78	.17	1.06	0.74-1.53	.75
TCA	49	1.88	1.00-3.54	.05	2.57	1.36-4.84	.004	1.40	0.68-2.89	.36
Other	110	1.27	0.81-1.97	.30	1.27	0.78-2.08	.33	0.85	0.46-1.57	.60

Abbreviations: BAI, Beck Anxiety Inventory; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of mental disorders – fourth edition; HDL, high-density lipoprotein; IDS-SR, Inventory of Depressive Symptoms self-report; MDD, major depressive disorder; OR, odds ratio by multivariate logistic regression analysis; SSRI, selective serotonin re-uptake inhibitor; TCA, tricyclic antidepressant.
Model 2: adjusted for age, sex, years of education, clinic site, oral contraceptive use, smoking status, alcohol use and physical activity.
*: Reference group to the subsequent groups.
°: Controls (n=629) were excluded from these analyses.

Table 3. Continued

	n	Hypertension OR	95% CI	*p*	Hyperglycemia OR	95% CI	*p*
Model 2							
DSM-IV diagnosis							
Controls*	629	1.00			1.00		
Current pure anxiety	266	0.97	0.69-1.36	.86	1.09	0.74-1.59	.68
Current pure MDD	261	0.75	0.54-1.05	.10	1.12	0.76-1.66	.57
Current MDD and anxiety	690	0.90	0.69-1.17	.43	1.09	0.81-1.47	.58
Anxiety severity (BAI)°							
Normal*	316	1.00			1.00		
Mild	380	0.97	0.69-1.37	.87	0.87	0.58-1.30	.49
Moderate	336	1.06	0.74-1.51	.77	1.04	0.69-1.55	.86
Severe	185	1.41	0.91-2.18	.12	1.09	0.67-1.76	.73
Depression severity (IDS-SR)°							
Low*	112	1.00			1.00		
Mild	318	1.00	0.61-1.66	1.00	0.91	0.50-1.66	.76
Moderate	456	0.90	0.55-1.46	.66	0.96	0.54-1.71	.89
Severe	229	0.86	0.50-1.47	.57	0.99	0.53-1.84	.97
Very severe	102	0.94	0.50-1.77	.84	1.65	0.80-3.37	.17
Antidepressant use°							
None*	730	1.00			1.00		
SSRI	328	0.96	0.71-1.30	.78	1.01	0.71-1.42	.98
TCA	49	2.29	1.07-4.91	.03	1.38	0.70-2.71	.35
Other	110	1.35	0.83-2.21	.23	0.69	0.40-1.18	.18

Abbreviations: BAI, Beck Anxiety Inventory; CI, confidence interval; IDS-SR, Inventory of Depressive Symptoms self-report; MDD, major depressive disorder; OR, odds ratio by multivariate logistic regression analysis; SSRI, selective serotonin re-uptake inhibitor; TCA, tricyclic antidepressant.

Model 2: adjusted for age, sex, years of education, clinic site, oral contraceptive use, smoking status, alcohol use and physical activity.

*: Reference group to the subsequent groups.

°: Controls (n=629) were excluded from these analyses.

persisted in model 2. These results were not significantly altered by additional adjustment for antidepressant use (data not shown). TCA users demonstrated higher odds for having abdominal obesity, hypertriglyceridemia and hypertension, as compared to non-users of antidepressants. Additional adjustment for depression severity did not alter these results significantly (data not shown).

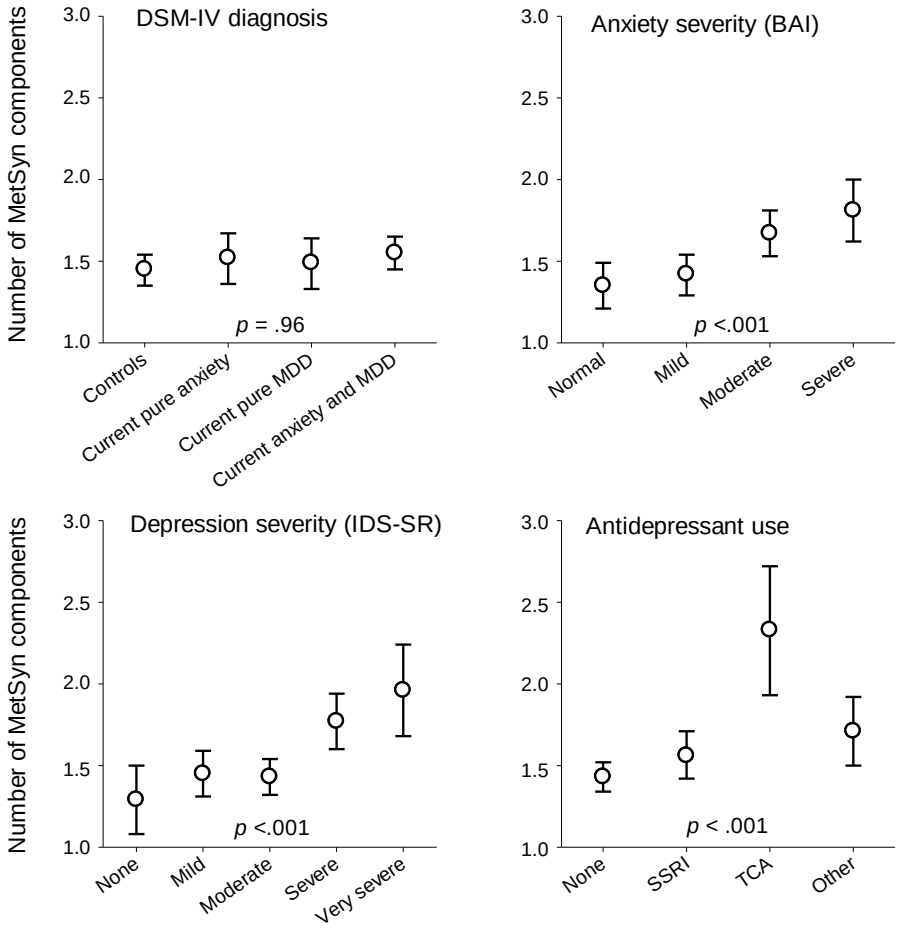

Figure 1. Dots indicate mean number of metabolic syndrome (MetSyn) components; bars indicate 95% confidence intervals. Analyses on DSM-IV diagnosis are based on the complete sample (n=1846). Analyses on anxiety severity group, depression severity group or antidepressant use are based on the sample excluding controls (n=1217). *p* by x^2 statistics. x^2 linear-by-linear test was applied for anxiety and depression severity.

2.4 DISCUSSION

In this large cohort study, the prevalence of the metabolic syndrome was uniformly not increased in subjects with either MDD or an anxiety disorder, as compared to controls. However, subjects with more severe depressive symptoms did have increased metabolic syndrome odds, which were mainly driven by increased abdominal adiposity, lower HDL cholesterol levels and hypertriglyceridemia. TCA users were also at increased odds for the metabolic syndrome, which was not only determined by the increased prevalence of abdominal obesity and hypertriglyceridemia, but also that of hypertension.

The finding that metabolic syndrome prevalence was increased in subjects with severe psychopathology, but not among diagnosis groups, indicates that symptom severity is more differentiating than diagnostic DSM-IV categories. The high co-morbidity between depression and anxiety[113,114] supports this indication. This implies that the use of dimensional instruments is a more sensitive approach, and therefore may be more helpful in the understanding of the complex relationship between psychopathology and the metabolic syndrome. This is supported by a study by Vogelzangs et al.,[25] in which they did not find an association between the metabolic syndrome and a dichotomous depression standard, but did report an association with a severity scale.

Abdominal adiposity, hypertriglyceridemia and low HDL cholesterol were the components that were increased in subjects with psychopathology. Previous studies also found these three components,[23,24,26-29,35,46-48,133,134,138,140,142] but rarely hypertension[20,21,102] or hyperglycemia,[24,47,73,138,140] to be more prevalent in subjects with anxiety or depression. This suggests that abdominal adiposity and dyslipidemia largely account for the increased metabolic syndrome odds in anxiety and depression, which is in line with a factor analytical study that demonstrated that lipids and abdominal adiposity form a distinct cluster within the metabolic syndrome.[115] These findings add to the general debate on whether the whole metabolic syndrome is more than the sum of its parts, and consequently on its usefulness as an unambiguous cluster in research and clinical practice,[116] at least in affective disorders.

Several possible explanations exist for the increased odds for abdominal obesity and dyslipidemia in subjects with more severe psychopathology. First, this might be a reflection of unfavorable lifestyle habits that are associated with anxiety and depression.[117] However, the lifestyle factors smoking, alcohol use and physical activity that were adjusted for in the present study, could only partly explain the associations. Unfortunately, we were unable to take dietary factors into account, while depression is associated with poor diets rich in carbohydrates and saturated fat.[118] A second -common causal- pathway might be the upregulation of the hypothalamic-pituitary-adrenal (HPA) axis. HPA axis perturbations may lead to psychopathology[67,119] and to visceral adipose tissue accumulation, which subsequently, through

inflammatory factor secretion by adipose tissue, might induce dyslipidemia.[120] Depression-related inflammation,[155,156] which might be enhanced by reduced levels of anti-inflammatory factors such as adiponectin in depression,[121] could also aggravate metabolic alterations in psychopathology. Finally, hyperactivity of the autonomic nervous system,[122] or another third factor, might underlie the metabolic dysregulation in severe psychopathology.

Tricyclic antidepressant users demonstrated a distinct metabolic pattern, likely induced by TCA side effects. Next to the antihistaminergic effects that induce weight gain[75,76] and subsequently dyslipidemia,[143] TCA use is also associated with hypertension[62] through peripheral α1 adrenergic receptor agonism.[63] As metabolic syndrome disturbances in TCA users and that in subjects with severe psychopathology overlap, these findings may be linked: TCA users are, at least before starting medication, more severely depressed than current SSRI users. However, TCA use remained an independent predictor of metabolic syndrome alterations after adjustment for depression severity.

The first limitation of our study is the cross-sectional design, which does not allow us to make causal inferences on whether psychopathology precedes metabolic alterations or vice versa. Second, the number of TCA users was relatively small, which could have led to some imprecision of effect estimates of the actual associations between TCA use and metabolic syndrome alterations. Strengths of our study are the large, psychopathology-based sample, the assessment of both DSM-IV diagnoses and disease severity scores, and the possibility to reliably illuminate the role of antidepressant use and individual metabolic syndrome components.

In conclusion, prevalence of the metabolic syndrome was not generally increased in large groups of subjects with anxiety and depressive disorders. However, the most severely depressed persons and TCA users had increased odds for the metabolic syndrome, which was driven by the abdominal adiposity and dyslipidemia components. To prevent CVD and diabetes mellitus, we recommend to screen for these metabolic syndrome components, especially in severely depressed patients, or when considering the start or continuation of TCA pharmacotherapy.

Associations between serum lipids and major depressive disorder

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Journal of Clinical Psychiatry 2010, 71 (6): 729-736

ABSTRACT

Background
Several studies have suggested an association between lipids or lipoproteins and depression, but findings are contradictory. However, previous studies did not always take into consideration potentially mediating factors or heterogeneity of symptoms, which may clarify contradicting findings.

Methods
We compared levels of serum total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol and triglyceride between 761 subjects with current major depressive disorder (MDD) (Composite International Diagnostic Interview, based on the DSM-IV), 1071 subjects with remitted MDD, and 629 controls, aged 18 to 65 years. Subjects participated in the baseline assessment of the Netherlands Study of Depression and Anxiety, which lasted from September 2004 to February 2007. We studied the impact of adjustment for sociodemographics, lifestyle-related covariates, and antidepressant use, and examined the association between specific psychopathological characteristics and lipid/lipoprotein levels.

Results
HDL cholesterol level was lower (p = .007) and triglyceride level was higher (p = .001) in current MDD versus remitted MDD and controls. After adjustment for level of education, body mass index (BMI), smoking status, and alcohol use, dissimilarities lost statistical significance. Depression severity, co-morbid dysthymia, and melancholic and atypical features were all associated with lipids/lipoproteins, but most associations attenuated after adjustment for covariates, especially BMI. The association between melancholic features and lower HDL cholesterol (p = .038), and between atypical depression and higher total and LDL cholesterol (p = .004 and p = .002, respectively) persisted after full adjustment.

Conclusions
Adverse lipoprotein patterns were found in patients with MDD. The fact that these associations diminished after adjustment for lifestyle-related factors, especially BMI, suggests that the unfavorable lipid/lipoprotein pattern among depressed subjects is mainly secondary to lifestyle-related factors. However, melancholic features were independently associated with lower HDL cholesterol, and atypical depression was independently associated with higher total and LDL cholesterol.

3.1 INTRODUCTION

Serum lipids and lipoproteins are argued to be associated with depression, but findings regarding this link have been inconsistent. Most studies have found lower total cholesterol in subjects with depressive symptoms versus controls.[34-40] Other studies have reported higher total cholesterol[34] or found no differences.[51-54]Levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride were assessed in relation to depression or depressive complaints as well,[32,35,36,39,40,123,124] but less extensively. Again, contradictory results were obtained.

Several possible explanations exist for these mixed findings. First, study designs differed widely. For example, various depression assessment scales were used, and the universal gold standard to identify clinical depression, the Diagnostic and Statistical Manual of mental disorders (DSM), was infrequently applied.[31,35,36,123,124] Furthermore, some samples were small,[36] contained a small proportion of depressed subjects,[31] covered a restricted age range, such as elderly[37,42,43,51,53] or adolescents,[37] or included either men[31,34,38-40] or women.[37] This reduces comparability of studies and generalizability of results to clinical practice.

Second, the inconsistencies in previous research might be due to the fact that major depressive disorder (MDD) is often approached as a homogeneous disorder. Therefore, its range of psychopathological characteristics has been ignored. Depressed subjects differ concerning depression severity, and often display co-morbid anxiety disorders or dysthymia. Also, suicidality regularly accompanies depression, which might also be associated with lipid/lipoprotein deviations.[41] Furthermore, some depressed subjects exhibit atypical or melancholic features, which may be more strongly associated with lipid/lipoprotein alterations.

A third explanation for the contradictory results is the potential mediation of lifestyle in the association between depression and lipids/lipoproteins. In previous studies, body mass index,[37,38,40,123,124] smoking behavior,[40] and alcohol use[38,40] were seldom taken into account, whereas depressed subjects on average have a higher body mass index,[125] are more likely to smoke,[126,127] and use either less[128] or more alcohol[74] compared to non-depressed subjects. Moreover, obesity,[129] smoking,[75] and alcohol use[130] modify lipid/lipoprotein metabolism, and are important anchor points in the management of an unhealthy lipid profile.[97] Another possible confounder might be antidepressant use, as some are known to induce antihistaminergic side effects: for example, weight gain.[58,131]

To our knowledge, this is the largest sample in which the association between lipids/lipoproteins and DSM-diagnosed MDD is studied. Our sample includes men and women over a broad age range. We distinguish between controls, those with a remitted MDD, and those with a current MDD, since residual symptoms in persons with a remitted depression are commonly found,[132] and, therefore, we expect the associations in our study to be graded over the control, remitted depression, and current depression groups. By investigating the role of

psychopathological characteristics, lifestyle, and antidepressant use, we aim to elucidate aspects that mainly influence the association between lipids/lipoproteins and depression.

3.2 METHODS

Subjects

Subjects participated in the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA), which lasted from September 2004 to February 2007 and included 2981 persons aged 18 to 65 years. Subjects were recruited from community, primary care, and mental health care in 5 Dutch regions (Amsterdam, Emmen, Groningen, Heerenveen, Leiden). The baseline assessment comprised a face-to-face interview, written questionnaires, and biologic measurements. The detailed study design is described elsewhere.[95] The study protocol was approved by the Ethical Review Board of each participating center, and all subjects signed informed consent at baseline assessment.

For the current analyses, 3 groups were included, i.e., subjects with an MDD diagnosis in the past month (i.e., "current MDD," n=802), subjects with an MDD diagnosis before the last month (i.e., "remitted MDD," n=1123), and those who never had a depressive or anxiety disorder (i.e., "controls," n=652), resulting in a preliminary sample size of 2577. Excluding cases with one or more missing values on total, HDL, or LDL cholesterol, triglyceride, or depression severity (see below) resulted in a sample of 2461 subjects (i.e., 761 with current MDD, 1071 with remitted MDD, and 629 controls).

Major depressive disorder

Major depressive disorder (MDD) was diagnosed according to the Diagnostic and Statistical Manual for mental disorders, fourth edition (DSM-IV) criteria using the Composite International Diagnostic Interview (CIDI).[108]

Psychopathological characteristics

For subjects with current MDD, various psychopathological characteristics were assessed. Depression severity was assessed by the 30-item Inventory of Depressive Symptoms self-report (IDS-SR),[133] ranging from 0 to 84. Atypical depression was coded as "absent/present," as done before,[134] based on the following IDS-SR items: a score of 0, 1, or 2 on item 8 for mood reactivity as well as two or more of the following: a score of 3 on item 28 for leaden paralysis; a score of 2 or 3 on item 12 or item 14 for weight gain; a score of 2 or 3 on item 4 for hypersomnia; a score of 3 on item 27 for interpersonal sensitivity. Similarly, the presence of melancholic features was coded as "absent/present," with the following criteria: a score of 2 or 3 on item 19 for capacity for pleasure, or 3 on item 8 for mood responsiveness, and three or more of the following: a score of 2 or 3 on item 10 for quality of mood; a score of 0 on item 9a for morning mood, a

score of 3 on item 3 for early awakening; a score of 2 or 3 on item 23 or 24 for psychomotor changes; a score of 2 or 3 on item 11 or 13 for anorexia; a score of 2 or 3 on item 16 for feelings of guilt. The presence of co-morbid current (past month) anxiety disorder (social phobia, agoraphobia with or without panic disorder, or generalized anxiety disorder) and co-morbid current dysthymia was identified by the CIDI. Suicide attempt in history (absent/present) was determined by a single question.[135]

Lipids/lipoproteins

Blood samples were taken around 8:47 AM (SD=0.20 min), after a mean 11 h 15 minutes (SD=111 min) overnight fasting period. The samples were transported to a laboratory within one hour. Levels of total, LDL, and HDL serum cholesterol as well as triglyceride were determined according to routine laboratory methods in all 5 participating laboratories. All methods were standardized through periodical external quality assessments by the Dutch Foundation for Quality Assessment in Clinical Laboratories. The maximum intra-assay variation coefficients of the methods were 0.8% for total cholesterol, 0.8% for LDL cholesterol, 1.0% for HDL cholesterol, and 1.5% for triglycerides. The maximum inter-assay variation coefficients were 1.7% for total cholesterol, 1.2% for LDL cholesterol, 1.3% for HDL cholesterol, and 1.8% for triglycerides.

Covariates

Sociodemographic variables (age, sex, level of education), smoking status (never/former/current), alcohol use (mean of 0/1–2/>2 glasses per day), presence of cardiovascular disease (CVD) or diabetes, and use of oral anticonceptives were assessed by standardized questionnaires. Level of education was classified as basic (i.e., elementary education or less), intermediate (i.e., lower or intermediate vocational education), or high (i.e., higher vocational, college, or university education). CVD was defined as the self-reported cardiac infarct, angina pectoris, heart failure, heart rhythm disorders, or cardiac surgery. Diabetes diagnosis was identified through self-report and/or the present use of antidiabetics. Use of antidiabetics, lipid-lowering medication (ATC code[111] C10) and antidepressants (tricyclic antidepressant [TCA]/selective serotonin re-uptake inhibitor [SSRI]/other) in the past month was registered by observation of drug containers brought in. Antidepressants were subdivided into SSRI (ATC code N06AB), TCA (ATC code N06AA), and other antidepressants (monoamine oxidase inhibitors N06AG, nonselective N06AF, and antidepressants classified as N06AX). Height and weight were measured to calculate body mass index (BMI). Because a nonlinear association between depressive symptoms and BMI is conceivable, BMI was divided into 4 categories (< 18.5, 18.5–24.99, 25–29.99, and ≥ 30 kg/m^2).[136]

Statistical analyses

Differences between study groups were analyzed by analysis of variance (ANOVA) for quantitative variables, or x^2 linear-by-linear test for categorical variables. Lipid and lipoprotein data were naturally log transformed because of their positively skewed distribution, and geometric mean values are presented. Potential nonlinear (i.e., curved) associations between depression and lipids/lipoproteins were explored by plotting mean IDS-SR total score and the prevalence of diagnoses (current MDD, lifetime MDD, controls) by lipid/lipoprotein quintiles. Correlations between overall lipid/lipoprotein levels were calculated by Pearson's correlation coefficient. Geometric mean values (and 95% confidence intervals [CIs]) were calculated by analysis of covariance (ANCOVA), to compare lipid/lipoprotein levels (dependent variables) between study groups (factor variable), adjusting for basic sociodemographic and health covariates (i.e., age, sex, level of education, use of lipid-lowering medication, use of oral anticonceptives (yes/no), CVD, and diabetes) in model 1, adjusting for additional lifestyle-related covariates (i.e., basic covariates and smoking status, alcohol use, and BMI categories) in model 2, and additionally adjusting for use of antidepressants in model 3. Cohen's *d* (the difference in group geometric means, divided by their pooled standard deviation) was calculated as a measure of effect size. Linear regression analyses were used to assess associations between IDS-SR total score and other psychopathological characteristics (as separate independent variables) and lipid/lipoprotein levels (as continuous dependent variables) after basic (model 1) and additional (model 2 and model 3) adjustment in subjects with current MDD. In additional analyses, we excluded subjects using lipid-lowering medication and subjects with CVD or diabetes, and we additionally adjusted for laboratory site. Statistical significance was inferred at $p < .05$. All statistical analyses were undertaken with SPSS 14.0 (SPSS Inc., Chicago, Illinois, USA).

3.3 RESULTS

Table 1 shows the characteristics of the study groups. The mean age of the sample was 41.9 years (SD = 12.9) and 33.1% were male. Subjects with current or remitted depression were less educated than controls but did not differ statistically in age, sex, or diabetes and CVD prevalence. Subjects with a current MDD had a higher BMI, and tended to use less alcohol than the other two groups. Subjects with a remitted MDD demonstrated a higher depression severity score (IDS-SR) as compared to controls but a lower score than subjects with a current MDD.

Because the plotted distribution pattern of mean IDS-SR total score and of depression diagnoses across quintiles of lipid/lipoprotein levels did not indicate curved associations (data not shown), all subsequent analyses were based on linear models. Correlations between lipid/lipoprotein levels ranged from –.14 (for LDL and HDL cholesterol) through .88 (for total and LDL cholesterol). Table 2 presents lipid/lipoprotein levels across study

Table 1. Characteristics according to study group for 2461 subjects

Characteristics n	Current MDD 761	Remitted MDD 1071	Controls 629	*p**
Age	41.7 (40.9-42.6)	42.4 (41.6-43.1)	41.2 (40.1-42.4)	.18
Sex (% men)	33.6	29.5	38.6	.08
Level of education (%)				<.001
Basic	10.1	5.2	3.5	
Intermediate	64.9	56.6	52.8	
High	25.0	38.2	43.7	
Body Mass Index (%)				<.001
< 18.5	3.0	1.8	2.2	
18.5 – 24.99	43.6	52.0	54.4	
25.0 – 29.99	30.9	30.8	29.9	
≥ 30.0	22.5	15.4	13.5	
Smoking status (%)				.97
Never	27.1	23.7	36.4	
Former	27.7	35.6	36.2	
Current	45.2	40.7	27.3	
Alcohol use (%)				.012
<1 glasses/day	66.5	61.3	57.9	
1-2 glasses/day	16.8	23.8	23.7	
>2 glasses/day	16.7	14.9	18.4	
Use of oral anticonceptives (%)	17.6	17.6	18.9	.54
Antidepressant medication use (%)				
Selective serotonin re-uptake inhibitors	30.6	19.8	0.6	<.001
Tricyclic antidepressants	3.9	3.5	0.2	<.001
Other antidepressants	10.8	6.3	0.2	<.001
Diabetes (%)	8.5	6.9	6.2	.09
Cardiovascular disease (%)	6.2	6.2	5.6	.65
Use of lipid lowering medication (%)	8.5	6.5	6.0	.06
Depression severity (IDS-SR)	35.9[a] (35.1-36.7)	19.8[b] (19.1-20.4)	8.6[c] (8.0-9.2)	<.001
Melancholic features *(%)*	17.3	1.5	0.0	<.001
Atypical features *(%)*	27.2	6.8	1.4	<.001
Co-morbid anxiety disorder (%)	62.9	33.1	0.0	<.001
Co-morbid dysthymia (%)	28.5	2.3	0.0	<.001
History of suicide attempt (%)	23.1	12.0	1.4	<.001

Abbreviations: IDS-SR, Inventory of Depressive Symptoms self-report; MDD, major depressive disorder.
Means (95% confidence intervals) or percentages are given, when appropriate.
*: overall *p* by analysis of variance for quantitative variables or x^2 linear-by-linear test for categorical variables.
[abc]: Superscript letters which are dissimilar between groups indicate that the post hoc *p* values of corresponding groups differ significantly ($p<0.05$ after Bonferroni correction).

Table 2. Serum lipid and lipoprotein levels (mg/dL) in controls and subjects with a remitted or current major depressive disorder.

	Current MDD		Remitted MDD		Controls		*p*
n	761		1071		629		
	Mean	95% CI	Mean	95% CI	Mean	95%CI	
Total cholesterol							
Crude	193.3	190.5-196.1	193.7	191.3-196.1	191.4	188.4-194.5	.51
Model 1	193.8	191.3-196.4	193.0	190.9-195.1	191.9	189.2-194.7	.61
Model 2	193.3	190.9-195.9	192.9	190.8-195.0	192.6	189.9-195.4	.93
Model 3	192.2	189.7-194.7	192.7	190.6-194.8	194.4	191.5-197.3	.53
LDL cholesterol							
Crude	119.7	117.0-122.3	117.2	114.9-119.5	115.6	112.9-118.4	.12
Model 1	119.6	117.2-122.1	117.0	115.0-119.0	116.0	113.4-118.6	.11
Model 2	118.9	116.5-121.3	117.0	115.0-119.0	116.9	114.3-119.5	.42
Model 3	117.9	115.6-120.4	116.8	114.8-118.7	118.4	115.7-121.2	.57
HDL cholesterol							
Crude	59.2[a]	58.0-60.3	61.4[b]	60.4-62.4	61.4[b]	60.1-62.7	.007
Model 1	59.8	58.8-60.9	60.7	59.8-61.6	61.7	60.5-62.9	.08
Model 2	60.7	59.7-61.7	60.7	59.8-61.5	60.7	59.7-61.8	.99
Model 3	60.6	59.6-61.6	60.7	59.8-61.5	60.8	59.7-62.0	.97
Triglycerides							
Crude	104.8[a]	101.1-108.5	97.1[b]	94.1-100.1	95.7[b]	91.9-99.7	.001
Model 1	103.3[a]	99.9-106.9	97.9[b]	95.2-100.7	95.8[b]	92.3-99.4	.008
Model 2	101.0	97.8-104.3	98.3	95.7-100.9	97.9	94.6-101.4	.34
Model 3	100.1	96.9-103.4	98.1	95.5-100.7	99.3	95.7-102.9	.62

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDD, major depressive disorder.
Geometric means are presented, based on estimated marginal means, calculated by analysis of covariance (ANCOVA).
Model 1: adjusted for age, sex, level of education, use of lipid lowering medication, use of oral anticonceptives, CVD and diabetes.
Model 2: additionally adjusted for smoking status, alcohol use and BMI categories.
Model 3: additionally adjusted for antidepressant use.
[ab]: Superscript letters which are dissimilar between groups indicate that in post hoc analyses groups differ significantly ($p<0.05$ after Bonferroni correction).
To convert total, LDL or HDL cholesterol values from mg/dL to mmol/L, divide by 38.7. To convert triglyceride values from mg/dL to mmol/L, divide by 88.6.

groups. In crude analyses, total and LDL cholesterol levels did not differ significantly between groups. Lower HDL cholesterol level was found in the current MDD versus the remitted MDD and control groups (post hoc *p* values after Bonferroni correction were .01 and .03, respectively), with a small effect size for current MDD versus controls (*d* = –0.137). Furthermore, higher triglyceride levels in the current MDD group versus the remitted MDD and control groups were found (post hoc *p* values after Bonferroni correction were .005 and .003, respectively), with a small effect size for current MDD versus controls (*d* = 0.178). Subjects with remitted MDD and controls did not differ significantly with regard to HDL cholesterol or triglyceride levels. Adjustment for covariates in model 1 reduced HDL cholesterol differences between groups to statistically non-significant. Both education level and BMI as the only covariate already reduced these differences to statistically non-significant. Differences in triglyceride levels between study groups in crude analyses (*p* = .001) and in model 1 (*p* = .008) were not found after additional adjustment in model 2 (*p* = .34). BMI largely explained the differences in triglyceride levels between groups. Additional adjustment for antidepressant use in model 3 did not change associations importantly.

Associations between psychopathological characteristics (i.e., independent variables) and lipids/lipoproteins (i.e., continuous dependent variables) were assessed in currently depressed subjects (see Table 3). Crude associations are not shown because associations did not change importantly after adjustment for covariates in model 1. In model 1, statistically significant, positive associations were found between IDS-SR total score and total cholesterol (β = .073, *p* = .025), LDL cholesterol (β = .082, *p* = .015), and triglyceride levels (β = .102, *p* = .003), and an inverse association was seen with HDL cholesterol (β = –.118, *p* = .001). However, associations were no longer statistically significant after additional adjustment in model 2. Again, BMI as the only covariate already resulted in statistically non-significant associations. The presence of atypical depression (n=207; 27.,2% of the currently depressed) was associated with higher levels of total and LDL cholesterol as well as triglycerides and lower HDL cholesterol levels. The associations between atypical features and total (β = .096, *p* = .004) and LDL cholesterol (β = .102, *p* = .002) remained statistically significant after full adjustment in model 3. Corresponding effect sizes for current MDD with versus without atypical features were small to modest (*d* = 0.234 and *d* = 0.253, respectively). Associations between melancholic features (n=131; 17.2% of the currently depressed) and triglycerides and inverse HDL cholesterol found in model 1, were somewhat attenuated in model 2 and model 3. The association between melancholic features and HDL cholesterol remained statistically significant (β = –.066, *p* = .038), with a small to modest effect size for current MDD with versus without melancholic features (*d* = –0.203). Other psychopathological characteristics (co-morbidity of dysthymia or anxiety or

Table 3. Associations between lipids/lipoproteins and psychopathological characteristics in 761 subjects with a current major depressive disorder

Psychopathological characteristics		Total cholesterol		LDL cholesterol		HDL cholesterol		Triglycerides	
	n*	β	*p*	β	*p*	β	*p*	β	*p*
Model 1									
Depression severity (IDS-SR)		.073	.025	.082	.015	-.118	.001	.102	.003
Atypical features	207	.110	.001	.122	<.001	-.075	.031	.067	.05
Melancholic features	131	.047	.15	.052	.13	-.092	.008	.074	.03
Co-morbid anxiety disorder	479	.006	.84	-.018	.60	-.008	.82	.002	.99
Co-morbid dysthymia	217	.019	.55	.006	.86	-.062	.07	.083	.014
Suicide attempt in history	176	.053	.11	.039	.24	.014	.69	.027	.44
Model 2									
Depression severity (IDS-SR)		.063	.06	.056	.10	-.034	.28	.045	.17
Atypical features	207	.107	.001	.116	.001	-.038	.24	.031	.34
Melancholic features	131	.048	.14	.051	.13	-.069	.029	.060	.07
Co-morbid anxiety disorder	479	-.002	.95	-.028	.40	.017	.58	-.020	.54
Co-morbid dysthymia	217	.014	.66	.002	.94	-.035	.27	.057	.08
Suicide attempt in history	176	.050	.13	.033	.33	.040	.21	.007	.84
Model 3									
Depression severity (IDS-SR)		.047	.16	.036	.29	-.031	.34	.036	.29
Atypical features	207	.096	.004	.102	.002	-.035	.28	.023	.48
Melancholic features	131	.035	.29	.034	.31	-.066	.038	.050	.13
Co-morbid anxiety disorder	479	-.007	.83	-.034	.30	.019	.54	-.023	.47
Co-morbid dysthymia	217	.007	.83	-.007	.84	-.033	.30	.053	.10
Suicide attempt in history	176	.045	.17	.027	.41	.040	.20	.004	.90

β coefficients indicate the standardised beta by linear regression analyses
Abbreviations: HDL, high-density lipoprotein; IDS-SR, Inventory of Depressive Symptoms self-report; LDL, low-density lipoprotein.
*: n refers to the number of the 761 currently depressed subjects with the concerning psychopathology characteristic.
Model 1: adjusted for age, sex, use of lipid lowering medication, use of oral anticonceptives, education level, CVD and diabetes.
Model 2: additionally adjusted for smoking status, alcohol use and BMI categories.
Model 3: additionally adjusted for antidepressant use.

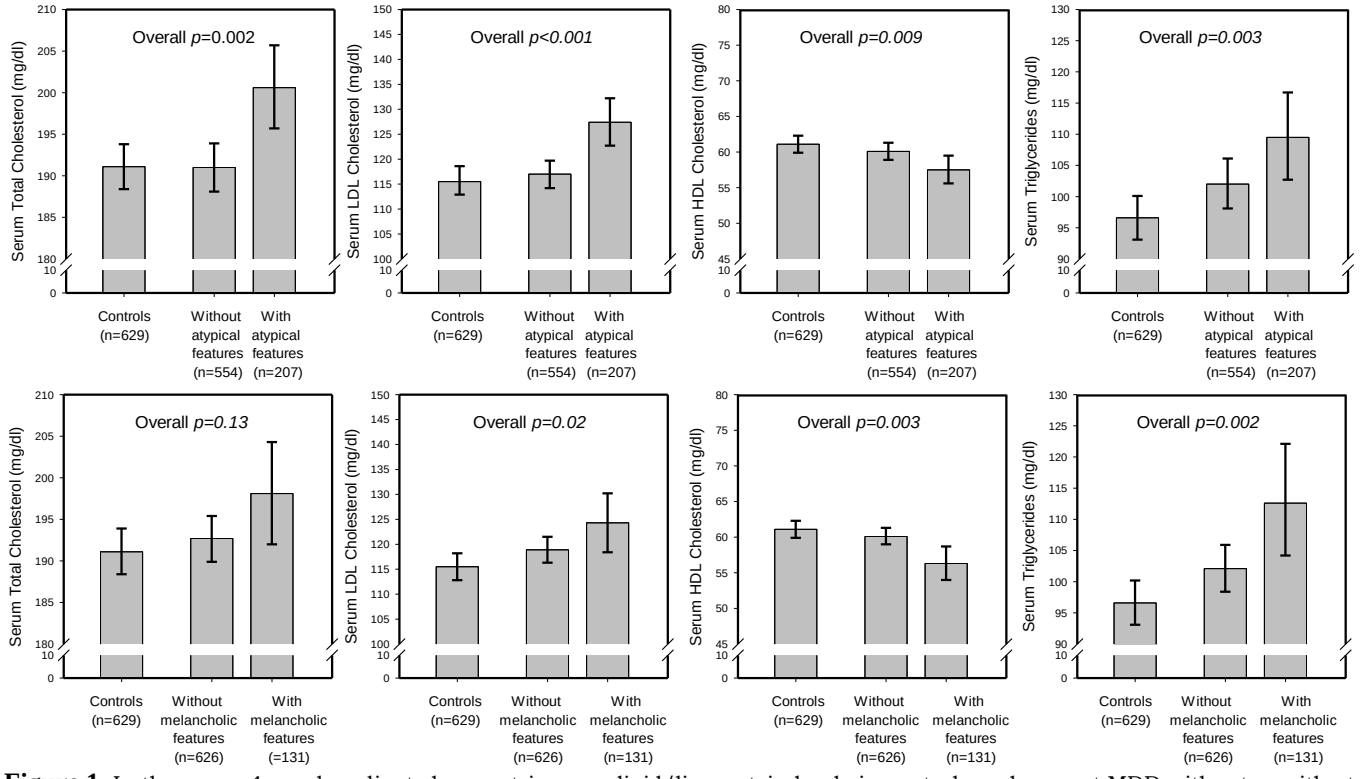

Figure 1. In the upper 4 graphs adjusted geometric mean lipid/lipoprotein levels in controls and current MDD without or with atypical features are presented. In the lower 4 graphs adjusted geometric mean lipid/lipoprotein levels in controls and current MDD without or with melancholic features are presented.

Bars indicate geometric means, basically adjusted for age, sex (male / female), use of lipid lowering medication (yes / no), use of oral anticonceptives (yes / no), education level (basic / intermediate / high), CVD (yes / no) and diabetes (yes / no) in analysis of covariance (ANCOVA); error bars indicate 95% confidence intervals.

suicide attempt in history) were not associated with lipid/lipoprotein levels after additional adjustment (model 2 and model 3).

Figure 1 shows that geometric mean total and LDL cholesterol levels were higher and HDL cholesterol and triglyceride levels were lower in MDD with atypical features versus MDD without atypical features or controls. Also, geometric mean LDL cholesterol and triglyceride levels were higher and HDL cholesterol levels were lower in MDD with melancholic features, compared to MDD without melancholic features or controls. Additional analyses that excluded subjects using lipid-lowering medication or those suffering from CVD or diabetes and analyses that were additionally adjusted for laboratory site showed largely similar results (data not shown).

3.4 DISCUSSION

This large-scale study showed that currently depressed subjects had significantly lower mean HDL cholesterol and higher triglyceride levels compared to subjects with a remitted depression and healthy controls. No differences were found for total and LDL cholesterol levels. Although control subjects and those with remitted and current depression displayed a graded increase in depression severity scores, we did not find graded differences in lipid levels among study groups. Among currently depressed subjects, lipids/lipoproteins were especially unfavorable among those with high depression severity and atypical and melancholic features. Differences in lipids/lipoproteins between study groups and most associations with psychopathology characteristics attenuated after adjustment for smoking status, alcohol use and, especially, BMI. Yet, atypical features remained associated with higher levels of total and LDL cholesterol, and melancholic features remained associated with lower HDL cholesterol levels, even after additional adjustment for antidepressant use.

Equality of total cholesterol among study groups is in line with some previous studies,[47,123,124,137] but contradicts others.[31,34-40] However, we found high levels of total cholesterol in atypical depression only, and insufficient attention for depression heterogeneity in previous research possibly accounts for these discrepant results. Also, variability in study design might have contributed to these varying results. Our finding of lower HDL cholesterol levels in depression is in line with previous findings.[32,36] However, one study[124] found higher instead of lower HDL cholesterol levels and lower instead of higher triglyceride levels in major depressed subjects compared to controls. The fact that their depressed participants visited a general health screening unit, and consequently might have been preoccupied with health, might explain these findings. Furthermore, their sample size was small (n=107), and participants were of Taiwanese origin, which might account for cultural and other differences (e.g., in genetic background and diet) compared to our study. In line with our findings, depression severity has previously been associated with higher total cholesterol level.[33]

Only few studies investigating lipids/lipoproteins in depression adjusted analyses for factors like smoking,[40] alcohol use,[38,40] and BMI.[37,38,40,123,124] One study[123] that adjusted for BMI found no differences in lipids/lipoproteins between depressed and non-depressed elderly. Likewise, an association between low total cholesterol level and more severe depressive complaints was attenuated after adjustment for lifestyle-related factors.[137] Combined with the attenuation in our study of associations between lipids/lipoproteins and depression after adjustment for smoking, alcohol use, and BMI, these findings suggest that this association is not direct, but rather secondary to health-related factors. Depressed persons have less healthy eating habits,[126] are more likely to be obese,[125] more often smoke,[47,127] and use either less[128] or more alcohol[74] compared to non-depressed persons. In the present study, these tendencies were also found regarding obesity and decreased alcohol use. As a consequence, obesity,[129] smoking,[75] and alcohol use[130] might have affected lipid/lipoprotein metabolism. The hypothesis of an indirect relationship between depression and lipids/lipoproteins is supported by statin trials in which no effect[138,139] or even a protective effect[140] of total cholesterol reduction on depression or suicide risk has been found. Our finding of a lower BMI and current smoking status in subjects with a remitted depression compared to subjects with a current depression and the remitted subjects' lipid profiles being comparable to controls also supports this hypothesis. Alternatively, increased BMI might partly be the result of an adverse lipoprotein pattern in depression through an as yet unknown mechanism. Still, other (biologic) mechanisms may be involved, for example, hypothalamic-pituitary-adrenal axis dysregulation,[141] or a low-grade inflammatory process as observed in depression may result in altered lipid metabolism (possibly through an increase in lipid peroxidation through oxidative stress).[142] Otherwise, obesity might lead to depression through increased bodily pain or psychosocial factors, such as a negative self-body image.[143] Another possible confounder in the association between depression and lipids/lipoproteins is the use of antidepressants. Despite its known antihistaminergic side effects, such as weight gain, especially of the tricyclic class,[58,131] use of antidepressants was not taken into account in previous studies. However, the use of antidepressants did not explain the associations between depression and lipids/lipoproteins in the present study.

The fact that study groups displayed a graded increase in depression severity score yet we did not find graded differences in lipid levels among study groups, suggests that alterations in lipid levels are dependent on a current depressive state rather than on a history of lifetime depression. This is in line with a study by Olusi and Fido,[35] in which lipid levels tended to normalize after clinical recovery from MDD.

Persistent dyslipidemia in atypical depression could be explained by two of its diagnostic criteria that might increase total and LDL cholesterol levels:[144] an increased appetite and/or weight, and leaden

paralysis, which might reduce physical activity. The continual association between melancholic features and lower HDL cholesterol level might be explained by the metabolic syndrome,[141] which comprises reduced HDL cholesterol[97] and is thought to be associated with depression[23] through shared underlying biologic pathways, such as hypercortisolism.[25]

Finally, although previous research suggests that both CVD and diabetes more often occur in depressed subjects as compared to controls,[145,146] we did not find a significant difference in CVD or diabetes prevalence between controls and subjects with a current or remitted depression. This may reflect the rather young age of our sample in which these somatic conditions are not yet highly prevalent.

Our study has some limitations. Because of our cross-sectional analyses, no causal inferences can be made. Furthermore, nutritional data, which were not available, could have helped to study underlying mechanisms of our results. A strength of our study is the large sample size, which provides enough subjects with depression to reliably differentiate the association between lipids/lipoproteins and several psychopathological characteristics. Importantly, depression was diagnosed according to the gold standard, DSM-IV, and important potential confounders were taken into account.

In conclusion, we found that current depression was associated with an unfavorable lipid and lipoprotein profile, especially in patients with melancholic and atypical features but that this association is to a large extent due to underlying lifestyle-related factors, especially obesity. Unfavorable lipid/lipoprotein patterns are associated with an increased CVD morbidity and mortality risk[97] and could therefore contribute to the increased CVD risk among the depressed.[147] Consequently, it could be advisable for care providers to promote a healthy lifestyle, especially obesity prevention/reduction, within psycho-education for their depressed patients.

Symptom dimensions of depression and anxiety and the metabolic syndrome

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Psychosomatic Medicine 2011, 73: 257-264

ABSTRACT

Background
It was our objective to investigate the associations of depression and anxiety symptoms with the metabolic syndrome using a dimensional approach. The association between depression and anxiety on the one hand, and the metabolic syndrome as a cluster or its individual components on the other hand, is equivocal. The categorical nature of the Diagnostic and Statistical Manual of mental disorders might partly explain the inconsistent findings.

Methods
In 2433 Netherlands Study of Depression and Anxiety participants (mean age, 42.3 years; 33.1% male), three symptoms dimensions -lack of positive affect (depression specific); negative affect (aspecific); and somatic arousal (anxiety specific)- were assessed by a shortened adaptation of the Mood and Anxiety Symptom Questionnaire (MASQ). The association between symptom dimensions and metabolic syndrome components (i.e., waist circumference, triglycerides, high-density lipoprotein cholesterol, glucose, and mean blood pressure) was analyzed, using linear regression analysis.

Results
The occurrence rate of the metabolic syndrome was 20.1% (n=490). Somatic arousal, but not positive affect and negative affect, was strongly associated with four out of five metabolic syndrome components, especially waist circumference, triglycerides, and blood pressure ($\beta = 0.046$, $p < .01$; $\beta = 0.077$, $p < .001$; and $\beta = 0.069$, $p < .001$, respectively), and with the total number of metabolic syndrome components ($\beta = 0.098$, $p < .001$).

Conclusions
Our results demonstrate a strong association of most of the metabolic syndrome components with the somatic arousal dimension, but not with the negative affect and positive affect scales.

4.1 INTRODUCTION

Mood and anxiety disorders are related to an increased risk of cardiovascular morbidity and mortality.[147,1] The metabolic syndrome is a cluster of cardiovascular risk factors (i.e., elevated waist circumference, triglycerides, blood pressure, and fasting glucose, and reduced high-density lipoprotein [HDL]) cholesterol)[17] and is thought to partly mediate this relationship.[148] The association between depression and anxiety and the metabolic syndrome has been extensively investigated. Most studies[149] focused on the association between depression and the cluster of the metabolic syndrome and its individual components. Other studies,[23,103] however less numerous, investigated the association between anxiety and both the metabolic syndrome cluster and its individual components. In addition, in a recent publication,[150] we examined whether disorder status and symptom severity were associated with the metabolic syndrome. No significant difference was found between subjects with and without psychopathology (both depression and/or anxiety). Only the subgroups of the most severely depressed or anxious subjects had increased occurrence rates of the metabolic syndrome, an association predominantly driven by abdominal obesity and dyslipidemia. Despite these observations, the question remains whether a complete mood disorder diagnosis or rather only specific symptom dimensions are related to the metabolic syndrome and whether the dichotomous metabolic syndrome diagnosis or only some of its components are related to psychopathology dimensions.

There are three major reasons that could explain why this question has so far remained unanswered. First, the studies have been conducted in widely differing samples, which limits the possibilities to formulate a broadly generalizable model. For instance, there have been differences in the settings (e.g., clinical population or the general population),[151] age of the subjects (an elderly population or young adult patients),[48,152] and the assessment of psychopathology (questionnaires versus clinical diagnoses).[49,153] Second, the categorical diagnostic approach (using the Diagnostic and Statistical Manual of mental disorders, fourth edition [DSM-IV]) for depressive and anxiety disorders, lumping together disparate symptom clusters, may have limited the power to detect subtle associations.[154] Patients with the same diagnosis can be very different in terms of their symptom profiles, whereas other individuals with important mental health problems fail to meet the diagnostic criteria due to symptom heterogeneity. Third, like the DSM-IV diagnosis, the metabolic syndrome concept is also heterogeneous, and is the subject of substantial debate.[116,155] Because at least three of five components are needed to fulfil the criteria of the metabolic syndrome, there are numerous combinations of components possible that all lead to the same metabolic syndrome diagnosis. Studies[156] have shown that sometimes only specific components of the metabolic syndrome are associated with depression, which casts doubt over the usability of the total metabolic syndrome concept in psychopathology research. It is possible that, in the large variety of

depression/anxiety symptoms, some are "specifically" associated with a distinct metabolic syndrome component (e.g., energy loss, often leading to decreased physical activity, might lead to elevated waist circumference [WC]). Based on the criticized definition of the metabolic syndrome and the possible specific associations between diagnostic and metabolic syndrome symptoms, it would thus be informative to investigate the association between specific depression/anxiety symptoms, on the one hand, and the metabolic syndrome, both defined as a cluster of symptoms and as individual components, on the other hand.

So far, research on the association between depression and anxiety and the metabolic syndrome has mainly focused on categorical and heterogeneous assessments of affective disorders symptomatology or anxiety and depression severity scales.[157,158] In addition, diagnoses show overlapping criteria and co morbidity rates are high.[159,160] To overcome these problems, diagnoses should be more homogeneous and not dichotomous. A feasible alternative for categorical diagnoses is the use of a dimensional approach. Within a dimensional approach, a patient is described in terms of coexisting different symptom domains or dimensions, and not in terms of presence or absence of psychopathology. Each dimension provides specific information on the level of a specific symptom domain, running from absent or healthy to severe. Importantly, dimensions are continuous by principle. Along a continuous scale, changes from one level to another are subtle, whereas in a dichotomous scale, changes are rough and restricted (e.g., depressed versus non-depressed). This makes continuous variables more sensible for detection of (small) differentiating factors, thus increasing statistical power.[162]

A well-known dimensional model is the tripartite model for depression and anxiety, which distinguishes three symptom dimensions.[14] The broad "negative affect" dimension describes general symptoms of psychological distress (e.g., lack of concentration or pessimism) that are seen both in depression and anxiety and could account for their high co-morbidity. The (lack of) "positive affect" dimension (also called anhedonic depression), covers anhedonic symptoms, which are mainly specific to depression. The "somatic arousal" dimension covers symptoms of hyperarousal (e.g., palpitations, shortness of breath, and dizziness), which are specific for anxiety, especially panic disorder. The dimensional model was not developed for detection of DSM-IV diagnoses, but rather to provide a descriptive alternative for the presence or absence of psychopathological symptoms in a subject. The tripartite model was developed to circumvent the lack of diagnostic specificity due to the high levels of co morbidity observed in depression and anxiety, one of the major problems of the DSM-IV "golden standard." Typifying patients in terms of their negative affect, positive affect, and somatic arousal scores has two advantages: first, co morbidity is circumvented; and second, based on the profile of the scores, patients can be described in more specific terms of symptomatology. Several studies[163,164] have shown these specific

dimensions to be specifically increased in depression (positive affect) and anxiety (mainly panic disorder, somatic arousal) and that negative affect was more indicative for overall severity across patients.

The aim of the present study was to investigate the relationship between the symptom dimensions of depression and anxiety of the tripartite model, and the metabolic syndrome and its individual components within the Netherlands Study of Depression and Anxiety (NESDA), as a dimensional approach makes it possible to look more specifically into these associations.

4.2 METHODS

Subjects

Subjects selected for these analyses were baseline participants of NESDA, a cohort study among 2981 individuals aged 18 years through 65 years. Respondents were recruited in the community, in primary care, and in specialized mental healthcare settings from September 2004 through February 2007, throughout The Netherlands. All subjects completed a medical examination, a face-to-face interview, and self-report questionnaires. A detailed description of NESDA is reported elsewhere.[95] The study protocol was approved by the Ethical Review Board of each participating centre and all subjects signed an informed consent.

In the same study sample, tricyclic antidepressant (TCA) users were found to have a significantly increased prevalence of the metabolic syndrome.[150] This association was not found for users of other types of antidepressants, such as selective serotonin re-uptake inhibitors.[150] Therefore, the relatively small group of TCA users (n=80) was excluded from our analyses, so that the results would not be affected by the potential confounding influence of TCAs. Subjects with missing metabolic syndrome or Mood and Anxiety Symptom Questionnaire (MASQ) values (n=468) were excluded as well, resulting in a sample of 2433 (81.6%) subjects. An important number of the included subjects comprised healthy controls or remitted patients (n=1449), whereas other subjects had a current diagnosis of pure depression (n=222), pure anxiety (n=226), or co morbid disorder (n=536). No inpatients were included. The included subjects did not differ from the excluded group in sex distribution, presence of cardiovascular disease (CVD), and physical activity. Included subjects were older (42.3 years versus 40.0 years, p <.001), were more educated (12.3 versus 11.3 years, p <.001), were less often smokers (35.8% current smokers versus 50.9%, p <.001), and consumed more alcohol (16.4% consumed >2 glasses/day versus 15.3%, p <.001) compared with the excluded subjects.

MASQ dimensions

The three dimensions of the tripartite model were measured with the 30-item adaptation (MASQ-D30) of the MASQ.[164, 165] The MASQ-D30 was previously validated and showed reliability and validity within the NESDA study.[15, 163, 166] The MASQ-D30 consists of three ten-item scales, representing negative affect, positive affect and somatic arousal (see Table 1). On each item, participants were asked to rate how much in the past week they have experienced "feelings, sensations, problems and experiences that people sometimes have" on a 5 point scale, 1 being "not at all" and 5 being "extremely." Higher scores indicate more severe symptom levels for that specific dimension.

Table 1. Individual symptoms incorporated in the three dimensions of the MASQ-D30

Negative Affect	Positive Affect	Somatic Arousal
Felt confused	Felt successful	Startled easily
Felt worthless	Felt really happy	Felt nauseous
Felt irritable	Felt optimistic	Felt dizzy or light-headed
Felt hopeless	Felt like I was having a lot of fun	Was trembling or shaking
Blamed myself for a lot of things	Felt like I accomplished a lot	Had pain in my chest
Felt dissatisfied with everything	Felt like I had a lot to look forward to	Had hot or cold spells
Felt pessimistic about the future	Felt really talkative	Was short of breath
Felt inferior to others	Felt really 'up' or lively	Muscles were tense or sore
Had trouble making decisions	Felt like I had a lot of energy	Heart was racing or pounding
Worried a lot about things	Felt really good about myself	Had trouble swallowing

The metabolic syndrome

The metabolic syndrome and its components, when expressed as dichotomous variables (i.e., elevated WC, triglycerides, blood pressure, and fasting glucose, and reduced HDL cholesterol), were exactly defined according to the revised criteria of the National Cholesterol Education Program-Adult Treatment Panel III.[17] WC was measured with a measuring tape at the central point between the lowest rib and the highest point of the iliac crest, on light clothing. Triglycerides, HDL cholesterol, and glucose levels were determined by standardized routine laboratory assays, and diastolic and systolic blood pressures were measured during supine rest (OMRON M4 IntelliSense Digital Blood Pressure Monitor, HEM-752A, Omron Healthcare, Inc., Bannockburn, Illinois). Use of triglyceride or HDL cholesterol-influencing medication and use of antihypertensive or glucose reducing drug were registered. In addition, we used continuous variables for the metabolic syndrome components (which is preferable when aiming for more statistical power).[162] In these analyses, we "adjusted" the values for those subjects, using a metabolic syndrome component influencing

medication. This was done following the methods described in several previous publications.[167,168] For the use of fibrates, 0.10 mmol/L (3.8 mg/dL) was subtracted from HDL cholesterol, and 0.67 mmol/L (60 mg/dL) was added to the triglycerides. For the use of nicotinic acid, 0.15 mmol/L (5.8 mg/dL) was subtracted from HDL cholesterol, and 0.19 mmol/L (17 mg/dL) was added to the triglycerides. For the use of antidiabetic medication and a glucose level of < 7 mmol/L (126 mg/dL), a value of 7 mmol/L (126 mg/dL) was given to glucose, as was done previously.[25] Mean blood pressure (MBP) was expressed as the arithmetic mean of systolic and diastolic blood pressures, which were both measured twice during supine rest on the right arm (OMRON M4 IntelliSense Digital Blood Pressure Monitor, HEM-752A, Omron Healthcare, Inc.) and averaged over the two measurements. For persons using antihypertensive medication, 10 mm Hg was added to systolic blood pressure, and 5 mm Hg was added to diastolic blood pressure, in line with earlier studies.[25] These values represent the average decline in blood pressure in antihypertensive medication trials.[169,170]

Severity scales

Information on depression and anxiety severity was collected during the baseline measurement of the NESDA study,[95] using the Beck Anxiety Inventory (BAI)[171] and the Inventory of Depressive Symptoms self-report (IDS-SR),[110] in which the most severe groups were defined as "severe anxiety symptoms" with a score of ≥ 29 on the BAI and "very severe depressive symptoms" with a score of ≥ 49 on the IDS-SR. Previous NESDA research[150] indicated that the prevalence rates of the metabolic syndrome were increased in those with severe anxiety symptoms (n=185) in crude models and independently increased in those with very severe depressive symptoms (n=102) after fully adjusted models. Because information on the BAI and IDS-SR scores was available for our sample, we decided to investigate whether the previous found associations in the same cohort between the highest scores of the BAI and IDS-SR severity scales and metabolic derangements would be driven by symptom dimensions.

Covariates

Covariates were grouped into two types of variables: sociodemographic and lifestyle variables. Sociodemographic variables included age, sex, and years of education. Lifestyle characteristics included smoking status (never/former/current), alcohol use (<1/1–2/>2 drinks per day), both assessed by standardized questionnaires, and physical activity, which was assessed by the International Physical Activity Questionnaire[112] and expressed in 1000 metabolic equivalent of task (MET)-minutes in the past week. MET reflects the ratio of the associated metabolic rate for specific activities divided by the resting metabolic rate multiplied by the minutes performed activity. CVD was considered to be present when participants self-reported a diagnosis of coronary heart disease, cardiac arrhythmia,

angina, heart failure, or myocardial infarction, confirmed with the use of cardiovascular medication. Medication use of any kind within the past month was registered by observation of drug containers brought in and coded according to the Anatomical Therapeutic Chemical Classification System.[111]

Statistical analyses

Sample characteristics were summarized, using means and standard deviations (SD) for quantitative variables and by percentages for categorical variables. Multivariate linear regression analyses were conducted to assess the association between each MASQ-D30 dimensions (i.e., positive affect, negative affect and somatic arousal) and the individual continuous metabolic syndrome components and the total number of metabolic syndrome components. Analyses for each dimension were performed separately. To normalize residuals, non-normally distributed dependent variables were naturally log-transformed. After running crude models, we adjusted for basic covariates (i.e., age, sex, and years of education) in model 1, and for additional lifestyle-related covariates (i.e., smoking status, alcohol use, and physical activity) in model 2. Because sex differences in the association between anxiety, depression, and the metabolic syndrome have previously been observed,[21, 156] appropriate interaction terms with sex were explored. To evaluate the influence of prevalent CVD, participants diagnosed with CVD were excluded in a sensitivity analysis.

To evaluate whether the earlier described association between severity of depressive and anxious symptoms and metabolic syndrome abnormalities were driven by symptom dimensions, additional regression analyses were performed. We analyzed the association of BAI and IDS-SR severity categories with the individual metabolic syndrome components and the total number of components by performing linear regression analyses, adjusting for models 1 and 2 covariates, and additionally adjusting for those symptom dimensions that demonstrated to be associated significantly with the metabolic syndrome components in the main analyses.

Multivariate logistic regression analyses were performed to assess the association between the SDs of continuous scores of the three symptom dimensions and the metabolic syndrome diagnosis. All assumptions for linearity were tested and fulfilled. All tests were two-tailed with p <.05 denoting statistically significance. Statistical analyses were done with SPSS 16.0 (IBM Company, Chicago, Illinois, USA).

4.3 RESULTS

Sample characteristics are shown in Table 2. The mean age was 42.3 years (SD 13.1), 33.1% were men, and mean number of years of education was 12.3 years (SD 3.3). The criteria for the metabolic syndrome were fulfilled by 20.1% (n=490). The reported means and SDs for each dimension are calculated from the continuous values of all subjects included (n=2433) for that dimension.

Table 2. Sample characteristics in 2433 subjects

General characteristics		
Age	42.3	(13.1)
Sex (% men)	33.1	
Years of education	12.3	(3.3)
Cardiovascular disease	5.8	
Smoking status (%)		
Never	29.3	
Former	34.9	
Current	35.8	
Alcohol use (%)		
< 1 glasses/day	61.0	
1-2 glasses/day	22.4	
> 2 glasses/day	16.4	
Physical activity (1000 MET minutes)	3.7	(3.06)
Metabolic syndrome components		
Waist circumference (cm)	88.7	(13.8)
HDL cholesterol (mmol/L)	1.6	(0.4)
Triglycerides (mmol/L)	1.3	(0.8)
Glucose (mmol/L)	5.2	(0.9)
Systolic blood pressure (mmHg)	136.2	(19.7)
Diastolic blood pressure (mmHg)	81.5	(11.1)
Mean blood pressure (mmHg)	108.9	(14.7)
Number of metabolic syndrome components	1.45	(1.3)
Metabolic syndrome (%)	20.1	
MASQ symptom dimensions		
Positive affect	33.4	(9.7)
Negative affect	20.0	(8.6)
Somatic arousal	15.7	(6.1)

Means and standard deviations are given for age, years of education, physical activity, number of metabolic syndrome components and the three symptom dimensions. Percentages are given for sex, smoking status, alcohol use, and presence of metabolic syndrome. Abbreviations: HDL, high-density lipoprotein; MASQ, Mood and Anxiety Symptom Questionnaire; MET, metabolic equivalent of task.

Outcomes of the linear regression analyses between MASQ-D30 dimensions and metabolic syndrome components are shown in Table 3. Positive affect showed a significant association with every metabolic syndrome component in the crude model. Adjustments in model 1 led to a decrease of the β with >10% and to non-significant associations with WC, fasting glucose levels, and MBP. Analyses with the separate covariates of model 1 showed age to be the most important confounder. Associations of positive affect with triglycerides and HDL cholesterol became statistically non-significant after adjustment for lifestyle factors (model 2). No significant associations were found for negative affect with any of the metabolic syndrome components, in the unadjusted and fully adjusted models. On the contrary, in the crude unadjusted model, somatic arousal showed a significant association with all metabolic syndrome components except for fasting glucose. The associations for somatic arousal remained significant in both adjusted models with regard to WC (WC_{crude}: β = 0.061, p = .003; $WC_{model\ 2}$: β = 0.046, p = .01), triglycerides ($Trig_{crude}$: β = 0.077, p <.001; $Trig_{model\ 2}$: β = 0.046, p = .02) and MBP (MBP_{crude}: β = 0.069, p <.001; $MBP_{model\ 2}$: β = 0.068, p <.001). The significant crude association of somatic arousal with HDL cholesterol weakened after adjustment in model 1, and further in model 2 to a non-significant level. Also, the association of somatic arousal with the number of metabolic syndrome components (Nr.) remained highly statistically significant throughout all models ($Nr._{crude}$: β = 0.098, p <.001; $Nr._{model\ 2}$: β = 0.062, p <.001).

The graded, positive association between somatic arousal and the number of metabolic syndrome components, and between somatic arousal and quartiles of the individual fully adjusted metabolic syndrome components are shown in Figure 1. In sensitivity analyses in which 141 subjects with CVD were excluded, results did not change (data not shown). None of the interaction terms between dimensions with sex were statistically significant, which suggests that associations were largely similar for men and women.

To evaluate whether another measure for somatic symptoms would give comparable results, we repeated the linear regression model analyses with the validated BAI somatic subscale.[171] These analyses confirmed an association for the somatic BAI subscale and a much less consistent association for the nonsomatic BAI subscale. The associations with the BAI somatic scale score remained significant in the fully adjusted models for the number of metabolic syndrome components (Nr. metabolic syndrome: β = 0.072, p <.001), and all metabolic syndrome components, except for HDL cholesterol, which showed a trend toward significance with a β = -0.033, p = .08 (WC: β = 0.056, p <.001; Trig: β = 0.083, p <.001; Gluc: β = 0.038, p = .04; MBP: β = 0.046, p = .01). There was a strong intercorrelation between the somatic symptom dimension of the MASQ and the subscale of the BAI (r_{sBAI} = 0.73, p <.001). We did not analyze associations with subscales of the IDS-SR because earlier work by Wardenaar et al.[172] did identify three subscales but none of these was a

Table 3. Linear regression for associations between MASQ dimensions and metabolic syndrome components in 2433 subjects

	Waist circumference		Triglycerides		HDL cholesterol		Glucose		Blood pressure		Number of metabolic syndrome components	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
Negative affect												
Crude	.070	.001	.097	<.001	-.063	.002	.079	<.001	.076	<.001	.107	<.001
Model 1	-.001	.94	.044	.02	-.039	.04	.027	.15	.008	.64	.036	.05
Model 2	-.009	.60	.021	.29	-.012	.52	.026	.17	.009	.63	.019	.29
Positive affect												
Crude	-.002	.93	.031	.12	-.036	.08	.008	.68	-.028	.17	.018	.37
Model 1	.016	.34	.042	.03	-.017	.36	.036	.05	-.001	.94	.033	.07
Model 2	.011	.51	.022	.25	.001	.08	.037	.05	-.002	.90	.020	.27
Somatic arousal												
Crude	.061	.003	.077	<.001	-.056	.01	.025	.22	.069	<.001	.098	<.001
Model 1	.050	.01	.064	.001	-.045	.02	.023	.21	.062	<.001	.074	<.001
Model 2	.046	.01	.046	.02	-.018	.32	.023	.22	.068	<.001	.062	.001

β, standardized beta by linear regression analyses.

Abbreviations: HDL, high-density lipoprotein; MASQ, Mood and Anxiety Symptom Questionnaire.

Model 1: adjusted for age, sex and years of education.

Model 2: additionally adjusted for smoking status, alcohol use and physical activity.

clear somatic subscale (in factor analyses, the rather restricted somatic items were attributed to all three subscales). So, no valid somatic IDS-SR subscale exists. Therefore, it is not appropriate to use a subscale in a comparative analysis. To explore whether results would also be consistent for the nonsomatic symptom subscale, we also conducted linear regression analyses with the nonsomatic BAI subscale (BAI subjective scale score). We expected that associations for the subjective BAI subscale would be similar to those for the positive affect and negative affect dimensions of the MASQ-30, which was confirmed. None of the associations with the BAI subjective scale score were statistically significant in the fully adjusted models, with exception of the number of metabolic syndrome components ($\beta = 0.041$, $p = .02$).

Regression analyses performed to investigate whether previously found positive associations between metabolic syndrome abnormalities and symptom severity were driven by symptom dimensions, in particular the somatic arousal dimension, showed the following: Initial significant outcomes (in which the number of metabolic syndrome components was the dependent variable and BAI and IDS-SR severity categories were the independent variables) lost statistical significance after adjustment with the somatic arousal dimension. This means that the earlier described associations between the high severe groups according to the BAI and IDS-SR with the metabolic syndrome were largely attributable to a high somatic arousal score.

Logistic regression analyses of the symptom dimensions with the metabolic syndrome showed a small but significant crude relationship between positive affect and the metabolic syndrome. Negative affect was not significantly associated with the metabolic syndrome. The initial significant crude relationship between somatic arousal and the metabolic syndrome remained statistically significant throughout multivariable adjustment (odds ratio per SD increase, 1.15; 95% confidence interval, 1.04 –1.28; $p = .008$, see Table 4). Analyses in which the associations of BAI or IDS severity categories with the metabolic syndrome were adjusted for somatic arousal, showed that the severity category indicator lost statistical significance after adjustment.

Table 4. Logistic regression for the association between standard deviations (SDs) of continuous scores on MASQ dimensions and the odds of metabolic syndrome in 2433 subjects

	OR	95% CI	*p*
Positive Affect			
Crude	1.16	1.05-1.28	.004
Model 1	1.02	0.92-1.14	.67
Model 2	0.99	0.88-1.10	.99
Negative Affect			
Crude	1.01	0.92-1.12	.78
Model 1	1.01	0.99-1.02	.28
Model 2	1.04	0.93-1.16	.51
Somatic Arousal			
Crude	1.19	1.08-1.31	<.001
Model 1	1.18	1.06-1.30	.002
Model 2	1.15	1.04-1.28	.008

Abbreviations: OR, odds ratio per SD increase by logistic regression analysis; CI, confidence interval; MASQ, Mood and Anxiety Symptom Questionnaire.
Model 1: adjusted for age, sex, years of education.
Model 2: additionally adjusted for lifestyle factors: smoking status, alcohol use and physical activity.

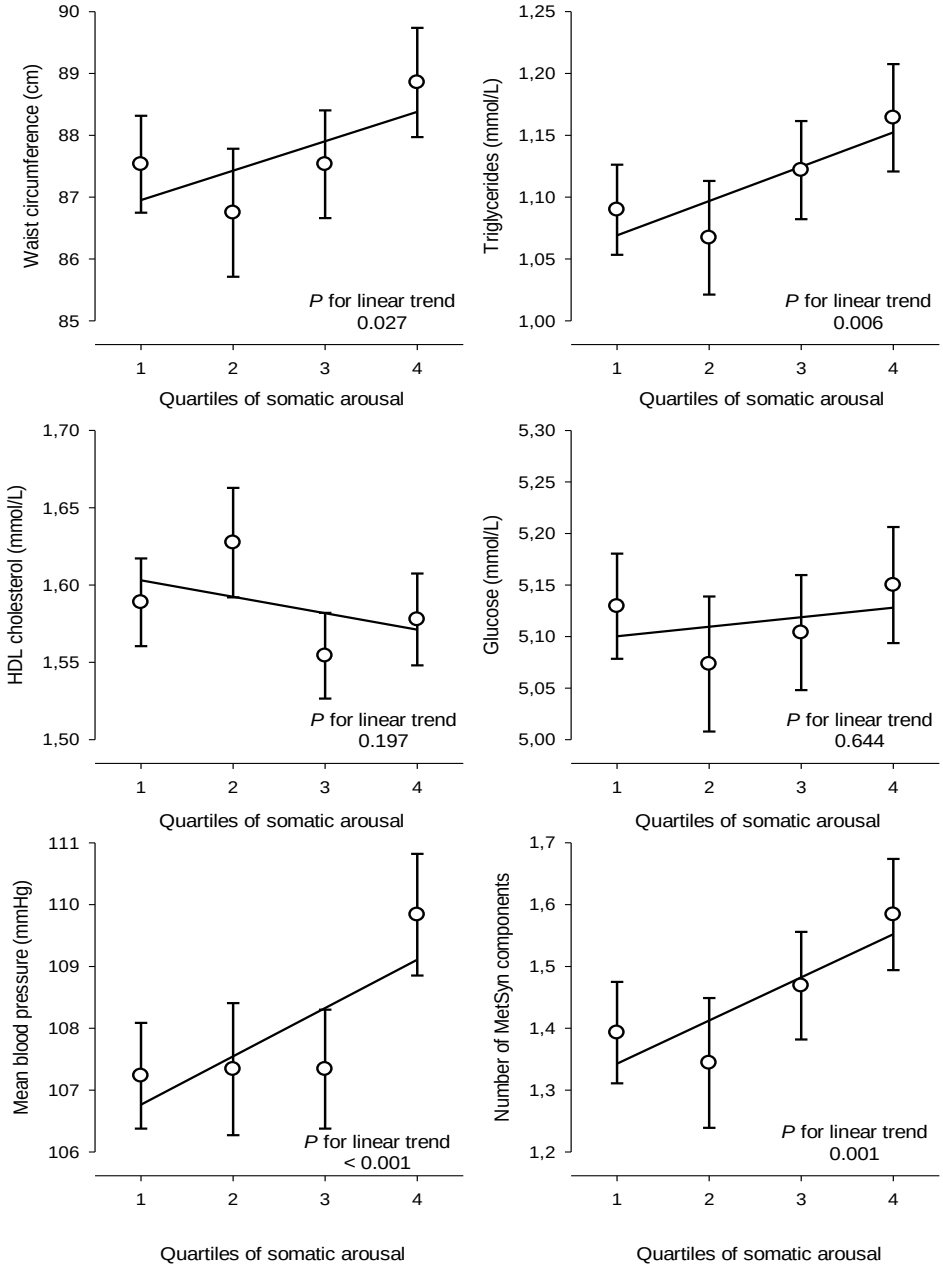

Figure 1. Adjusted (geometric) means across quartiles of somatic arousal on the MASQ-D30, for the individual metabolic syndrome components and the total number of metabolic syndrome components. Data are adjusted for age, sex, educational level, alcohol use, smoking status and physical activity. Error bars indicate 95% confidence intervals of the mean, and regression lines are shown. $n_{quartile\ 1}$=744; $n_{quartile\ 2}$=436; $n_{quartile\ 3}$=652; $n_{quartile\ 4}$=601.

4.4 DISCUSSION

The main finding of this study is that only the somatic arousal symptom dimension is strongly and independently associated with most of the metabolic syndrome components (especially waist circumference [WC], triglycerides, and mean blood pressure [MBP]) and shows a graded association with the number of metabolic syndrome components. Using a dimensional approach, somatic arousal was thus associated with an increased metabolic risk. No independent associations of the metabolic syndrome with negative affect and positive affect were observed. These results are supported by our finding that the somatic scale of the BAI is associated with the metabolic syndrome components, whereas the non-somatic scales are not.

Approaching depression and anxiety dimensionally, the aspecific negative affect dimension and the depression specific positive affect dimension did not show any association with the metabolic syndrome. We only found a strong and consistent relationship between the somatic arousal dimension and multiple metabolic syndrome components. This is in line with previous research on symptom dimensions of especially depression in relation to somatic outcomes, in which the somatic/affective sub-dimension, rather than other important dimensions (e.g., cognitive/affective and appetitive), was most strongly associated with cardiovascular risk and outcome.[173,174] It seems we are looking at a specific sub-dimension: the "somatic depression/anxiety" sub-dimension. On the one hand, this subtype could be reflective of underlying dysregulated homeostasis mechanisms due to anxious or depressed mood states, such as inflammation,[72] impaired hypothalamus-pituitary-adrenal axis function,[68,175] or a higher sympathetic and lower parasympathetic autonomic tone.[176] Elevated levels of inflammatory markers could induce a depressive episode;[177] altered lipid patterns caused by high levels of cortisol[141,148] could lead to other lipid-related symptoms (overweight, abdominal obesity, and hypertriglyceridemia);[161,178] and activation of the sympathetic nervous system leads to increased blood pressure[179] and thus to hypertension.[148,180] This network of pathways can thus result in an increased metabolic or cardiovascular risk and cardiovascular disease. On the other hand, the reverse mechanism could be active: Ongoing metabolic dysregulations could be causing (especially somatic arousal) symptoms of depression and anxiety.[22,181-184] Regardless of the underlying mechanisms and the direction of causality, the dose-response gradient between the number of metabolic syndrome components and levels of somatic arousal indicates that when more somatic arousal symptoms are present, more metabolic syndrome abnormalities are present. Apart from biological mechanisms, other processes may be involved during a depressive episode as a consequence of anhedonia, such as altered lifestyle patterns (poor diet and decreased physical activity),[185,186] which might induce metabolic changes and cardiovascular risk factors.

Previous research based on NESDA data[150] showed that the prevalence rates of the metabolic syndrome were increased in those with the highest levels of anxiety or depressive symptoms based on the BAI and the IDS-SR. After adjustment for the MASQ somatic arousal dimension, the earlier described associations lost statistical significance. These results indicate that the earlier described association between the metabolic syndrome and the most severe depression and anxiety symptom scales can be explained by the fact that these persons had high scores on the somatic arousal dimension.

In terms of metabolic risk evaluation and detection, a dimensional approach has more differentiating capacities compared with the widely used diagnostic DSM-IV categories. The somatic symptom dimension could therefore be the key feature in the association between depression/anxiety and somatic outcomes.

Using a dimensional approach, the level of a symptom dimension varies differentially between diagnostic groups (e.g., singular depression, singular anxiety, or co-morbid state). At the same time, all symptom dimensions can be present at a significant level within every diagnostic group. This means that the clinical presentation of a subject is dependent on the symptom dimension(s) with the highest scores. Our results demonstrate that the somatic arousal dimension is associated with several metabolic syndrome components. The fact that somatic arousal levels are not equally high for every depressed and/or anxious subject might explain the inconsistent findings in literature on the association with the metabolic syndrome.

Our study has several strengths. This is, to our knowledge, the first study describing the relationship of depression and anxiety dimensions in relation to the metabolic syndrome. We not only approached the metabolic syndrome and its components as continua, in line with the idea that metabolic syndrome components have a natural continuous distribution,[187] but also distinguished depression and anxiety symptom dimensions.[187] Because we chose this approach, we were able to show a dose-response gradient with somatic arousal levels. Furthermore, the results are based on a large sample, making results reliable. Finally, in the analyses, we adjusted for a substantial number of covariates, minimizing the chance that the findings can be explained by confounding.

This study presents some limitations. First, the tripartite model is a rather simple dimensional model. Probably, there are more relevant subdimensions present.[188] Second, the sample includes both healthy controls and subjects with (remitted) psychopathology, who were recruited from the community as well as mental healthcare settings. As inpatients were excluded, our results cannot be generalized to this group. Third, the concept of the metabolic syndrome has been criticized,[116,155] and our findings support the idea that it may be worthwhile to study (the number of) individual metabolic components in addition to a dichotomous metabolic syndrome variable. Finally, due to the cross-sectional design,

our results cannot be used to make any causal inferences. Prospective studies, especially across more heterogeneous populations, would help to understand the direction of the potential causal relationship.

In this sample, in which previously the association between a categorical diagnosis on the one hand and the metabolic syndrome components on the other hand, was found only for the most severe depressive symptoms,[150] we demonstrate a strong association between the somatic arousal symptom dimension and the metabolic syndrome and its individual components, especially WC, triglycerides, and blood pressure, and the number of metabolic syndrome components. Not every depressed subject is at increased metabolic risk. But our findings suggest that those with an elevated somatic arousal level are. Those with elevated non-somatic dimensions scores (i.e., positive affect and negative affect) did not show an increased metabolic risk. This indicates the additional value of a dimensional approach in terms of metabolic risk evaluation. In addition, we found that the association between depression severity (BAI severity categories) and the metabolic syndrome is, in part, driven by the somatic arousal dimension. Although our results need to be replicated, the discriminating ability of a dimensional approach could facilitate the identification of those with a higher metabolic risk within a clinical population with apparently the same diagnoses.

Longitudinal relationship of depressive and anxiety symptoms with dyslipidemia and abdominal obesity

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ABSTRACT

Introduction
Previous research indicates that patients with severe symptoms of depression or anxiety are prone towards the development of dyslipidemia and abdominal obesity. We aimed to study these associations longitudinally.

Methods
Among 2126 Netherlands Study of Depression and Anxiety (NESDA) participants, we studied whether severity of depressive (Inventory of Depressive Symptoms) or anxiety (Beck Anxiety Inventory) symptoms at baseline was associated with changes in lipids (i.e., total, high or low-density [HDL or LDL] cholesterol and triglycerides) or waist circumference (WC) during a 2-year follow-up period. We also examined whether changes in severity of symptoms were associated with changes in lipid or WC levels over these 2 years. Analyses were adjusted for age, sex, education and tobacco consumption in multivariate linear regression analyses.

Results
Baseline symptoms of depression or anxiety predicted a decrease in HDL cholesterol (adjusted β = -.062, p = .003 and β = -.050, p = .02, respectively) and an increase in WC (adjusted β = .060, p = .01 and β = .053, p = .02, respectively) over 2 years. Reduction of symptoms of depression or anxiety over time did not coincide with an amelioration of lipid or WC values.

Conclusions
People with initially severe symptoms of depression or anxiety showed a subsequent decrease in HDL cholesterol levels and an increase in abdominal obesity over time, independent of a potential reduction in symptom severity in this time period. Therefore, those people are at elongated and increasing risk of dyslipidemia and obesity, predisposing them to cardiovascular disease.

5.1 INTRODUCTION

Patients with depression and anxiety are prone to the cardiovascular disease (CVD) risk factors dyslipidemia (i.e., increased total cholesterol, low-density lipoprotein [LDL] cholesterol and triglyceride levels and lower high-density lipoprotein [HDL] cholesterol) and abdominal obesity (i.e., increased waist circumference [WC]).[23-26,43,45,106,107] Associations of depression or anxiety with the other classic cardiovascular risk factors hyperglycemia and hypertension are less consistent and strong: most studies on hyperglycemia[20,21,23-30,44,46] or hypertension[22-26,28-30,43-46,47-49] did not find significant associations, while only some did (See for hyperglycemia:[22,43,45] and for hypertension:[21,27,44]. Previously we also reported an increased prevalence of dyslipidemia and obesity and not of hyperglycemia and hypertension in patients with depression or anxiety. These prominent associations of depression and anxiety with dyslipidemia and abdominal obesity may contribute to the generally increased risk of CVD in patients with depressive[100] and anxiety disorders.[189] Therefore, we aimed to further explore the associations of depression and anxiety with dyslipidemia and obesity.

Most previous studies on dyslipidemia and obesity in depression and anxiety had cross-sectional designs. To further disentangle these relationships, it is important to also study associations over time. This may reveal whether or not depression or anxiety are associated with sustained dyslipidemia and obesity, and whether changes in depression or anxiety status over time go together with changes in lipid or obesity levels.

Most existing longitudinal studies focused on depression diagnoses,[35,41,190] while scales for severity of symptoms are likely to detect the more subtle differences and changes in depressive or anxiety state. Because of their continuous nature,[312,313] severity scales allow more precise (longitudinal) associations of depression or anxiety with lipid or obesity values than associations based on dichotomous diagnoses. In line with this thought, it was found in several cross-sectional analyses that the severity of symptoms is more strongly related to lipid levels and abdominal obesity than diagnostic categories.[25,117,150]

Despite the importance, only a few longitudinal studies explored associations of depression severity with lipids and/or obesity,[28,191,192] and no studies reported on severity of anxiety. Concerning severity of depression, Pulkki-Raback et al.[28] found that baseline severity of depression predicted WC but not HDL cholesterol or triglyceride levels 9 years later. Vogelzangs et al.[192] reported that among 2088 elderly, baseline depression severity did not predict changes in WC over 5 years. Deisenhammer et al.[191] found that change in depression severity score over a 4 week period was not accompanied by changes in total, LDL and HDL cholesterol or in triglycerides among 50 patients with MDD.

Given the limited research so far, longitudinally studying severity of depression and anxiety in relation to dyslipidemia and abdominal obesity importantly adds to this research field. Furthermore, depression and

anxiety are highly co-morbid, with co-morbidity rates of over 60 percent.[12,13] Therefore, it is valuable to examine how depression and anxiety independently relate to dyslipidemia and abdominal obesity.

The present study examined within the Netherlands Study of Depression and Anxiety (NESDA) whether depressive or anxiety symptoms at baseline predicted an increase in abdominal obesity or dyslipidemia over a 2-year follow-up period. We also intended to study whether 2-year changes of depressive or anxiety symptoms over time coincided with 2-year changes in lipid and abdominal obesity values. Because severity of depressive and anxiety symptoms have been found to be related to dyslipidemia and obesity, we expected that symptoms of depression and anxiety predicted an aggravation of dyslipidemia and abdominal obesity, and we also hypothesized that changes in severity of depression or anxiety went together with lipid and abdominal obesity changes. Finally, as relatively more studies found depression to be related to dyslipidemia[20-30] (versus[45-49] finding no association) or abdominal obesity[20,23-28,43-46] (versus[49] finding no association) than anxiety ([20]found anxiety to be related to dyslipidemia while[26,29,47] found no association, and none[23,26,29,47] found anxiety to be related to abdominal obesity), we expected that depression severity dominates anxiety severity in relation to dyslipidemia and abdominal obesity.

5.2 METHODS

Subjects

Subjects participated in the baseline (data collection from September 2004 to February 2007) and 2-year follow-up (data collection from September 2006 to February 2009) assessment of the Netherlands Study of Depression and Anxiety (NESDA), a cohort study including 2981 persons aged 18 to 65 years. Subjects were recruited from community (n=564, 18.9%), primary care (n=1610, 54%, of which 373, 12.5% subjects had never had a depressive or anxiety disorder), and mental health care settings (n=807, 27.1%) in the Netherlands. Subjects with personal or family history of depression and anxiety as well as healthy controls that never had experienced any depressive or anxiety disorder were recruited in order to reflect a range of settings and stages of psychopathology. See for further details:[95]. The baseline and 2-year follow-up assessment both comprised a face-to-face interview, written questionnaires and biological measurements, as described in detail elsewhere.[95,96] According to the Composite Interview Diagnostic Instrument (CIDI, version 2.1), at baseline 2329 subjects had a lifetime depressive or anxiety disorder (i.e., social phobia, panic disorder with or without agoraphobia or generalized anxiety disorder) of which 1701 during the 6 months prior to the baseline interview, and 652 subjects had never had a depressive or anxiety disorder.[95] The response rate at 2-year follow-up was 87.1%.[193] The study protocol was approved by the Ethical Review Board of each participating centre, and all subjects signed informed consent.

Subjects who did not attend the 2-year follow-up assessment (n=385) or who otherwise lacked data on severity of depression or anxiety or on lipid or WC measures either at baseline or at the 2-year follow-up assessment (n=470) were excluded from analyses. This resulted in the current sample of 2126 subjects, aged 18-65 years at baseline. Subjects who were excluded due to missing data were younger (mean age 40.1 [SD 12.9] versus 42.6 [SD 13.1], p <.001), more often female (69.9 versus 65.0%, p = .01) and had less years of education (mean 11.7 [SD 3.3] versus 12.4 [SD 3.3], p <.001) than those without missing data. Also, excluded subjects more often had an MDD (43.5 versus 34.9%, p <.001) or an anxiety disorder (50.5 versus 41.1%, p <.001) in the 6 months preceding the baseline assessment.

Severity of depression and anxiety

Because we previously found no cross-sectional associations of obesity and lipid measures with MDD or anxiety disorder diagnoses but only with severity scales for depression and anxiety, we now examine longitudinal associations of severity of depression and anxiety with lipids and abdominal obesity. *Depression severity* was assessed by the 30-item Inventory of Depressive Symptoms self-report (IDS-SR) ranging from 0 to 84.[133] *Anxiety severity* was assessed by the 21-item self-report Beck Anxiety Inventory (BAI) ranging from 0 to 63.[171]

Cronbach´s alphas were .90 at baseline and .89 at 2-year follow-up for the IDS-SR. Cronbach´s alphas were .92 at both time points for the BAI. Those values are considered acceptable.[287] Test-retest reliability correlation coefficients were .72 for the IDS-SR and .69 for the BAI, which mark a high to moderate test-retest reliability.

Lipid and abdominal obesity measures

HDL cholesterol, LDL cholesterol, triglycerides and WC were previously found to be cross-sectionally associated with severity of depressive and anxiety symptoms in NESDA.[117,150] Total, HDL and LDL cholesterol as well as triglyceride levels were determined using routine standardised laboratory methods. To account for medication use, HDL cholesterol, LDL cholesterol and triglyceride values were adjusted according to changes observed in clinical trials, as previously performed.[25] Medication use within the past month was registered by observation of drug containers brought in, and ATC coded.[111] For persons using fibrates, 0.10 mmol/L was subtracted from HDL cholesterol, and 0.67 mmol/L was added to triglycerides.[167,168] For persons using nicotid acid, 0.15 mmol/L was subtracted from HDL cholesterol, and 0.19 mmol/L was added to triglycerides. For persons using LDL-lowering medication, 0.74 mmol/L was added to LDL cholesterol.[194] A sensitivity analysis including the original lipid values, and lipid affecting medication use as a covariate, yielded largely similar results to the original findings reported in this paper. WC was measured with a measuring tape at the central point

between the lowest front rib and the highest front point of the pelvis, upon light clothing.

Covariates

Sociodemographic variables included age, sex and years of education at baseline. Since tobacco use likely is a confounder, number of tobacco (i.e., cigarette, cigar or pipe) consumptions a day - as assessed through standardised questionnaires - was taken into account.

Exercise was not taken into account as a covariate as in a recently published article[340] we reported that exercise did not play a significant role in the associations of dyslipidemia or obesity with depression or anxiety. For certainty, we did additional analyses including physical activity as a covariate, and indeed physical activity did not affect associations significantly (data not shown).

Statistical analyses

Baseline, 2-year follow-up and 2-year change characteristics of the sample were expressed in percentages for categorical variables, and in means (95% confidence intervals, CIs) for continuous variables. Paired-sample T tests were performed to explore whether mean 2-year changes were statistically significant; McNemar's test was used for paired dichotomous variables. 2-year changes in lipid or obesity, and in severity of depression or anxiety were computed as follow-up values minus baseline values. Linear regression analyses were conducted 1) to confirm associations of baseline severity of depression and anxiety with baseline lipid and obesity values that we previously reported,[117,150] and to further examine 2) whether baseline severity of depression or anxiety predicted 2-year changes in lipid or WC values (while adjusting for baseline lipid or WC values), 3) and if 2-year change in severity of depression or anxiety was accompanied by 2-year changes in lipid or WC levels (while adjusting for baseline depression or anxiety severity and the concerning lipid or WC values). All analyses were then adjusted for age, sex, years of education and tobacco consumption. Because of the co-morbidity of depression and anxiety, analyses on depression severity were additionally adjusted for anxiety severity scores and vice versa in order to understand how depression and anxiety collaborate in relation to dyslipidemia and obesity.[341] Since sex differences in the association between anxiety, depression and cardiovascular risk factors have been observed before,[21,43,105] sex × depression severity / anxiety severity interaction terms were examined in adjusted models. To ensure that associations were not due to CVD, all 118 subjects with prevalent medicated CVD (i.e., stroke, myocardial infarction, angina pectoris or coronary heart disease, as assessed by standardized questionnaires and observation of drug containers brought in) at baseline were excluded in a sensitivity analysis. Previously, we found subjects who used tricyclic antidepressants (TCAs) but not those on other kinds of antidepressants to be prone to dyslipidemia and obesity.[150] Therefore, an additional sensitivity analysis

was performed by excluding subjects who used TCAs at baseline (n=10), at 2-year follow-up (n=13) or at both time points (n=42). TCA use within the past month was registered by observation of drug containers brought in and ATC coded.[111] All statistical analyses were done with SPSS 18.0 (IBM company, Chicago, Illinois, USA).

5.3 RESULTS

Sample characteristics at baseline and 2-year follow-up as well as changes between these time points are presented in Table 1. Mean age at baseline was 42.6 years (95% confidence interval [CI] 42.0-43.2), and 35.1% were male. The mean depression severity score significantly diminished over time, as did the mean anxiety severity score. HDL cholesterol levels decreased during 2 years of follow-up. Triglyceride levels and WC significantly increased over time. Associations of baseline severity of depression and anxiety with baseline lipid and obesity values (data not shown) were similar to the results we reported earlier.[117,150] At baseline, severity of depression was associated with higher triglycerides and WC (adjusted β = .061, p = .003 and β = .093, p <.001, respectively); baseline severity of anxiety was associated with lower HDL cholesterol (adjusted β = -.048, p = .02) and higher triglyceride and WC levels (adjusted β = .066, p = .002 and β = .077, p <.001, respectively).

Table 1. Baseline, 2 year follow-up and 2 year change characteristics of 2126 subjects

Characteristics	Baseline	2 year follow-up	p*	2 year changes
Age (years, at baseline)	42.6 (42.0-43.2)			
Sex (% men)	35.1			
Years of education	12.4 (12.2-12.5)			
Tobacco consumptions a day	4.6 (4.3-5.0)	4.1 (3.8-4.5)	<.001	-0.5 (-0.7- -0.3)
Depression severity (IDS-SR)	20.5 (19.9-21.1)	16.0 (15.4-16.5)	<.001	-4.5 (-5.0- -4.1)
Anxiety severity (BAI)	11.3 (10.9-11.8)	8.8 (8.4-9.1)	<.001	-2.6 (-2.9- -2.3)
Waist circumference (cm)	89.0 (88.5-89.7)	89.8 (89.2-90.4)	<.001	0.7 (0.5-1.0)
Total cholesterol (mmol/L)	5.2 (5.1-5.2)	5.1 (5.1-5.2)	.051	-0.03 (-0.1-0.0)
LDL cholesterol (mmol/L)	3.2 (3.2-3.3)	3.2 (3.2-3.3)	.14	0.02 (-0.01-0.05)
HDL cholesterol (mmol/L)	1.6 (1.6-1.7)	1.6 (1.5-1.6)	<.001	-0.10 (-0.11- -0.9)
Triglycerides (mmol/L)	1.3 (1.25-1.32)	1.3 (1.3-1.4)	.003	0.05 (0.02-0.08)
Lipid affecting medication use (%)	7.3	8.1	.054	0.8

Abbreviations: BAI, Beck Anxiety Inventory; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IDS-SR, Inventory of Depressive Symptoms self-report.
Means (95% confidence intervals) or percentages are given, when appropriate.
*: p by paired-sample t test for means, and McNemar's test statistics for lipid medication use.

Table 2 shows crude and adjusted associations of severity of baseline depression and anxiety with 2-year changes in lipid and obesity values. Baseline severity of depression was associated with a significant increase in WC over 2 years (basically adjusted β = 0.60, p = .01, respectively) and a decline in HDL cholesterol (basically adjusted β = -.062, p = .003). Baseline severity of anxiety was also associated with a significant increase in WC (adjusted β = .053, p = .02) and a decline in HDL cholesterol over 2 years (adjusted β = -.050, p = .02) and an. The associations of more severe symptoms of anxiety at baseline with increasing waist circumference (β =

.053 to .017, i.e., Δ -67.9%) and with lowering of HDL cholesterol levels (β = -.050 to -.002, i.e., Δ -95.0%) were significantly explained by co-morbid symptoms of depression. Associations of depression severity with increasing waist circumference (β .060 to .047, i.e., Δ -21.7%) and with lowering of HDL cholesterol levels (β -.062 to -.061, i.e., Δ -1.6%) were less substantially explained by co-morbid symptoms of anxiety. There was no considerable multicollinearity in these models (variance inflation factors were all 2.5). Adjustment for tobacco use did not affect the associations. No associations were found of baseline depression or anxiety severity with changes in total or LDL cholesterol or in triglyceride levels.

Table 3 shows crude and adjusted associations of 2-year change in severity of depressive and anxiety symptoms with 2-year changes in lipids and WC. Changes in depression or anxiety severity were not accompanied by significant changes in lipid or WC values. Adjustment for tobacco consumption did not affect these findings.

Repeated analyses including sex × depression severity / anxiety severity interaction terms showed no statistically significant interaction (*p* ranged from .11 to .99). This suggests that associations do not significantly differ for men or women. Sensitivity analyses in which 118 subjects with CVD or 65 subjects who were using TCAs at either time point were excluded, yielded similar results.

Table 2. Associations of baseline depression and anxiety severity with 2 year changes in lipid and obesity values

	2 year changes in lipid and obesity values									
	Total cholesterol		LDL cholesterol		HDL cholesterol		Triglycerides		Waist circumference	
Baseline depression severity (IDS-SR)	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
Crude	-.003	.90	-.004	.85	**-.046**	.04	-.001	.95	.026	.23
Adjusted[a]	-.003	.87	.001	.95	**-.062**	.003	-.008	.71	**.060**	.01
Baseline anxiety severity (BAI)	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
Crude	.013	.54	.006	.77	-.022	.31	.012	.57	.026	.24
Adjusted[a]	.006	.79	.008	.69	**-.050**	.02	.024	.29	**.053**	.02

Abbreviations: BAI, Beck Anxiety Inventory; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IDS-SR, Inventory of Depressive Symptoms self-report.
β coefficients indicate the standardised beta by linear regression analysis. Statistically significant (p<.05) associations are marked bold.
All analyses are adjusted for the concerning baseline lipid or obesity values.
[a]: Adjusted for age, sex, years of education, and baseline as well as 2 year change in tobacco consumption.

Table 3. Associations of 2 year change in depression and anxiety severity with 2 year changes in lipid and obesity values

	2 year changes in lipid and obesity values									
	Total cholesterol		LDL cholesterol		HDL cholesterol		Triglycerides		Waist circumference	
2 year changes in depression severity (IDS-SR)	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
Crude	.014	.53	.013	.56	**.049**	.03	.004	.87	.008	.73
Adjusted[a]	.017	.46	.008	.73	.045	.06	-.002	.95	.025	.32
2 year changes in anxiety severity (BAI)	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
Crude	.012	.60	.017	.42	.032	.14	-.023	.30	-.016	.47
Adjusted[a]	.008	.71	.018	.46	.032	.18	-.026	.30	.003	.90

Abbreviations: BAI, Beck Anxiety Inventory; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IDS-SR, Inventory of Depressive Symptoms self-report.
β coefficients indicate the standardised beta by linear regression analysis. Statistically significant (p<.05) associations are marked bold.
All analyses are adjusted for the concerning baseline depression or anxiety severity and lipid or obesity values.
[a]: Adjusted for age, sex, years of education, and baseline as well as 2 year change in tobacco consumption.

5.4 DISCUSSION

Earlier we reported that more severe symptoms of depression and also of anxiety made people prone to dyslipidemia and abdominal obesity.[117, 150] In this longitudinal follow-up study, we observed that people who had more severe symptoms of depression or anxiety at baseline displayed a further decline in HDL cholesterol levels and an increase in abdominal obesity over the subsequent 2 years. These associations were driven by depression severity: anxiety severity seemed to be related to increasing dyslipidemia and abdominal obesity mainly through its close relationship with depression.[341] Finally, a reduction of symptoms of depression or anxiety over this time period did not go together with amelioration of lipid or abdominal obesity values.

So far no comparable studies concerning symptoms of anxiety have been reported. Moreover, we were to our knowledge the first to study the relative contribution of depression and anxiety to the development of dyslipidemia and abdominal obesity. Our results showed that anxiety severity rather is a proxy risk factor for depression severity in aggravating dyslipidemia and abdominal obesity.[341]

Our finding that baseline severity of depression predicted progressive abdominal obesity over the subsequent 2 years corresponds to another study that reported that baseline severity of depression predicted an increased abdominal obesity value after 9 years.[28] Our finding is also in line with a meta-analysis which revealed that baseline depression was associated with an increased odds ratio for developing overall obesity over time (47). Yet another study found no predictive relationship over 5 years.[192] Our finding that symptoms of depression predicted a decline in HDL cholesterol levels was not replicated over 9 years.[28] Conversely, our result that a reduction of depressive symptoms did not coincide with changes in HDL cholesterol was largely comparable to an earlier study over a period of 1 month in which a reduction in depression score did not coincide with changes in HDL cholesterol.[191] Our findings are also in line with the observation that patients with severe depressive symptoms after myocardial infarction who were successfully treated for their depression showed no improvement in their high risk of cardiac mortality.[75]

The fact that a reduction in severity of depression or anxiety did not go together with changes in HDL cholesterol or abdominal obesity, indicates that reductions of depressive or anxiety symptoms do not manifest themselves as improved dyslipidemia or obesity, at least over a rather short term of 2 years. This finding, together with the observed worsening of dyslipidemia and abdominal obesity independent of an improved mental state, indicates that probably multiple relatively stable etiological factors connect a liability to depression and anxiety to lower HDL cholesterol and to abdominal obesity. Among these possible mechanisms are lifestyle, biological, and genetic factors. A first possible lifestyle mechanism is smoking. Smoking lowers HDL cholesterol,[19,75] and people with depressive or anxiety disorders smoke more regularly.[118]

Moreover, they often have difficulty with smoking cessation after mood improvement, possibly due to antidepressant effects of nicotine.[145,197] Sustained smoking could thus have lead to decreased HDL cholesterol levels in people with initially more severe symptoms of depression or anxiety. Smoking did however not explain our results. A second underlying lifestyle factor could be that people who are vulnerable to depression or anxiety, independent of their current mental state, continue to eat more carbohydrates and (saturated) fat.[118] Persistent unhealthy dietary habits may have led to increases in dyslipidemia and abdominal obesity. A biological mechanism may be low-grade inflammation. People with depressive[200,72,199] or anxiety disorders[73] display higher levels of inflammation than controls. At the same time, inflammation causes a reduction in HDL lipoproteins[51] and also induces obesity through leptin resistance.[201,202] As baseline symptoms of depression predict augmentation of inflammation[203] and inflammation may not decline after recovery from depression,[204] chronic inflammation in people who are vulnerable to depression or anxiety might cause progressive dyslipidemia and abdominal obesity. This may be independent of an improved mood. Lastly, it is possible that symptoms of depression and anxiety share genetic and complex biological etiological substrates with HDL cholesterol and abdominal obesity. For instance, gene-environment interactions may have activated the hypothalamic-pituitary-adrenal axis, which subsequently has led to depression as well as to aggravation of obesity.[205] Mechanistic factors may however normalize in the longer term. Our previous observation that HDL cholesterol values in people with a remitted depression during lifetime were similar to those of controls[117] supports this premise.

In addition, it is noteworthy that depressive and anxiety symptoms declined significantly over the 2-year follow-up period. Due to our recruitment method, a large proportion of our subjects had prevalent depressive or anxiety disorders at baseline. Although residual symptoms of depression and anxiety are common, it is estimated that over half of patients with depression show clinical recovery after two years,[342] and also anxiety disorders seem to decline over time.[343,344] This common decline in symptoms of depression and anxiety may have explained the significant decrease of depression and anxiety symptoms in our general sample. Moreover, part of the improvement may be ascribed to regression to the mean effects.

A first important limitation of our study is that changes in depression and anxiety severity and in lipid and obesity values over time showed relatively low variability. This might be caused by the high proportion of subjects from mental health care, who are more likely to have longstanding disorders[9] which may have caused a slower improvement in symptoms of depression and anxiety in the general group. This may have limited the power to detect longitudinal associations. Second, the 2-year time interval between assessments might have been too short to establish

a degree of relieve in depression or anxiety symptoms that was able to account for considerable lipid or obesity changes. A major strength of our study is the prospective design, through which we were able to extensively explore the longitudinal associations of depression and anxiety severity with lipid and obesity patterns. Strength of our recruitment procedures was that because we oversampled subjects in different stages of psychopathology, we could analyse the impact of current and prolonged symptomatology of depression and anxiety with relatively high precision. Another main strength is the assessment of the severity of depression and anxiety using validated scales as well as the assessment of lipid and obesity values at both time points in a large cohort. Furthermore, severity of anxiety symptoms had not yet been prospectively studied in relation to metabolic risk factors. Exploration of this association adds importantly to the existing longitudinal literature, as symptoms of anxiety have been found to be almost as strong markers for dyslipidemia and abdominal obesity as symptoms of depression.

In conclusion, we found that people with more severe symptoms of depression or anxiety showed a decrease in HDL cholesterol levels and an increase in abdominal obesity over the subsequent 2 years, independent of a reduction in symptoms of depression or anxiety. These findings could be of clinical importance. As low HDL cholesterol as well as abdominal obesity are important risk factors for CVD,[17] those people are at elongated and increasing risk of CVD. It is important for clinicians to be aware of an increased CVD risk in patients with depressive and anxiety disorders, that does not seem to fade after remission of symptoms. These patients should therefore be continuously evaluated for the presence of metabolic risk factors as targets for prevention and treatment.

Increased sympathetic and decreased parasympathetic activity rather than changes in hypothalamic-pituitary-adrenal axis activity is associated with metabolic abnormalities

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Journal of Clinical Endocrinology & Metabolism 2010, 95 (5): 2458-2466

ABSTRACT

Introduction
Stress is suggested to lead to metabolic dysregulations as clustered in the metabolic syndrome, but the underlying biological mechanisms are not yet well understood. We examined the relationship between two main stress systems, the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, with the metabolic syndrome and its components.

Methods
The design was baseline data (years 2004–2007) of a prospective cohort: the Netherlands Study of Depression and Anxiety (NESDA). The study comprised general community, primary care, and specialized mental health care. This study included 1883 participants aged 18–65 years. Autonomic nervous system measures included heart rate, respiratory sinus arrhythmia (RSA; high RSA reflecting high parasympathetic activity), and preejection period (PEP; high PEP reflecting low sympathetic activity). HPA axis measures included the cortisol awakening response, evening cortisol, and a 0.5 mg dexamethasone suppression test as measured in saliva. Metabolic syndrome was based on the updated Adult Treatment Panel III criteria and included high waist circumference, serum triglycerides, blood pressure, serum glucose, and low high-density lipoprotein cholesterol.

Results
RSA and PEP were both independently negatively associated with the presence of the metabolic syndrome, the number of metabolic dysregulations as well as all individual components except high-density lipoprotein cholesterol (all $p < 0.02$). Heart rate was positively related to the metabolic syndrome, the number of metabolic dysregulations, and all individual components (all $p < 0.001$). HPA axis measures were not related to metabolic syndrome or its components.

Conclusion
Our findings suggest that increased sympathetic and decreased parasympathetic nervous system activity is associated with metabolic syndrome, whereas HPA axis activity is not.

6.1 INTRODUCTION

It has often been hypothesized that stress leads to metabolic dysregulations.[206-208] In response to stress, two main stress systems, the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis, are both centrally activated.[207,208] Persistent (over)activation of these stress systems could lead to metabolic alterations, such as high blood pressure, serum triglycerides, serum glucose, waist circumference, and low high-density lipoprotein (HDL) cholesterol.[208-210] The metabolic syndrome consists of a cluster of these metabolic abnormalities and predisposes to cardiovascular disease (CVD)[211,212] and diabetes.[213] Whether both stress systems are associated with the metabolic syndrome has only partially been examined.[122,209,210]

Some studies have shown evidence for a role of ANS dysfunction in the metabolic syndrome. For sympathetic nervous system (SNS) activity, measured by, for example, muscle sympathetic nerve activity, elevated levels were found in subjects with the metabolic syndrome.[214,215] However, Grassi et al.[215] showed that different measures of SNS activity show divergent associations with the metabolic syndrome; therefore, evidence for the relationship between purely sympathetic activity and the metabolic syndrome remains ambiguous and cannot be considered conclusive. More evidence is present for a negative relationship between parasympathetic nervous system (PNS) activity and the metabolic syndrome,[216-218] although inconsistencies have been found. For example, PNS activity (as reflected by the high frequency spectra of heart rate variability) was unassociated[217,219] as well as negatively associated with having the metabolic syndrome.[216,218] Studies have also shown inconsistent results for the association of PNS activity with various metabolic dysregulations.[216-218] In addition, some studies were limited by rather short periods of physiological recordings or no consideration of cardiovascular disease and cardiac medication.[216-218]

Cortisol measured in saliva is considered a reliable and noninvasive indicator of HPA axis activity.[220] Although there are several studies that examined the association between salivary cortisol and the metabolic syndrome or its components, the relationship is still not elucidated. Results are inconsistent concerning the direction of the relationship as well as the aspect of the cortisol diurnal rhythm that might be involved. For instance, no,[221,222] negative,[223,224] and positive[225,226] associations have been reported between salivary morning cortisol or cortisol awakening response and components of the metabolic syndrome. Studies specifically examining evening cortisol and metabolic syndrome components are scarce, mostly reporting no association.[221,224] Results regarding cortisol suppression after dexamethasone ingestion showed less suppression after dexamethasone to be associated with hypertension[224] and all other metabolic syndrome components,[223] whereas Putignano et al.[222] reported no association with obesity. However, previous studies were rather small, measured morning cortisol by only one salivary sample, or did not adjust for important covariates such as sleep duration and awakening time.

Therefore, we examined the association between metabolic syndrome and its components with multiple extensive measures of both ANS and HPA axis activity in a large cohort study considering important covariates to explore to what extent both stress systems are involved in metabolic abnormalities.

6.2 METHODS

Subjects

Data are from The Netherlands Study of Depression and Anxiety (NESDA), a large longitudinal cohort study among 2981 adults (18–65 years), 95.2% of North European ancestry (see Ref.[95]). Respondents were recruited from the community, in primary care through a screening procedure conducted among 65 general practitioners, and in specialized mental health care when newly enrolled at one of the 17 participating mental health organization locations. The research protocol was approved by the ethical committee of participating universities and all respondents provided written informed consent.

Of the total sample, we excluded 80 persons using tricyclic antidepressants because of their effect on the ANS,[227] HPA axis,[68] and metabolic syndrome.[105] Of the 2901 remaining participants, we excluded 27 pregnant or breast-feeding women and 158 participants on corticosteroids because of their effects on the HPA axis, leaving a sample of 2716 respondents. Of 109 participants, no ANS data were available, another 695 did not return (sufficient) saliva samples for HPA axis activity assessment, and of 29 persons data on metabolic abnormalities were missing. Therefore, the present study sample consisted of 1883 participants.

Participants in the present study sample (n=1883) did not differ from the excluded participants (n=833) in presence of the metabolic syndrome (21.1 vs. 23.4%, $p = .17$) or CVD (5.8 vs. 7.1%, $p = .18$) but were less often female (64.9 vs. 68.9%, $p = .02$), older (43.0 vs. 39.9 years, $p < 0.001$), and more educated (12.4 *vs.* 11.7 years, $p < 0.001$).

The metabolic syndrome

The metabolic syndrome was defined according to the American Heart Association and National Heart, Lung, and Blood Institute's update of the U.S. National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria.[17] The NCEP-ATP III guidelines define the metabolic syndrome as a presence of three or more of the following criteria: i) waist circumference 102 cm or greater in men and 88 cm or greater in women, ii) triglycerides 1.7 mmol/L or greater (150 mg/dL) or medication for hypertriglyceridemia, iii) HDL cholesterol less than 1.03 mmol/L (40 mg/dL) in men and less than 1.30 mmol/L (50 mg/dL) in women or medication for reduced HDL cholesterol, iv) systolic blood pressure (SBP) 130 mmHg or greater and/or diastolic blood pressure 85 mmHg or greater or antihypertensive medication, and v) fasting plasma glucose 5.6 mmol/L

or greater (100 mg/dL) or antidiabetic medication. The number of metabolic syndrome components was used as an indicator of severity of metabolic abnormalities.[105]

Metabolic syndrome components

In addition to the metabolic syndrome, associations with continuous levels of individual metabolic components were examined to investigate consistency across components. Waist circumference was measured with a measuring tape at the central point between the lowest front rib and the highest front point of the pelvis on light clothing. Triglycerides, HDL cholesterol, and glucose were determined using routine standardized laboratory methods. To incorporate medication use into the continuous variable, for persons using antidiabetic medication when glucose level was less than 7.0 mmol/L (126 mg/dL), a value of 7.0 mmol/L (126 mg/dL) was assigned.[17] Similarly, for persons using fibrates, 0.10 mmol/L (3.8 mg/dL) was subtracted from HDL cholesterol and 0.67 mmol/L (60 mg/dL) was added to triglycerides.[17] For persons using nicotinic acid, 0.15 mmol/L (5.8 mg/dL) was subtracted from HDL cholesterol and 0.19 mmol/L (17 mg/dL) added to triglycerides, based on mean changes after medication treatment.[17] SBP and diastolic blood pressure were measured twice during supine rest on the right arm with the Omron M4-I, HEM 752A, and were averaged over the two measurements. For persons using antihypertensive medication, 10 mm Hg was added to the SBP.[62]

ANS

During the visit to the research centers, The Netherlands Study of Depression and Anxiety subjects were wearing the Vrije Universiteit ambulatory monitoring system. The Vrije Universiteit ambulatory monitoring system is a light-weight, unobtrusive device that records the electrocardiogram (ECG) and changes in thorax impedance (dZ) from six surface electrodes placed at the chest and on the back of the subjects.[228, 229] The interbeat interval time series was extracted from the ECG signal to obtain heart rate, an indicator of combined SNS and PNS activity. To separately index the cardiac effects of both ANS branches, pre-ejection period (PEP; high PEP reflects low SNS activity) and respiratory sinus arrhythmia (RSA; high RSA reflects high PNS activity) were extracted from the combined dZ and ECG signals.

The PEP reflects noradrenergic inotropic drive to the left ventricle and was obtained from the dZ/dt signal, ensemble averaged across 1-min periods time locked to the R-wave of the ECG. The PEP was defined as the interval from the B point (upstroke) to the X point (incisura) of the dZ/dt signal, as described in detail elsewhere.[229] The RSA reflects cardiac parasympathetic activity and was obtained by combining the interbeat interval time series with the filtered (0.1–0.4 Hz) dZ signal, which corresponds to the respiration signal. RSA was obtained by subtracting the shortest interbeat interval (IBI) during heart rate acceleration in the

inspiratory phase from the longest IBI during deceleration in the expiratory phase for all breaths, as described in detail elsewhere.[228] Automated scoring of IBI, RSA, and PEP was checked by visual inspection, and valid data were averaged over 90.2 ± 23 min time to create a single PEP, RSA, and heart rate value.

To additionally investigate whether patterns of sympathetic and parasympathetic co-activation or parallel activation/inhibition were related to the metabolic syndrome, two measures of autonomic balance were acquired following the approach of Berntson et al.[230]. Cardiac autonomic balance (CAB) was calculated as the difference between normalized values of RSA and PEP [formula = zRSA − (−zPEP) (because increased sympathetic control is associated with shortened PEP values, PEP was multiplied by −1)] such that low values reflect parallel high sympathetic and low vagal cardiac control (unfavorable cardiac pattern) and high values reflect low sympathetic and high vagal cardiac control (favorable cardiac pattern). Cardiac autonomic regulation (CoAR) was calculated as the sum of the normalized values of RSA and PEP [formula = zRSA + (−zPEP)] and low values represent co-inhibition (low SNS and low PNS activity) and high values co-activation (high SNS and high PNS activity) of the two cardiac branches.

HPA axis

As described in more detail elsewhere,[231] respondents were instructed to collect saliva samples at home on a regular (working) day, which has shown a reliable and minimally intrusive method to assess the active, unbound form of cortisol.[220] The median time between the interview and saliva sampling was 9.0 d (25th to 75th percentile: 4–22). Saliva samples were obtained using Salivettes (Sarstedt, Germany) at seven time points. The cortisol awakening response includes four sampling points; at awakening (T1) and 30 (T2), 45 (T3), and 60 (T4) min later. Two evening values were collected at 2200 h (T5) and 2300 h (T6). Dexamethasone suppression was measured by cortisol sampling the next morning at awakening (T7) after ingestion of 0.5 mg dexamethasone directly after the saliva sample at 2300 h (T6). Samples were stored in refrigerators and returned by mail. After receipt, Salivettes were centrifuged at 2000 g for 10 min, aliquoted, and stored at −80 C. Cortisol analysis was performed by competitive electrochemiluminescence immunoassay (E170; Roche, Basel, Switzerland), as described in Van Aken et al.[232] The functional detection limit was 2.0 nmol/L and the intra- and inter-assay variability coefficients in the measuring range were less than 10%. Data cleaning excluded values greater than 2 SD above the mean (i.e., above 59.6–123.6 nmol/L for T1–T4, 40.9 nmol/L for T5, 59.8 nmol/L for T6, and 35.6 nmol/L for T7).

One-hour awakening cortisol. The area under the curve with respect to the increase (AUCi) and ground (AUCg) were calculated using the formulas described by Pruessner et al.[233] The AUCg is an estimate of the total cortisol secretion over the first hour after awakening, and the AUCi is a

measure of the dynamic of the cortisol awakening response, more related to the sensitivity of the system, emphasizing changes over time.[234] For area under the curve calculations, all four morning samples were required (n=1584).

Evening cortisol. Because the correlation between the two evening values was high (r = 0.52, $p < 0.001$), the mean of the two values was used for analyses to reflect evening cortisol (n=1871).

Dexamethasone suppression test. A total of 1712 of the 1781 subjects with cortisol sample T1 and T7 (96.1%) had taken the 0.5 mg dexamethasone after 2300 h on the first sampling day. We used a cortisol suppression ratio calculated by cortisol value at awakening on the first day (T1) divided by cortisol value at awakening the next day (T7) after ingestion of 0.5 mg dexamethasone the evening before.

Covariates

Sociodemographic factors included sex, age, and years of attained education. Use of oral contraceptives (yes/no) and menopause (yes/no) were identified by self-report. Smoking status was categorized into never smoked, former smoker, and current smoker. Daily alcohol use was categorized into no, mild to moderate (maximal 2 U/d), and heavy (>2 U/d). Physical activity was assessed by the International Physical Activity Questionnaire[235] and expressed in 1000 metabolic equivalent of task (MET-)minutes in the past week. Cardiovascular disease (including coronary disease, cardiac arrhythmia, angina, heart failure, and myocardial infarction) was ascertained by self-report. Furthermore, it was determined whether subjects were using heart medication by copying the names of medicines from the containers brought in by the subjects. Using the World Health Organization's anatomical therapeutic chemical (ATC) classification, medication was classified. Use both of beta-blockers (ATC code C07, used daily or more than 50% of the time) and other heart medication (ATC codes C01 [cardiac therapy], C02 [antihypertensives], C03 [diuretics], C04 [peripheral vasodilators], C05 [vasoprotectives], C08 [calcium channel blockers], or C09 [renin and angiotensin agents]) was ascertained. Additionally, for analyses with cortisol measures, sampling factors that have been shown to influence cortisol measures by Vreeburg et al.[231] were included. Respondents reported time of awakening and working status on the sampling day. Season was categorized into dark months (October through February) and months with more daylight (March through September). Average sleep duration during the last week was assessed using the Insomnia Rating Scale[236] and dichotomized into sleeping more or less than 6 hours a night.

Statistical analyses

Baseline characteristics were compared across metabolic syndrome status using x^2 and ANOVA statistics. Partial correlation coefficients (adjusting for age, sex, and education) between ANS and cortisol measures were

calculated to examine the inter-correlations between both stress systems. Multiple logistic regression analyses were conducted with ANS measures (i.e., heart rate, RSA, or PEP) and salivary cortisol measures (i.e., AUCg, AUCi, evening cortisol, or cortisol suppression ratio) as independent variables and metabolic syndrome as the dependent variable. Multiple linear regression, adjusted for all covariates, was used to analyze the association of ANS and salivary cortisol measures with either the number of metabolic syndrome components (0–5) or continuous individual metabolic syndrome components as dependent variables. All metabolic syndrome components were normally distributed, except for triglycerides and glucose levels, which were log transformed before analyses. If linear regression with the number of metabolic syndrome components yielded significant results; fully corrected analysis of covariance analyses were performed to compare the mean ANS and HPA axis values of persons with increasing number of metabolic syndrome components (i.e., 0, 1, 2, 3, 4, and 5) and investigate linearity. $p \leq 0.05$ was regarded as statistically significant. All analyses were conducted using SPSS 15.0 (SPSS Inc., Chicago, Illinois, USA).

6.3 RESULTS

In our sample, 21.2% met the criteria for the metabolic syndrome; 25.1% met none of the criteria, 31.3% one, 22.4% two, 12.9% three, 6.4% four, and 1.9% all five criteria. Sample characteristics are presented in Table 1. Persons with the metabolic syndrome were more likely to be male, older, and less educated, a nondrinker or heavy drinker, a former smoker, using heart medication, or having prevalent CVD and were less likely to be using oral contraceptives than persons without the metabolic syndrome. Persons with the metabolic syndrome showed on average a lower RSA, CAB, and CoAR, higher heart rate, and shorter PEP, whereas no differences were seen in cortisol measures, except for a trend toward less suppression after dexamethasone.

Table 2 shows the results of the partial correlations between HPA axis measures and ANS measures adjusted for age, sex, and education. In contrast to an expected inter-correlatedness because of shared central activation of both stress systems, ANS measures did not significantly correlate with HPA axis measures (all $p > 0.11$).

After full adjustment, RSA, heart rate, and PEP were significantly related to the metabolic syndrome as well as the number of metabolic abnormalities (see Table 3 and Figure 1). The odds for the metabolic syndrome increased when RSA and PEP decreased, indicating that decreased parasympathetic and increased sympathetic activity are associated with increased likelihood of metabolic syndrome. Lower RSA

Table 1. Sample characteristics

	Metabolic syndrome		
	No	**Yes**	
n	1484	399	p^a
Sociodemographics			
Age, mean (SD), y	41.1 (13.0)	50.4 (10.1)	<.001
% Female	68.5	51.6	<.001
Education, mean (SD), y	12.7 (3.2)	11.3 (3.3)	<.001
Health factors			
Physical activity, mean (SD), 1000 MET min/week	3.7 (3.0)	3.6 (3.0)	.36
% Smoking			
Non-smoker	32.0	22.6	
Former smoker	35.2	45.1	<.001
Current smoker	32.8	32.3	
% Alcohol use			
Non drinker	14.4	19.5	
Mild/moderate drinker	69.9	61.2	.003
Heavy drinker	15.7	19.3	
% Use beta-blockers	4.3	22.1	<.001
% Use other heart medication	5.7	30.3	<.001
% Use of oral contraceptives	19.5	6.8	<.001
% Post-menopausal women	18.7	26.6	.001
% Cardiovascular disease	5.7	11.5	<.001
Time of awakening, mean (SD), h:min	7:31 (1:16)	7:19 (1:06)	.006
% Working on day of sampling	63.4	56.4	.01
% Sampling in month with more day light	58.6	57.9	.79
% ≤ 6 hours of sleep	24.7	32.3	.002
Autonomic measures			
RSA, mean (SD), ms	46.1 (24.5)	32.2 (19.8)	<.001
HR, mean (SD), beats/min	71.1 (9.3)	72.0 (10.5)	.06
PEP, mean (SD), ms	122.9 (16.2)	119.8 (21.9)	.005
CAB, mean (SD)	0.158 (1.33)	-0.593 (1.57)	<.001
CoAR, mean (SD)	0.053 (1.33)	-0.323 (1.42)	<.001
HPA-axis measures			
AUCg,mean (SD), nmol/l/h	19.0 (7.1)	19.6 (6.9)	.18
AUCi, mean (SD), nmol/l/h	2.4 (6.2)	2.1 (6.6)	.48
Mean evening level, mean (SD), nmol/l	5.4 (3.5)	5.6 (3.0)	.31
Cortisol suppression ratio[b], mean (SD)	2.9 (1.7)	2.7 (1.6)	.10

Table 1. Continued

Continuous measures of metabolic syndrome			
Waist circumference, mean (SD), cm	85.0 (11.2)	103.3 (11.8)	<.001
Systolic BP, mean (SD), mmHg	133.0 (17.8)	151.8 (19.4)	<.001
Glucose, mean (SD), mmol/l[c]	4.9 (1.1)	5.9 (1.2)	<.001
HDL cholesterol, mean (SD), mmol/l	1.7 (0.4)	1.3 (0.4)	<.001
Triglycerides, mean (SD), mmol/l[c]	1.0 (1.5)	1.8 (1.6)	<.001
No. of metabolic components, mean (SD), no.	1.0 (0.8)	3.5 (0.7)	<.001

Abbreviations: SD, standard deviation; MET, metabolic equivalent of task; RSA, respiratory sinus arrhythmia; HR, heart rate; PEP, pre-ejection period; AUCg/i, area under the curve with respect to the ground/increase; BP, blood pressure; HDL, high-density lipoprotein.
[a]: based on x^2 and analysis of variance for dichotomous or categorical and continuous measures respectively.
[b]: cortisol suppression ratio = cortisol T1/ cortisol T7 after 0.5 mg dexamethasone
[c]: glucose and triglyceride levels are back-transformed

Table 2. Correlations coefficients of partial correlation between HPA-axis and ANS measures[a]

	AUCg nmol/l/h	AUCi nmol/l/h	Evening cortisol nmol/l/h	Suppression ratio
RSA, ms	-.031	-.027	-.016	-.010
HR, beats/min	.040	.038	.020	.039
PEP, ms	.037	.006	.046	-.038
CAB	.020	-.002	.043	-.037
CoAR	-.039	-.013	-.030	.041

Abbreviations: RSA, respiratory sinus arrhythmia; HR, heart rate; PEP, pre-ejection period; AUCg/i, area under the curve with respect to the ground/increase.
[a]: adjusted for age, sex and education.

and PEP were also associated with the number of metabolic syndrome components present (see Table 3 and Figure 1). A higher heart rate was associated with increased odds for the metabolic syndrome and an increase in number of metabolic syndrome components. None of the HPA axis measures was associated with the metabolic syndrome or with the number of its components (see Table 3).

Table 4 shows the associations of ANS and HPA axis measures with the different continuous metabolic syndrome components. Again, salivary cortisol measures were not significantly related to the continuous metabolic syndrome components. However, RSA (increased PNS activity) and PEP (decreased sympathetic activity) were negatively associated with waist circumference ($\beta = -0.078$, $p = .005$ and $\beta = -0.143$, $p < .001$, respectively), triglycerides ($\beta = -0.092$, $p = .002$ and $\beta = -0.081$, $p = .001$, respectively), and SBP ($\beta = -0.111$, $p < .001$ and $\beta = -0.115$, $p < .001$, respectively). RSA was also negatively associated with glucose ($\beta = -0.066$, $p = .02$). Heart rate was positively associated with waist circumference ($\beta =$

0.111, $p < 0.001$), triglycerides (β = 0.186, $p < 0.001$), SBP (β = 0.150, $p < 0.001$), and glucose (β = 0.140, $p < .001$) and negatively associated with HDL cholesterol (β = −0.062, $p = .01$).

Table 3. Adjusted[a] associations between the stress systems and metabolic syndrome and number of metabolic syndrome components.

	Metabolic syndrome		Number of metabolic syndrome components	
	OR (95% CI)	*p*	β	*p*
Autonomic nervous system				
RSA, per 10 ms i	0.81 (0.74-0.90)	<.001	-.110	<.001
HR, per 10 bpm i	1.72 (1.46-2.02)	<.001	.220	<.001
PEP, per 10 ms i	0.87 (0.80-0.94)	<.001	-.132	<.001
CAB, per 1 unit i	0.75 (0.67-0.84)	<.001	-.163	<.001
CoAR, per 1 unit i	1.06 (0.94-1.20)	.31	.045	.12
HPA axis				
AUCg, per 10 nmol/l/h i	1.07 (0.88-1.29)	.50	.008	.72
AUCi, per 10 nmol/l/h i	1.05 (0.85-1.30)	.65	-.003	.87
Evening cortisol, per 10 nmol/l i	0.84 (0.57-1.23)	.36	-.012	.56
Cortisol suppression ratio, per 1 unit i	1.05 (0.87-1.26)	.64	.004	.87

Abbreviations: OR, odds ratio; CI, confidence interval; β, standardized beta; i, increase; RSA, respiratory sinus arrhythmia; HR, heart rate; PEP, pre-ejection period; CAB, cardiac autonomic balance; CoAR, cardiac autonomic regulation; HPA, hypothalamic-pituitary-adrenal; AUCg/i, area under the curve with respect to the ground/increase.
[a]: based on logistic and linear regression analyses adjusted for age, sex, education, oral contraceptive use, menopause, cardiovascular disease, physical activity, smoking, alcohol use, use of beta-blockers and other heart medication. For HPA axis, analyses were additionally adjusted for working, awakening time, season and sleep.

When we performed a multivariable analysis in which PEP and RSA were entered together, the odds ratios (ORs) and βs remained largely similar to the separate univariable analyses [e.g., for the metabolic syndrome, RSA OR = 0.83 (95% CI: 0.75–0.92) and PEP OR = 0.88 (95% CI: 0.82–0.95), *p*'s < 0.001], suggesting that both branches are independently associated with the metabolic syndrome and its components. To further investigate whether associations for sympathetic (PEP) and parasympathetic activity (RSA) with metabolic syndrome components were independent from each other, additional analyses were performed with the CAB and CoAR (see Table 3). Results showed that the CAB, reflecting reciprocal SNS activation and PNS inhibition, significantly decreased the odds of metabolic syndrome [per 1 U increase in CAB OR = 0.75 (95% CI: 0.67–0.84)]. Moreover, higher CAB was negatively associated with the number of metabolic dysregulations and all individual components of the metabolic syndrome (except for HDL cholesterol). The CoAR, reflecting SNS and PNS co-activation, did not associate with any of the metabolic measures.

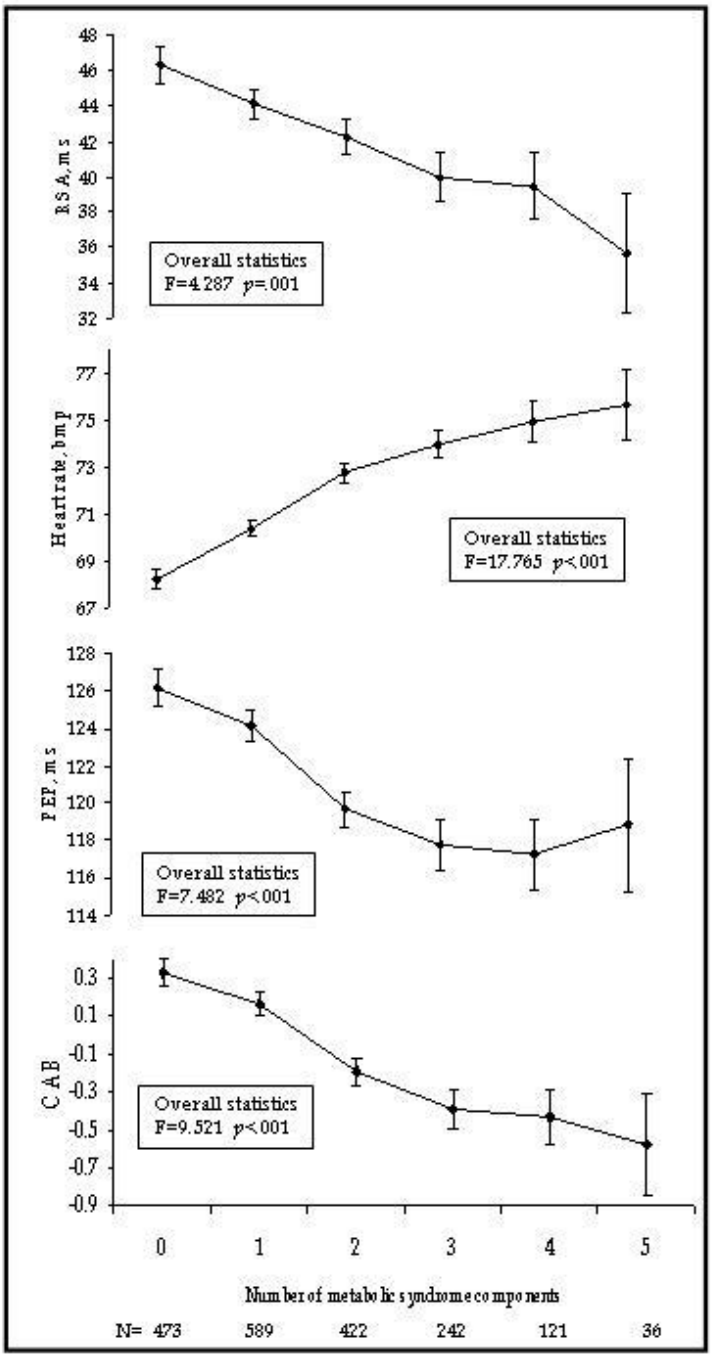
RSA, ms
48
46
44
42
40
38
36
34
32
Overall statistics
F=4.287 p=.001
Heartrate, bmp
77
75
73
71
69
67
Overall statistics
F=17.765 p<.001
PEP, ms
128
126
124
122
120
118
116
114
Overall statistics
F=7.482 p<.001
CAB
0.3
0.1
-0.1
-0.3
-0.5
-0.7
-0.9
Overall statistics
F=9.521 p<.001
0
1
2
3
4
5
Number of metabolic syndrome components
N= 473
589
422
242
121
36

Table 4. Adjusted[a] associations between the stress systems and the individual components of the metabolic syndrome

	Waist circumference		Triglycerides[b]		HDL cholesterol		SBP		Glucose[b]	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
Autonomic nervous system										
RSA, ms	-.078	.005	-.092	.002	.003	.93	-.111	<.001	-.066	.02
HR, bpm	.111	<.001	.186	<.001	-.062	.01	.151	<.001	.140	<.001
PEP, ms	-.143	<.001	-.081	.001	.031	.20	-.115	<.001	-.031	.20
CAB	-.155	<.001	-.113	<.001	.023	.36	-.150	<.001	-.056	.02
CoAR	.083	.01	.019	.49	-.030	.26	.038	.12	-.011	.69
HPA axis										
AUCg, nmol/l	-.028	.21	.024	.31	.021	.36	.000	.99	-.015	.52
AUCi, nmol/l	-.039	.07	.013	.57	-.015	.50	-.014	.50	-.016	.47
Evening cortisol, nmol/l	-.023	.25	.029	.18	.002	.92	.035	.08	-.014	.53
Suppression ratio	.023	.25	.003	.91	-.005	.83	-.014	.49	.005	.81

Abbreviations: HDL, high-density lipoprotein; SBP, systolic blood pressure; β, standardized beta; RSA, respiratory sinus arrhythmia; HR, heart rate; PEP, pre-ejection period; CAB, cardiac autonomic balance; CoAR, cardiac autonomic regulation; HPA, hypothalamic-pituitary-adrenal, AUCg/i, area under the curve with respect to the ground/increase.
[a]: based on linear regression analyses adjusted for age, sex, education, oral contraceptive use, menopause, cardiovascular disease, physical activity, smoking, alcohol use, use of betablockers and other heart medication. For HPA axis, analyses are additionally adjusted for working, awakening time, season and sleep.
[b]: log transformed.

6.4 DISCUSSION

In this large study, we found that decreased PNS and increased SNS activity were associated with metabolic syndrome and its components, whereas HPA axis measures were not. The activity of the ANS and HPA stress systems was not correlated. These results suggest that in contrast to HPA axis dysregulation, ANS dysregulation is strongly associated with metabolic syndrome and might therefore partly be involved in its unfavorable consequences such as the incidence of cardiovascular disease.

The association of low PNS activity with the metabolic syndrome corroborates the findings of some groups[216,218] and contrasts with other groups reporting no association. Previous studies had also reported on the associations between measures of SNS activity and metabolic syndrome, but the evidence was scarce and results were inconsistent.[122,215] The present study provides consistent evidence for an association of increased SNS activity (i.e., lower PEP) with the metabolic syndrome and individual metabolic components.

Although the effects of PEP and RSA on metabolic syndrome and its components were partly independent, a pattern of parallel high SNS and low PNS activity was most strongly associated with metabolic syndrome. In contrast, a pattern of low SNS activity and low PNS activity or high SNS activity with high PNS activity did not show association with the metabolic syndrome. Our findings are strikingly congruent to results of Berntson et

al.[230], who reported a similar relationship between ANS and diabetes. Taken together, these results suggest that especially the combination of increased SNS activity and decreased PNS activity is related to the metabolic syndrome, whereas high SNS activity in the presence of high PNS activity or low PNS activity in the presence of low SNS activity are not.

In line with several studies,[122,221] we found no relationship between salivary HPA axis measures and the metabolic syndrome or its components. These results suggest that the HPA axis is not dysregulated in persons with metabolic syndrome. Most studies that did find associations between salivary cortisol measures and several metabolic syndrome components were not comparable with our study because they studied solely men, used small samples, included only obesity measures, or used just one or two morning samples.[225,226] Important work has been done by Rosmond et al.[237], who reported that in men, a reduced variation in the diurnal cortisol pattern was associated with metabolic dysregulations and predicted higher risk of cardiovascular events after 5 years. However, it is unclear how this abnormal cortisol pattern relates to our salivary cortisol measures. Other studies have found metabolic syndrome to be more frequently accompanied by increased urinary cortisol rather than plasma or saliva cortisol (e.g., Ref.[122]), which could be a result of increased cortisol excretion in combination with increased metabolism. Alternatively, HPA axis hyperresponsiveness after corticotrophin releasing hormone stimulation[238] or acute stress might be more strongly related to metabolic abnormalities, whereas basal activity remains intact.

It is a general belief that the autonomic nervous system and the HPA axis stress systems are highly intertwined[239] because both systems are centrally activated in response to stress, e.g., by the hypothalamus. In addition, both stress systems arouse each other: CRH, which drives HPA axis activity, also seems to stimulate sympathetic flow,[240] and central catecholamines, an ANS marker, seem to stimulate the HPA axis.[241] Although many hypotheses linking the two systems have emerged, previous studies directly correlating ANS and HPA axis measures under resting conditions are scarce. Our results suggest that both systems do not correlate very strongly, and only ANS activity is associated with an unfavorable metabolic state. Both stress systems are responsive and dynamic systems with different temporal courses. Previous studies showed that ANS activity remained high after repeated stress, whereas the HPA axis was desensitized and did not respond with hyperactivity,[242] which might explain why the ANS and HPA axis did not correlate in our study. In addition, results of a study on the metabolic syndrome in relation to HPA axis and ANS measures in a sample of 180 men[122] are in accordance with ours; they reported strong associations between ANS measures and the metabolic syndrome, whereas HPA axis measures were not associated. Finally, it is possible that correlations between the ANS and the HPA axis become more apparent in response to acute stress but are lower when subjects are not experiencing acute stress, such as in our study.

Our study had several strengths, including a large sample size and multiple measures of the HPA axis and sympathetic as well as parasympathetic activity. In addition, it was presented that a specific pattern of parallel decrease in parasympathetic and increase in sympathetic activity was most strongly associated with metabolic dysregulations and the metabolic syndrome. Furthermore, all components that constitute the metabolic syndrome were separately analyzed, and the inter-correlation of both stress systems was investigated. Finally, our sample size enabled us to take important covariates into account. However, some limitations have to be acknowledged as well. First, because analyses were cross-sectional, our results do not indicate any causal direction of the associations found. Future longitudinal studies are warranted to further examine the relationship between the HPA axis, the ANS and metabolic dysregulations. Second, noncompliance with cortisol sampling could have occurred because it was logistically and financially not feasible to electronically monitor compliance.

To conclude, although the ANS was strongly associated with metabolic syndrome and its individual components, the HPA axis was not. In particular, a parallel decrease in parasympathetic and increase in sympathetic activity were associated with metabolic dysregulations and could therefore have an important role in its higher risk of cardiovascular disease.

The impact of biological stress systems and lifestyle on dyslipidemia and obesity in anxiety and depression

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Psychoneuroendocrinology 2012 epub ahead of print

ABSTRACT

Background
Dyslipidemia and obesity have been observed in persons with severe anxiety or depression, and in tricyclic antidepressant (TCA) users. This likely contributes to the higher risk of cardiovascular disease (CVD) in anxiety and depressive disorders. We aimed to elucidate whether biological stress systems or lifestyle factors underlie these associations. If so, they may be useful targets for CVD prevention and intervention.

Methods
Within 2850 Netherlands Study of Depression and Anxiety (NESDA) participants, we evaluated the explaining impact of biological stress systems (i.e., the hypothalamic-pituitary-adrenal [HPA] axis, autonomic nervous system [ANS] and inflammation) and lifestyle factors (i.e., tobacco and alcohol use, and physical activity) on adverse associations of anxiety and depression severity and TCA use with high and low-density lipoprotein cholesterol, triglycerides, body mass index and waist circumference. Through linear regression analyses, percentual change (%Δ) in β was determined and considered significant when %Δ>10.

Results
The inflammatory marker C-reactive protein had the most consistent impact (explaining 14 to 53% of the associations of anxiety and depression severity and TCA use with lipid and obesity levels), followed by tobacco use (explaining 34 to 43% of the associations with lipids). The ANS mediated all associations with TCA use (explaining 32 to 61%). The HPA axis measures did not explain any of the associations.

Conclusions
Increased dyslipidemia and (abdominal) obesity risk in patients with more severe anxiety disorders and depression may be partly explained by chronic low-grade inflammation and smoking. TCAs may increase metabolic risk through enhanced sympathetic and decreased parasympathetic ANS activity. That the HPA axis had no impact in our sample may reflect the possibility that the HPA axis only plays a role in acute stress situations rather than under basal conditions.

7.1 INTRODUCTION

The classical cardiovascular disease (CVD) risk factors dyslipidemia (i.e., high total, low-density lipoprotein [LDL] cholesterol or triglycerides, or low high-density lipoprotein [HDL] cholesterol) and (abdominal) obesity are found to be more common in patients with anxiety disorders and depression.[23-26,43,45,106,107,200] Previously, we demonstrated that not all anxious or depressed patients display higher dyslipidemia and obesity risk. Dyslipidemia and obesity appeared to be particularly present in those with more severe anxiety or depression symptomatology,[117] and in users of tricyclic antidepressants (TCAs).[150] Dyslipidemia and obesity were not related to the use of selective serotonin re-uptake inhibitors (SSRIs) or other antidepressants. The associations of dyslipidemia and obesity with more severe symptoms of depression and anxiety and with TCA use likely contribute to the generally increased prevalence of CVD[100,101] and diabetes mellitus[243] in persons with depressive and anxiety disorders. In order to create anchor points in prevention and treatment of CVD and diabetes, it is of importance to understand the underlying mechanisms.

Several underlying mechanisms may be involved. Hypothalamic-pituitary-adrenal (HPA) axis dysregulation[67,69] as well as decreased parasympathetic and increased sympathetic autonomic nervous system (ANS) activity[200,227,244] and elevated inflammatory markers such as C-reactive protein (CRP), interleukin(IL)-6[72,73,200] and tumor necrosis factor-alpha (TNF-α)[199] have been detected in anxiety and depression and among TCA users.[227,245] Also, unfavourable lifestyle habits such as increased tobacco and alcohol use and decreased physical activity[74,118,128,246-248] have been observed in patients with mood disorders. In turn, these HPA axis,[120,209,249] ANS,[250] inflammatory[51] and lifestyle[75,97,130] alterations are thought to induce dyslipidemia and (abdominal) obesity. Those mechanisms could therefore lie in the causal pathway, ultimately increasing CVD risk in people with anxiety and depressive disorders. If so, they may be useful targets for prevention and intervention.

Within the Netherlands Study of Depression and Anxiety (NESDA) we aim to identify the mechanisms that underlie the relationship of anxiety and depressive severity and TCA use with dyslipidemia and obesity, with possible candidates being biological stress system (i.e., HPA axis, ANS and inflammation) perturbations or lifestyle (i.e., tobacco or alcohol use and physical activity). We are the first to evaluate the role of those potential mechanisms in concert, in a large cohort study.

7.2 METHODS

Subjects

Subjects participated in the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA), an 8-year longitudinal cohort study including 2981 persons aged 18 to 65 years. Subjects were recruited from community, primary care, and mental health care in the Netherlands. Persons with depressive and anxiety disorders as well as healthy controls

were included. For the current study, only cross-sectional baseline data were available. The baseline assessment comprised a face-to-face interview, written questionnaires and biological measurements. The study design has been described in detail elsewhere.[95] The study protocol was approved by the Ethical Review Board of each participating centre, and all subjects signed informed consent at the baseline assessment.

For the current analyses, we excluded 40 (1.3%) subjects with missing values on anxiety or depression severity or on TCA use (see below), and 91 (3.1%) subjects with missing values on lipid or obesity measures (see below), which resulted in a sample of 2850 (95.6%) subjects. In analyses on TCA use, subjects who used TCAs (n=78) were compared with subjects who did not use any antidepressant at all (n=2138), whereas all other analyses were conducted in the entire group (n=2850).

Anxiety and depression severity and TCA use

Anxiety severity was assessed by the 21-item self-report Beck Anxiety Inventory (BAI) ranging from 0 to 63.[171] Depression severity was assessed by the 30-item Inventory of Depressive Symptoms self-report (IDS-SR) ranging from 0 to 84.[110] TCA use (Anatomical Therapeutic Chemical [ATC][111] code N06AA) within the past month was registered by observation of drug containers brought in.

Lipid and obesity measures

HDL and LDL cholesterol, triglycerides, body mass index (BMI) and waist circumference (WC) were previously found to be associated with the aforementioned anxiety and depression characteristics in NESDA.[117, 150] HDL, LDL cholesterol and triglyceride levels were determined from fasting blood samples using routine standardised laboratory methods. To account for medication use, HDL cholesterol, LDL cholesterol and triglyceride values were adjusted according to medication effects observed in trials, as previously performed.[25] Medication use within the past month was registered by observation of drug containers brought in, and ATC coded.[111] For persons using fibrates, 0.10 mmol/L was subtracted from HDL cholesterol, and 0.67 mmol/L was added to triglycerides. For persons using nicotid acid, 0.15 mmol/L was subtracted from HDL cholesterol, and 0.19 mmol/L was added to triglycerides.[167,168] For persons using LDL-lowering medication, 0.74 mmol/L was added to LDL cholesterol.[194] Height and weight were measured to calculate BMI (=weight(kg)/height(m)^2). WC was measured with a measuring tape at the central point between the lowest front rib and the highest front point of the pelvis, upon light clothing. The distribution of residuals was normalized by natural log-transformation of HDL and LDL cholesterol, triglyceride, BMI and WC values.

Biological stress systems

The four *HPA axis* measures included area under the curve with respect to the increase (AUCi) and with respect to the ground (AUCg), mean evening cortisol and a cortisol suppression ratio after 0.5 mg dexamethasone intake. HPA axis measures were based on seven saliva samples taken by subjects at home. Details of assessment and analyses of HPA axis measures have been described in detail elsewhere.[231] The AUCg is an estimate of total cortisol secretion over the first hour after awakening, and the AUCi is a measure of the dynamic of the cortisol awakening response, more related to the sensitivity of the system, emphasizing changes over time.[234]

The five *ANS* measures included heart rate (HR), pre-ejection period (PEP) and respiratory sinus arrhythmia (RSA). Assessment and analyses of ANS measures are described in detail elsewhere.[176] HR is an indicator of combined sympathetic (SNS) and parasympathetic (PNS) nervous system activity; high PEP reflects low SNS activity; RSA reflects cardiac PNS activity.

The three *inflammation* markers included CRP, IL-6 and TNF-α. CRP, IL-6 and TNF-α were determined from initially frozen (at -80°C) serum. 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). Plasma IL-6 levels were measured in duplicate by a high-sensitivity enzyme-linked immunosorbent assay (PeliKine Compact™ ELISA, Sanquin, Amsterdam). Plasma TNF-α levels were assayed in duplicate at Good Biomarker Science, Leiden, The Netherlands, using a high-sensitivity solid phase ELISA (Quantikine® HS Human TNF-α Immunoassay, R&D systems Inc, Minneapolis, MN, United States).

Lifestyle

Number of *tobacco* (i.e., cigarette, cigar or pipe) *and alcohol consumptions* (i.e., glasses) a day were assessed through standardised questionnaires. *Physical activity* was assessed using the International Physical Activity Questionnaire,[112] and expressed in 1000 metabolic equivalent of task (MET)-minutes in the past week. MET-minutes reflect the ratio of the associated metabolic rate for specific activities divided by the resting metabolic rate, multiplied by minutes performed activity.

Covariates

Sociodemographic variables included age and sex. Use of corticosteroids (i.e., ATC code H02, R03BA, R03AK and D07, used more than 50% of the time), beta-blockers (i.e., ATC code C07, used more than 50% of the time), other heart medication (i.e., ATC-codes C01, C02, C03, C04, C05, C08 or C09) and anti-inflammatory (i.e., ATC-codes M01A, M01B, A07EB and A07EC) medication (no/yes) in the past month was identified.

Statistical analyses

Data were missing completely at random (MCAR: Little's MCAR test x^2 = 140.709, df = 334, p = 1.0) on ANS (n=146; 5.2%), HPA axis (n=936; 33.1%), inflammation (n=21; 0.7%) and lifestyle (n=151; 5.4%) variables. Multiple imputation by the iterative Markov chain method was therefore an appropriate way to impute missing data.[251] Age, sex, anxiety severity, depression severity, medication adjusted HDL, LDL cholesterol and triglyceride values, BMI, WC, use of TCAs, corticosteroids, beta-blockers, other heart medication and anti-inflammatory medication were considered as predictors.

Sample characteristics were summarized using means and standard deviations for quantitative variables and percentages for categorical variables. Linear regression analyses, basically adjusted for age, sex and medication use (see Covariates) were conducted to assess the basic associations of anxiety severity, depression severity and TCA use (all independent variables) with lipid (i.e., HDL and LDL cholesterol and triglycerides) and obesity measures (i.e., BMI and WC: all dependent variables). This resulted in basically adjusted beta-coefficients (β^as). Factors that could explain such an association should be associated with both the independent and the dependent variable.[252] Within the NESDA study we previously found that certain biological stress systems and lifestyle factors relate to anxiety, depression and TCA use,[62,68,69,227,253] as well as to lipids and obesity.[176] It is therefore feasible that biological stress systems and lifestyle factors (partially) explain associations of anxiety severity, depression severity and TCA use with lipids and obesity. To study this hypothesis, linear regression analyses were repeated, in turn including biological stress system (i.e., HPA axis, ANS or inflammation) and lifestyle measures (i.e., alcohol or tobacco consumption, or physical activity). When biological stress systems or lifestyle influenced β^as substantially (defined as a change = $[\beta^b * 100\%]/ \beta^a$ of more than 10%, i.e., % Δ > 10), the impact of their separate components was additionally studied. Then, the joint impact of all significant biological stress system and lifestyle mechanisms was studied by including them collectively. In order to more thoroughly evaluate the influence of CVD and diabetes, all 262 subjects with prevalent medicated CVD (i.e., stroke, myocardial infarction, angina pectoris or coronary heart disease, as assessed by standardized questionnaires and observation of drug containers brought in) or diabetes (a glucose value of ≥ 7.0 mmol/L or anti-diabetic medication use) were excluded in a sensitivity analysis. To more thoroughly exclude the possible effects of medication, all 698 (=24.5%) subjects using corticosteroids, anti-inflammatory drugs, beta-blockers, other heart medication or lipid-lowering medication were excluded in a second sensitivity analysis. In a third sensitivity analysis on anxiety and depression severity, all 78 subjects who used TCAs were excluded. All statistical analyses were undertaken with SPSS 18.0 (IBM Company, Chicago, Illinois, USA).

7.3 RESULTS

Table 1 shows the sample characteristics. The mean age of the sample was 42.0 years (SD 13.0) and 33.4% were male. 2.7% used TCAs, whereas 75.0% used no antidepressant at all.

Table 1. Sample characteristics among 2850 subjects with and without anxiety and depressive disorders

Anxiety and depression severity and TCA use		
Anxiety severity (BAI score)	12.1	(10.7)
Depression severity (IDS-SR score)	21.5	(14.1)
Use of tricyclic antidepressants (%)	2.7	
No antidepressant use (%)	75.0	
Lipid and obesity measures		
High-density lipoprotein (HDL) cholesterol (mmol/L)	1.6	(0.4)
Low-density lipoprotein (LDL) cholesterol (mmol/L)	3.2	(1.0)
Triglycerides (mmol/L)	1.3	(0.8)
Lipid lowering medication use (%)	7.1	
Body mass index (kg/m^2)	25.6	(5.0)
Waist circumference (cm)	89.1	(14.0)
Biological stress systems		
Hypothalamic-Pituitary-Adrenal (HPA) axis		
AUCg (nmol/L/h)	18.8	(7.2)
AUCi (nmol/L/h)	2.3	(6.4)
Mean evening level (nmol/L)	5.6	(3.4)
Cortisol suppression ratio*	2.8	(1.7)
Autonomic Nervous System (ANS)		
Heart rate (HR, bpm)	72.0	(9.7)
Pre-ejection period (PEP, ms)	119.5	(18.3)
Respiratory sinus arrhythmia (RSA, ms)	44.4	(25.9)
Inflammation		
C-reactive protein (CRP, mg/L)	2.8	(5.0)
Interleukin (IL)-6 (pg/mL)	1.3	(3.1)
Tumor necrosis factor-alpha (TNF-α, pg/mL)	1.1	(1.4)
Lifestyle		
Tobacco consumptions (n per day)	5.1	(8.8)
Alcohol consumptions (glasses per day)	0.9	(1.5)
Physical activity (in 1000 MET-minutes last week)	3.5	(3.1)
Covariates		
Age (years)	42.0	(13.0)
Sex (% men)	33.4	
Use of corticosteroids (%)	5.5	
Use of anti-inflammatory medication (%)	4.5	
Use of beta-blockers (%)	7.9	
Use of other heart medication (%)	11.5	
Cardiovascular disease (%)	5.7	
Diabetes (%)	4.9	

Abbreviations: AUCg, area under the curve with respect to the ground; AUCi, area under the curve with respect to the increase; BAI, Beck Anxiety Inventory; IDS-SR, Inventory of Depressive Symptoms self-report; MET, metabolic equivalent of task.
Means (standard deviations) are given for quantitative variables. Percentages are given for categorical variables.
*: cortisol at awakening divided by cortisol at awakening the next day after 0.5 mg dexamethasone ingestion.

Tables 2 to 4 show the basically adjusted associations of anxiety or depression severity and TCA use with lipid and obesity measures (i.e., basically adjusted beta-coefficient [β^a]), their associations adjusted for every biological stress system and lifestyle factor, and the relative change of these adjusted βs with respect to β^a (i.e., % Δ).

The associations of anxiety severity with lipid and especially obesity measures (Table 2) were significantly diminished when inflammation was taken into account, with a significant individual contribution of mainly CRP (% Δ ranged from 14.0 concerning LDL to 33.7 concerning BMI). HPA axis and ANS measures did not influence associations significantly. Tobacco use significantly influenced the associations of anxiety severity with lipids (% Δ ranged from 33.7 to 41.5). Alcohol use and physical activity did not explain these associations substantially. All significant mechanisms jointly reduced associations from 29.2 (for WC) to 53.7% (for HDL cholesterol). However, these mechanisms did not sufficiently explain the associations of anxiety severity with HDL cholesterol, triglycerides, BMI and WC: solely the association of anxiety severity with LDL cholesterol lost statistical significance.

The associations of depression severity with lipid and especially obesity measures (Table 3) were significantly diminished by inflammation, CRP (by 14.0% concerning LDL to 31.6% concerning BMI) in particular. HPA axis and ANS measures did not influence these associations significantly. Tobacco use significantly influenced the associations of depression severity with lipids (% Δ ranged from 24.6 to 42.6). Alcohol use and physical activity did not influence these associations substantially. All significant mechanisms jointly reduced associations from 27.4 (for WC) to 69.1% (for HDL cholesterol), but only the association of depression severity with HDL cholesterol lost statistical significance.

The associations of TCA use with lipid and especially obesity measures (Table 4) were significantly diminished (by 11.0 to 52.9%) by CRP. Associations were not significantly influenced by HPA axis measures. By addition of ANS measures, a significant reduction was established in the associations of TCA use with HDL cholesterol (% Δ = 42.2), LDL cholesterol (% Δ = 31.5), triglycerides (% Δ = 60.9), BMI (% Δ = 58.8) and WC (% Δ = 34.9). All individual ANS elements (i.e., HR, PEP and RSA) had significant impact. Tobacco use significantly influenced the associations of TCA use with HDL cholesterol (% Δ = 24.4) and triglycerides (% Δ = 18.8). Alcohol use and physical activity did not considerably affect associations. These mechanisms sufficiently explained the associations of TCA use with HDL cholesterol, triglycerides and BMI, although the associations of TCA use with LDL cholesterol and WC did not lose statistical significance.

Analyses on the original data (i.e., excluding subjects with imputed data; data not shown) showed largely similar results as compared to the analyses on multiple imputated data. Sensitivity analyses in which all 262 subjects with CVD or diabetes were excluded, sensitivity analyses in which

Table 2. Influence of biological stress systems and lifestyle factors on the relationship of anxiety severity with lipids and obesity (n=2850)

	HDL cholesterol		LDL cholesterol		Triglycerides		Body mass index		Waist circumference	
	β	% Δ[b]	B	% Δ[b]	β	% Δ[b]	B	% Δ[b]	β	% Δ[b]
Anxiety severity[a]	-.082**		.050*		.098**		.089**		.096**	
Adjusted for all biological stress systems	-.057*	**-30.5**	.043*	**-14.0**	.065**	**-33.7**	.067**	**-24.7**	.073**	**-24.0**
HPA axis	-.079**	-3.7	.049*	-2.0	.093**	-5.1	.092**	+3.4	.099**	+3.1
ANS	-.080**	-2.4	.050*	+0.0	.090**	-8.2	.093**	+4.5	.097**	+1.0
Inflammation[c]	-.059**	**-28.0**	.043*	**-14.0**	.072**	**-26.5**	.056*	**-37.1**	.065**	**-32.3**
CRP	-.064**	**-21.9**	.043*	**-14.0**	.075**	**-23.5**	.059**	**-33.7**	.068**	**-29.2**
IL-6	-.075**	-8.5	.048*	-4.0	.092**	-6.1	.080**	**-10.1**	.087**	-9.4
TNF-α	-.076**	-7.3	.050*	+0.0	.093**	-5.1	.085**	-4.5	.092**	-4.2
Adjusted for lifestyle[c]	-.038*	**-53.7**	.031	**-38.0**	.062**	**-36.7**	.093**	+4.5	.092**	-4.2
Tobacco use	-.048*	**-41.5**	.033	**-34.0**	.065**	**-33.7**	.097**	+9.0	.094**	-2.1
Alcohol use	-.081**	-1.2	.050*	-0.0	.098**	-0.0	.089**	-0.0	.096**	-0.0
Physical activity	-.080**	-2.4	.050*	-0.0	.094**	-4.1	.087**	-2.2	.094**	-2.1
Adjusted for significant mechanisms	-.038*	**-53.7**	.029	**-42.0**	.052*	**-46.9**	.057**	**-35.9**	.068**	**-29.2**

Abbreviations: ANS, autonomic nervous system; β, standardized beta by multivariate linear regression analysis; CRP, C-reactive protein; HDL, high-density lipoprotein; HPA, hypothalamic-pituitary-adrenal; IL-6, interleukin-6; LDL, low-density lipoprotein; TNF-α, tumor necrosis factor-alpha.

[a:] basically adjusted for age, sex and medication use.

[b]: percent change (% Δ) of β with respect to basically adjusted β[a] as an effect size of the magnitude of influence. Percentages >10% have been marked bold and are considered as significant.

[c]: when a biological stress system or lifestyle influenced β[a]s substantially (i.e., % Δ > 10), the impact of their separate components was additionally studied.

*: statistically significant β at the $p<.05$ level.

**: statistically significant β at the $p<.001$ level.

Table 3. Influence of biological stress systems and lifestyle factors on the relationship of depression severity with lipids and obesity (n=2850)

	HDL cholesterol		LDL cholesterol		Triglycerides		Body mass index		Waist circumference	
	β	% Δ[b]	β	% Δ[b]	β	% Δ[b]	B	% Δ[b]	β	% Δ[b]
Depression severity[a]	-.068**		.057*		.085**		.098**		.102**	
Adjusted for all biological stress systems	-.041*	**-39.7**	.049*	**-14.0**	.054*	**-36.5**	.073**	**-25.5**	.077**	**-24.5**
HPA axis	-.065**	-4.4	.056*	-1.7	.081**	-4.7	.101**	+3.1	.106**	+3.9
ANS	-.067**	-1.5	.057*	+0.0	.081**	-4.7	.103**	+5.1	.105**	+2.9
Inflammation[c]	-.043*	**-36.8**	.049*	**-14.0**	.057**	**-32.9**	.062**	**-36.7**	.069**	**-32.3**
CRP	-.049*	**-27.9**	.049*	**-14.0**	.061**	**-28.2**	.067**	**-31.6**	.074**	**-27.4**
IL-6	-.060**	**-11.8**	.054*	-5.3	.078**	-8.2	.087**	**-11.2**	.092**	-9.8
TNF-α	-.061**	**-10.3**	.057**	-0.0	.080**	-5.9	.093**	-5.1	.098**	-3.9
Adjusted for lifestyle[c]	-.028	**-58.8**	.040*	**-29.8**	.053*	**-37.6**	.099**	+1.0	.097**	-4.9
Tobacco use	-.039*	**-42.6**	.043*	**-24.6**	.057*	**-32.9**	.104**	+6.1	.101**	-1.0
Alcohol use	-.066**	-2.9	.057*	+0.0	.086**	+1.2	.097**	-1.0	.102**	-0.0
Physical activity	-.066**	-2.9	.057*	+0.0	.079**	-7.1	.096**	-2.0	.099**	-2.9
Adjusted for significant mechanisms	-.021	**-69.1**	.038*	**-33.3**	.041*	**-51.8**	.064**	**34.7**	.074**	**-27.4**

Abbreviations: ANS, autonomic nervous system; β, standardized beta by multivariate linear regression analysis; CRP, C-reactive protein; HDL, high-density lipoprotein; HPA, hypothalamic-pituitary-adrenal; IL-6, interleukin-6; LDL, low-density lipoprotein; TNF-α, tumor necrosis factor-alpha.

[a:] basically adjusted for age, sex and medication use.

[b]: percent change (% Δ) of β with respect to basically adjusted β[a] as an effect size of the magnitude of influence. Percentages >10% have been marked bold and are considered as significant.

[c]: when a biological stress system or lifestyle influenced β[a]s substantially (i.e., % Δ > 10), the impact of their separate components was additionally studied.

*: statistically significant β at the $p<.05$ level.

**: statistically significant β at the $p<.001$ level.

Table 4. Influence of biological stress systems and lifestyle factors on the relationship of TCA use with lipids and obesity (n=2203)

		HDL cholesterol		LDL cholesterol		Triglycerides		Body mass index		Waist circumference	
	n^	β	% Δ[b]	β	% Δ[b]	β	% Δ[b]	β	% Δ[b]	β	% Δ[b]
TCA use[a]	78	-.045*		.073**		.069*		.051*		.083**	
Adjusted for all biological stress systems		-.019	**-57.8**	.050*	**-31.5**	.017	**-75.4**	.013	**-74.5**	.046*	**-44.6**
HPA axis		-.046*	+2.2	.073**	+0.0	.066*	-4.3	.052*	+2.2	.083**	+0.0
ANS[c]		-.026	**-42.2**	.050*	**-31.5**	.027	**-60.9**	.021	**-58.8**	.054*	**-34.9**
HR		-.029	**-35.6**	.057*	**-21.9**	.030	**-56.5**	.030	**-41.2**	.062**	**-25.3**
PEP		-.040*	**-11.1**	.062*	**-15.1**	.059*	**-14.5**	.033	**-35.3**	.068**	**-18.1**
RSA		-.039*	**-13.3**	.063*	**-13.7**	.057*	**-17.4**	.043	**-15.7**	.074**	**-10.8**
Inflammation[c]		-.025	**-44.4**	.066*	-9.6	.046*	**-33.3**	.023	**-54.9**	.057*	**-31.3**
CRP		-.029	**-35.6**	.065*	**-11.0**	.048*	**-30.4**	.024	**-52.9**	.059**	**-28.9**
IL-6		-.042*	-6.7	.072**	-1.4	.066**	-4.3	.047*	-7.8	.079**	-4.8
TNF-α		-.039*	**-13.3**	.073**	-0.0	.065**	-5.8	.048*	-5.9	.080**	-3.6
Adjusted for lifestyle[c]		-.020	**-55.6**	.065*	**-11.0**	.054*	**-21.7**	.047*	-7.8	.079**	-4.8
Tobacco use		-.034	**-24.4**	.067**	-8.2	.056*	**-18.8**	.052*	+2.2	.081**	-2.4
Alcohol use		-.037*	**-17.8**	.072**	-1.4	.071**	+2.9	.048*	-5.9	.083**	+0.0
Physical activity		-.044*	-2.2	.073**	-0.0	.066**	-4.3	.051*	+0.0	.082**	-1.2
Adjusted for significant mechanisms		.003	**-93.3**	.048*	**-34.2**	.012	**-82.6**	.013	**-74.5**	.046*	**-44.6**

Abbreviations: ANS, autonomic nervous system; β, standardized beta by multivariate linear regression analysis; CRP, C-reactive protein; HDL, high-density lipoprotein; HPA, hypothalamic pituitary, adrenal; HR, heart rate; IL-6, interleukin-6; LDL, low-density lipoprotein; PEP, pre-ejection period; RSA, respiratory sinus arrhythmia; TCA, tricyclic antidepressant; TNF-α, tumor necrosis factor-alpha.

[a]: basically adjusted for age, sex and medication use.

[b]: percent change (% Δ) of β with respect to basically adjusted β[a] as an effect size of the magnitude of influence. Percentages >10% have been marked bold and are considered as significant.

[c]: when a biological stress system or lifestyle influenced β[a]s substantially (i.e., % Δ > 10), the impact of their separate components was additionally studied.

^: number of subjects that used TCAs.

*: statistically significant β at the $p<.05$ level.

**: statistically significant β at the $p<.001$ level.

Subjects who used TCAs (n=78) were compared with subjects who did not use antidepressants at all (n=2138). Subjects that used other antidepressants were not included in these analyses.

all 698 subjects using corticosteroids, anti-inflammatory drugs, beta-blockers, other heart medication or lipid-lowering medication were excluded, and sensitivity analyses on anxiety and depression severity in which all 78 subjects who used TCAs were excluded, also gave largely similar results (data not shown).

7.4 DISCUSSION

In this large study, we investigated the impact of biological stress systems (i.e., HPA axis, ANS and inflammation) and lifestyle factors (i.e., tobacco or alcohol use, and physical activity) on the associations of anxiety and depression severity and TCA use with dyslipidemia and obesity. The increased risk of dyslipidemia and especially of obesity among persons with more severe anxiety and depression symptoms may have been mediated by low-grade inflammation as marked by higher levels of CRP. Our data also suggest that lipid levels in persons with more severe symptoms of depression or anxiety were adversely affected by current smoking, which was more common among this group. We also found support for the hypothesis that TCA users are prone to obesity and dyslipidemia through the combined effects of inflammation, tobacco use and ANS alterations. HPA axis functioning did not explain increased dyslipidemia and obesity risk among those with severe anxiety or depression symptoms and in TCA users.

The higher risk of dyslipidemia and obesity among persons with more severe anxiety and depression symptoms may have been mediated by low-grade inflammation as defined by the inflammatory marker CRP among the anxious and depressed. Higher levels of inflammation have been observed in persons with anxiety[73] and depression.[72,199,200,254] This is supported by an overrepresentation of inflammation genes in depression[255] and a higher risk of depression in users of pro-inflammatory medication like interferon-alpha.[256] In turn, inflammation may induce dyslipidemia, by stimulating lipid release into the blood stream to fuel host defense and to block cytotoxic effects of inflammogens by binding to them.[51] Adipose tissue cells are highly sensitive to inflammatory signals, and release inflammatory markers themselves,[257] thereby further stimulating dyslipidemia. So, complex and bidirectional associations exist between inflammation, psychopathology, dyslipidemia and obesity. Consequently, increased inflammation among the severely anxious and depressed may induce dyslipidemia and obesity. The fact that we found CRP and not the cytokines IL-6 or TNF-α to be important, might be explained by the fact that CRP is the strongest inflammatory correlate of at least depression,[254] and because CRP is the most accurate and stable marker of systemic inflammation.[258] This probably made the results on CRP more cohesive.

The lifestyle factor tobacco use, and not alcohol use or physical activity, may also elucidate part of the association of depression and anxiety severity with dyslipidemia. Persons with anxiety disorders, and to a greater extent those with depression, smoke much more often than those

without psychopathology.[118] This is possibly due to an increased risk of smoking initiation, decreased cessation motivation, self-medication by nicotine[197] or shared (e.g., genetic) etiological factors.[259] Smoking is well known to detrimentally influence lipid levels.[75,97] It thus is a feasible mechanism in the association between psychopathology and dyslipidemia, and smoking cessation may be of great benefit.

The joint impact of CRP and tobacco use on the associations of anxiety and depression severity and TCA use with lipid measures was generally lower than the sum of their separate influences. This suggests some mechanistic overlap. Smoking is a major environmental factor that raises CRP levels.[260] Tobacco use might therefore have induced part of the increased CRP levels in psychopathology, which successively triggered dyslipidemia. Smoking cessation might therefore additionally reduce dyslipidemic effects through a diminution of inflammatory reactions.

Dyslipidemia and obesity in TCA users may have been partly mediated by increased CRP levels and smoking, but also by ANS alterations among TCA users. TCA use has already been associated with increased CRP levels.[60] Also, persons with depressive symptomatology who smoke, more often use antidepressants than depressed non- or former smokers.[261] As to the ANS, TCAs might reduce parasympathetic activity while increasing sympathetic activity,[227,244] which may also lead to metabolic alterations like dyslipidemia and obesity.[176]

Dyslipidemia and obesity among persons with severe anxiety and depression symptoms and in TCA users were not explained by HPA axis alterations. HPA axis deregulations have been associated though with anxiety and depressive disorders,[67,68,262] and with TCA use.[263] HPA axis deregulations have also been associated with visceral adipose tissue accumulation as well as with (subsequent) dyslipidemia.[209,120,249] Yet, several former studies on the association of HPA axis activity with psychopathology[264] or with dyslipidemia and obesity[221,176] did not report any association. The inconsistencies in earlier research in addition to our null finding might indicate that HPA axis alterations only play a role in certain subgroups.[25] It is also possible that the HPA axis only relates anxiety and depression to dyslipidemia and obesity in acute stress situations and not under basal conditions, such as in our study. Otherwise, urinary rather than salivary cortisol might play a role.[122]

Generally, no combination of putative pathways wholly seemed to explain the associations under study, since most associations of anxiety and depression severity and TCA use with lipid and most strongly with obesity measures remained statistically significant after adjustment for all influential mechanisms. Other mechanisms, such as poor diet rich in carbohydrates and saturated fat among those with anxiety and depression,[118] might (partly) account for residual associations. Also, insomnia and hypersomnia in patients with depression may have promoted obesity and dyslipidemia,[265-267] possibly through altered neuroendocrine processes such as insulin resistance.[268]

There are some limitations of our study that need to be discussed. A first limitation is the cross-sectional design, which did not allow us to make causal inferences on how psychopathology, dyslipidemia, obesity and biological stress systems or lifestyle are temporarily intertwined. Second, the variable concentration of some biological stress markers may have distorted our results. Third, we were unable to take all known biological stress parameters into account. Lastly, we did not have information on other possible mechanisms such as dietary factors. Strengths of our study are the large, psychopathology-based sample, and the assessment of various psychopathological characteristics as well as lipid and obesity measures. HPA axis, ANS and inflammatory factors were measured through well-validated methods. Moreover, we were the first to assess the role of various biological stress systems and lifestyle factors in concert.

In conclusion, the current study provides evidence for an influential role of low-grade inflammation (as defined by increased CRP levels) in the associations of anxiety and depression and TCA use with (abdominal) obesity and dyslipidemia, and of tobacco use in the association of psychopathology with dyslipidemia. ANS alterations may have played an additional role in dyslipidemia and obesity among TCA users. HPA axis functioning was not a significant mediator. Although our findings need to be confirmed, they increase our understanding of the possible mechanisms behind the increased dyslipidemia and obesity risk in mood disorders. If these mechanisms are indeed fundamental, interventions that dampen inflammation (e.g., smoking cessation, physical activity or antioxidant supplementation) and normalize ANS function (e.g., discontinue TCA use) could beneficially affect serum lipids and obesity.

Personality traits and childhood trauma as correlates of metabolic risk factors

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Progress in Neuro-Psychopharmacology & Biological Psychiatry 2012, 36: 85-91

ABSTRACT

Introduction
Personality and childhood trauma may affect cardiovascular disease (CVD) risk. However, evidence for an association with metabolic risk factors for CVD is limited and ambiguous. Moreover, despite their interrelatedness, personality and childhood trauma were not yet studied simultaneously. Therefore, we aimed to explore whether personality and childhood trauma are correlates of metabolic risk factors.

Methods
Among 2755 participants of the Netherlands Study of Depression and Anxiety (NESDA), we investigated through linear regression models whether Big Five personality traits (i.e., extraversion, openness, agreeableness, neuroticism and conscientiousness) and childhood trauma type (i.e., emotional neglect, and psychological, physical and sexual abuse) were correlates of metabolic risk factors (i.e., lipids, waist circumference (WC), glucose and blood pressure). Basic covariates (i.e., age, sex and income level), lifestyle, severity of depressive symptoms and years of education were taken into account.

Results
Openness was the most robust favorable correlate, and sexual abuse was an unfavorable correlate of lipids and WC, and of overall metabolic risk ($\beta = .035$; $p = .04$ and $\beta = -.070$; $p < .001$, respectively).

Conclusions
People with a low openness trait and those who experienced childhood sexual abuse are at higher risk of dyslipidemia and abdominal obesity.

8.1 INTRODUCTION

Cardiovascular disease (CVD) is a major and growing global health problem.[98] Therefore, it is important to identify persons at increased risk of CVD. Lower levels of conscientiousness[76, 269-271] and openness,[77] and higher levels of neuroticism[269] have been related to CVD and general morbidity and mortality. Furthermore, emotional neglect, and sexual or physical abuse during infancy increase risk of CVD in adult women.[272]

Personality and childhood trauma may affect risk of CVD through changes in metabolic risk factors for CVD that include dyslipidemia, abdominal obesity, hyperglycemia and hypertension. As these factors collectively predict over half of CVD cases,[16,17] they are important targets in CVD prevention and treatment.[18] Therefore, it is valuable to know which personality and childhood trauma characteristics are their strongest correlates.

Personality may influence metabolic risk factors[97] through engagement in healthier lifestyles.[78] This might for instance be via the search for external stimulation and social events, vulnerability for depressive symptoms,[79] and amount of self-discipline.[80,81] Trauma may increase risk of CVD through a related lower socio-economic status and unhealthy lifestyles, a higher prevalence of psychopathology due to a fragile character structure,[82-84] or by adverse (early) programming of the biological stress system,[120,273,274] for instance accompanying posttraumatic stress disorder.[275,276]

Several studies on the association of personality traits or childhood trauma with metabolic risk factors have been reported. Openness[277] and conscientiousness[277,278] have been favorably associated with lipid values and abdominal obesity. However, extraversion,[279-283] neuroticism[279-284] and agreeableness[283,284] were ambiguously related to lipids, obesity and blood pressure. Neglect,[85-87] as well as emotional,[85] physical[88] and sexual abuse[87,89,90] during childhood were related to (abdominal) obesity in adulthood.

Personality and trauma are bi-directionally related. Twin studies showed that over 20 percent of the variance in (traumatic) life events is due to genetic influences[91] that are largely mediated by personality.[92] Personality shapes ones personal environment and thus protects for or facilitates the experience of certain (traumatic) events.[92] Also, personality affects the appraisal of traumatic events.[93] The other way around, trauma affects ones perceptions and beliefs. As perceptions and beliefs are building blocks of personality structure, trauma may facilitate unfavorable personality development.[94]

No previous studies jointly investigated both personality characteristics and childhood trauma in relation to metabolic risk factors. The current study is based on a large cohort of subjects with extensive assessment of personality and childhood trauma. We aim to explore whether Big Five personality traits and childhood trauma are independent

correlates of metabolic risk factors for CVD within the Netherlands Study of Depression and Anxiety (NESDA).

8.2 METHODS

Subjects

Subjects participated in the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA), a cohort study including 2981 persons aged 18 to 65 years. NESDA subjects were recruited from community, primary care and specialized mental health care, and selected to represent a range of depressive and anxiety symptoms with subjects having no depressive or anxiety disorder ('controls'), having had disorders in the past, or having a current depressive or anxiety disorder. All subjects completed the baseline assessment, which comprised a face-to-face interview, written questionnaires and biological measurements. A detailed description of the study design can be found elsewhere.[95] For the current study, only cross-sectional baseline data were available. The study protocol was approved by the Ethical Review Board of each participating centre, and all subjects signed informed consent.

Earlier, we found that persons using tricyclic antidepressants (TCAs) have a different metabolic risk profile than other NESDA subjects.[150] We did not find any associations between the use of other antidepressants and metabolic risk factors. The distinctive profile in TCA users is likely induced by TCA side effects, as it was not explained by more severe depressive symptoms in TCA users. Because of their distinct metabolic risk factor profile, TCA users were excluded from the analyses. Of the remaining 2901 subjects, subjects with missing values on personality traits, childhood trauma or metabolic risk factors (see below) were excluded, resulting in the current sample of 2755 subjects. Included subjects (n=2755) did not differ significantly from excluded subjects (n=226) with regard to age (mean 41.9 versus 42.1, p = .80), sex (both 33.6% male, p = 1.00), or CVD prevalence (6.0% versus 4.9%, p = .48).

Personality traits

The Big Five personality traits *extraversion, openness, agreeableness, neuroticism* and *conscientiousness* were measured with the Dutch version[285] of the NEO-Five Factor Inventory (NEO-FFI).[286] The NEO-FFI was sent to participants by mail, and completed before the start of the interview. The NEO-FFI consists of 60 five-point Likert-scaled items, with answer categories from 0 ("strongly disagree") to 4 ("strongly agree**"**). Each of the personality traits is addressed by 12 items. Cronbach's alphas were .84 for extraversion, .69 for openness, .71 for agreeableness, .90 for neuroticism, and .75 for conscientiousness in the current sample. Those values are considered acceptable.[287]

Childhood trauma

Frequency of *emotional neglect, psychological abuse, physical abuse* and *sexual abuse* was assessed retrospectively by the Childhood Trauma Interview that was previously used in the Netherlands Mental health Survey and Incidence Study (NEMESIS).[13,82] Subjects were asked the following questions concerning their first 16 years of life: 1) "Were you emotionally neglected, meaning nobody ever listened to you at home, your problems and experiences were ignored, and you felt that there was no attention or support from your parents?", 2) "Were you psychologically abused, meaning being yelled at, falsely punished, subordinated to your siblings, or being blackmailed?", 3) "Were you being abused physically, meaning being hit, kicked, beaten up or other types of physical abuse?", and 4) "Were you sexually abused, meaning being touched or having to touch someone in a sexual way against your will?". Scores for each question were categorized into never (score 0), once / sometimes (score 1) or regular / (very) often (score 2).

Metabolic risk factors

High-density lipoprotein (HDL) cholesterol, triglycerides, waist circumference (WC), glucose, diastolic (DBP) and systolic (SBP) blood pressure, and an overall metabolic risk factor score were included as metabolic risk factors. Blood samples were taken after a mean of 11:14 h overnight fasting period (SD=1:50 h). HDL cholesterol and triglycerides were determined according to routine laboratory methods. To account for use of lipid-lowering medication, HDL cholesterol and triglyceride values were adjusted according to published changes, as has been done before.[25] Medication use within the past month was registered by observation of drug containers brought in, and ATC coded.[111] 0.10 mmol/L was subtracted from HDL cholesterol and 0.67 mmol/L was added to triglycerides for persons using fibrates.[167,168] HDL cholesterol was lowered by 0.15 mmol/L, and 0.19 mmol/L was added to triglycerides for persons using nicotid acid. WC was measured with a measuring tape at the central point between the lowest front rib and the highest front point of the pelvis, upon light clothing. Glucose levels were determined by routine laboratory methods. For persons using anti-diabetic medication with a glucose level below 7.0 mmol/L [126 mg/dL] a value of 7.0 mmol/L [126 mg/dL] was used in the analyses, as was done before.[25] DBP and SBP were both averaged over two measurements during supine rest on the right arm by the OMRON M4 IntelliSense (HEM-752A, Omron Healthcare, Inc., Bannockburn, Illinois, US). For persons using antihypertensive medication, 5 mmHg was added to DBP, and 10 mmHg to SBP, as described previously.[25] These values represent the average decline in blood pressure in antihypertensive medication trials.[169,170] In order to normalize residuals, HDL cholesterol, triglyceride, WC, glucose, DBP and SBP levels were naturally log-transformed. As a measure of severity of metabolic abnormalities, a continuous overall metabolic risk score was computed by

mediating z-scores (i.e., standardized scores) of a HDL cholesterol and triglycerides index (i.e., (-zHDL cholesterol + zTriglycerides) / 2), WC, glucose, and a blood pressure index (i.e., (zDBP + zSBP) / 2).

Covariates

Sociodemographic variables included *age*, *sex* and *income level*. Prevalent medicated *CVD* (i.e., stroke, myocardial infarction, angina pectoris or coronary heart disease) was assessed by standardized questionnaires and observation of drug containers brought to the interview. Personality and childhood trauma affect lifestyle,[80,81] and thereby metabolic risk factors.[78,97] Therefore, lifestyle factors were taken into account; number of *tobacco* (i.e., cigarettes, cigars or pipe) and *alcohol consumptions* a day were assessed through standardized questionnaires; *physical activity* was assessed using the International Physical Activity Questionnaire,[112] and expressed in units of 1000 metabolic equivalent of task (MET)-minutes in the past week. MET minutes reflect the ratio of the associated metabolic rate for specific activities divided by the resting metabolic rate, multiplied by minutes performed activity. Since depression is associated with personality,[79] childhood trauma[82] and metabolic risk factors,[117,150] *depression severity* - as assessed by the 30-item Inventory of Depressive Symptoms self-report (IDS-SR)[133] ranging from 0 to 84 - was taken into account as an additional covariate. *Years of education* were also included as an additional covariate.

Statistical analyses

Sample characteristics were summarized using means and standard deviations for normally distributed quantitative variables, medians and inter-quartile ranges for non-normally distributed quantitative variables, and percentages for categorical variables. Correlations between metabolic risk factors (except for the overall metabolic risk score) were calculated by Pearson's correlation coefficient. Separate associations of every personality trait, and each type of childhood trauma with individual continuous metabolic risk factors and with the overall metabolic risk score were assessed by linear regression analyses. Analyses were adjusted for age, sex, income and CVD, and for smoking, alcohol use and physical activity. To determine the relative importance of personality traits and childhood trauma, for all metabolic risk factors regression analyses were carried out, adjusted for age, sex, income, CVD, smoking, alcohol use and physical activity. Personality traits and childhood trauma types with $p<.10$ in the preceding separate analyses were entered simultaneously into the regression model. Adjusted R^2 was calculated to indicate the amount of variance in metabolic risk factors that was explained by the regression model. To explore the impact of depressive symptoms on the associations of personality and childhood trauma with metabolic risk factors, the latter models were additionally adjusted for depression severity. As openness is suggested to be related to intelligence,[288] it was additionally investigated

whether years of education accounted for multivariate associations of openness with metabolic risk factors. And since personality traits could affect metabolic risk factors especially in those who experienced childhood trauma, their interaction was tested by entering personality trait x childhood trauma interaction terms in fully adjusted models. In order to more thoroughly evaluate the influence of CVD, all 166 subjects with CVD (see Covariates) were excluded in sensitivity analyses. All statistical analyses were undertaken with SPSS 17.0 (IBM Company, Chicago, Illinois, USA).

8.3 RESULTS

Sample characteristics are presented in Table 1. The mean age of the sample was 41.9 years (SD = 13.1) and 33.6% was male. 6.0% of the sample had prevalent CVD. Emotional neglect was more frequently experienced regular or (very) often (20.4%) than once or sometimes (17.6%). Psychological, physical and sexual abuse were more frequently experienced once or sometimes (13.4, 9.9 and 9.3% respectively) than regular or (very) often (10.8, 2.8 and 1.3% respectively).

Correlations between metabolic risk factors ranged from -.09 (between HDL cholesterol and DBP) through .78 (between DBP and SBP). Table 2 shows the separate associations of personality traits and childhood trauma with continuous metabolic risk factors. Since associations did not differ importantly between the model that was adjusted for age, sex, income and CVD, and the model that was additionally adjusted for smoking, alcohol use and physical activity, solely the crude and the fully adjusted models are reported. In the fully adjusted model, extraversion was associated with a higher SBP. Openness was associated with higher HDL cholesterol levels, and with lower triglycerides, WC, SBP and overall metabolic risk. Agreeableness was associated with lower triglyceride levels, WC and overall metabolic risk. Neuroticism was associated with a higher DBP. Conscientiousness was associated with none of the metabolic risk factors. Regarding childhood traumas, emotional neglect was associated with lower SBP. Psychological and physical abuse both were related to lower levels of HDL cholesterol and to a higher WC and overall metabolic risk. Sexual abuse was associated with lower levels of HDL cholesterol, and with higher WC and overall metabolic risk. The amplification of associations of sexual abuse with HDL cholesterol, WC and overall metabolic risk, and of emotional neglect with SBP after adjustment, was determined by childhood traumas being more prevalent among women. Figure 1 illustrates that HDL cholesterol levels increase, and triglycerides and WC decline with a higher score on openness. It also exemplifies that HDL cholesterol diminishes and WC increase with a higher frequency of childhood sexual abuse.

In Table 3, the multivariate association model is presented. Personality traits and childhood trauma types with $p<.10$ in separate linear regression analyses (see adjusted model in Table 2) were entered

Table 1. Sample characteristics in 2755 subjects

Characteristics		
Age	41.9	(13.1)
Sex (% men)	33.6	
Income (per month, in Euros)	2100.0	(1300.0-2900.0)
CVD (%)	6.0	
Tobacco consumptions (n per day)	0.0	(0.0-8.6)
Alcohol consumptions (n per day)	0.4	(0.02-1.3)
Physical activity (1000 MET-minutes last week)	3.0	(1.4-4.9)
Depression severity (IDS-SR score)	19.0	(9.0-31.0)
Metabolic risk factors		
HDL cholesterol (mmol/L)[a]	1.6	(1.3-1.9)
Triglycerides (mmol/L)[b]	1.1	(0.8-1.5)
Lipid-lowering medication use (%)	6.9	
Waist circumference (cm)	87.0	(79.0-97.0)
Glucose (mmol/L)[c]	5.0	(4.7-5.5)
Antidiabetic medication use (%)	3.2	
Diastolic blood pressure (mmHg)	80.0	(73.5-88.5)
Systolic blood pressure (mmHg)	132.0	(121.5-147.5)
Antihypertensive medication use (%)	14.4	
Personality traits		
Extraversion	25.0	(7.3)
Openness	26.2	(6.0)
Agreeableness	31.8	(5.3)
Neuroticism	24.1	(9.4)
Conscientiousness	30.2	(6.1)
Childhood trauma		
Emotional neglect (%)		
Once / sometimes	17.6	
Regular / (very) often	20.4	
Psychological abuse (%)		
Once / sometimes	13.4	
Regular / (very) often	10.8	
Physical abuse (%)		
Once / sometimes	9.9	
Regular / (very) often	2.8	
Sexual abuse (%)		
Once / sometimes	9.3	
Regular / (very) often	1.3	

Means (standard deviations) and medians (inter-quartile ranges) are given respectively for normally and non-normally distributed quantitative variables.
Percentages are given for categorical variables.
[a] To convert to mg/dL, multiply by 39; [b] To convert to mg/dL, multiply by 89;
[c] To convert to mg/dL, multiply by 18
Abbreviations: CVD, cardiovascular disease; HDL, high-density lipoprotein; IDS-SR, Inventory of Depressive Symptoms self-report; MET, metabolic equivalent of task.

Table 2. Separate crude associations of personality traits and childhood trauma with metabolic risk factors in 2755 subjects

	HDL cholesterol		Triglycerides		WC		Glucose		DBP		SBP		Overall metabolic risk	
	β[a]	*p*	β[a]	*p*	β[a]	*p*	β[a]	*p*	β[a]	*p*	β[a]	*p*	β[a]	*p*
Crude														
Personality traits														
Extraversion	**.050**	.01	**-.061**	.001	**-.066**	.001	**-.070**	<.001	**-.077**	<.001	**-.037**	.05	**-.087**	<.001
Openness	**.098**	<.001	**-.074**	<.001	**-.131**	<.001	**-.043**	.02	**-.065**	.001	**-.079**	<.001	**-.119**	<.001
Agreeableness	**.136**	<.001	**-.099**	<.001	**-.115**	<.001	**-.062**	.001	-.031	.11	**-.045**	.02	**-.135**	<.001
Neuroticism	-.008	.67	-.004	.82	**-.043**	.03	**-.053**	.01	-.025	.18	**-.100**	<.001	**-.042**	.03
Conscientiousness	.049	.01	-.028	.15	.001	.96	.019	.31	.011	.56	**.052**	.01	-.008	.66
Childhood trauma														
Emotional neglect	.029	.12	.014	.46	**.042**	.03	**.066**	.001	**.049**	.01	-.011	.57	**.045**	.02
Psychological abuse	-.032	.09	**.041**	.03	**.083**	<.001	**.062**	.001	**.046**	.02	.012	.51	**.082**	<.001
Physical abuse	**-.040**	.04	**.043**	.02	**.071**	<.001	**.038**	.05	.021	.28	.006	.73	**.069**	<.001
Sexual abuse	-.006	.75	.008	.66	.022	.24	.004	.85	.022	.25	**-.041**	.03	.015	.43

[a] β coefficients indicate the standardised beta by linear regression analysis. Statistically significant (p<.05) associations are marked bold.
[b] Adjusted for age, sex, income, CVD, tobacco use, alcohol use and physical activity.
Abbreviations: CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure; WC, waist circumference.

Table 3. Multivariate association model of personality traits and childhood trauma in relation to metabolic risk factors in 2755 subjects

	HDL cholesterol		Triglycerides		WC		Glucose		DBP		SBP		Overall metabolic risk	
	β[a]	*p*	β[a]	*p*	β[a]	p	β[a]	p	β[a]	p	β[a]	p	β[a]	P
Personality traits														
Extraversion											.030	.08		
Openness	**.071**	<.001	**-.036**	.04	**-.092**	<.001			-.031	.07	**-.040**	.01	**-.070**	<.001
Agreeableness	.018	.32	**-.041**	.03	-.023	.20							-.031	.06
Neuroticism					.002	.93			**.040**	.02				
Conscientiousness														
Childhood trauma														
Emotional neglect			-.034	.06							**-.038**	.03		
Psychological abuse	-.018	.37			**.042**	.03	.031	.07					.033	.08
Physical abuse	-.012	.56			.025	.21							.019	.31
Sexual abuse	**-.043**	.02			**.041**	.02							**.035**	.04
Adjusted R^2	.22		.16		.29		.21		.21		.29		.34	

[a] β coefficients indicate the standardised beta by enter method linear regression analysis. Solely personality traits and childhood trauma types with $p<.10$ in separate analyses (see Table 2) were included. Statistically significant ($p<.05$) associations are marked bold.
Analyses were adjusted for age, sex, income, CVD, tobacco use, alcohol use and physical activity.
Abbreviations: CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure; WC, waist circumference.
Adjusted R^2 indicates the variance in metabolic risk factors that is explained by the regression model.

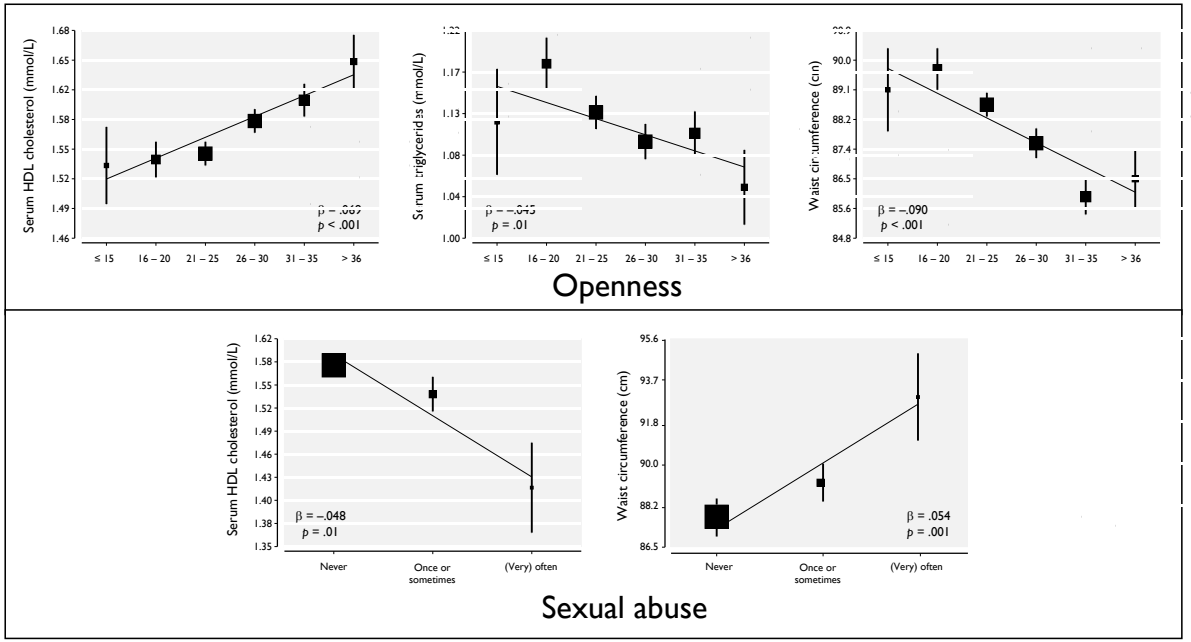

Figure 1.
The mean levels on logarithmic scales (with error bars representing standard errors) for HDL cholesterol, triglycerides and waist circumference according to categories of openness and for HDL cholesterol and waist circumference according to categories of childhood sexual abuse. The dotted lines indicate regression lines. The size of each square is proportional to the number of subjects. β coefficients and their *p* values indicate standardized betas by linear regression analyses. Means and betas were adjusted for age, sex, income, CVD, tobacco use, alcohol use and physical activity

simultaneously. The model was adjusted for age, sex, income, CVD, smoking, alcohol use and physical activity. Models were additionally adjusted for depression severity (data not shown). Openness was significantly associated with higher HDL cholesterol levels, and with lower triglycerides, WC, SBP and overall metabolic risk. Additional adjustment for depression severity did not reduce these associations considerably (i.e., by less than 10%). Agreeableness was associated with lower triglyceride levels, which was significantly determined by depression severity (β -.041 to -.025, i.e., 39.0% decrease). Neuroticism was associated with a higher DBP, which was significantly determined by depression severity (β .040 to -.016, i.e., 140.0% decrease). Emotional neglect was associated with a lower SBP. Psychological abuse related to a higher WC. Additional adjustment for depression severity considerably reduced this latter association (β .042 to .033, i.e., 21.4% decrease) to statistically non-significant. Physical abuse was not related to any of the metabolic risk factors any more. Sexual abuse remained associated with lower HDL cholesterol, and with higher WC and overall metabolic risk values. Additional adjustment for depression severity considerably reduced the associations of sexual abuse with WC (β .041 to .036 [p = .04], i.e., 12.2% decrease) and overall metabolic risk (β .035 to .031 [p = .06], i.e., 11.4% decrease). Adjusted R^2s ranged from .01 to .06 in crude models, and from .16 to .34 in adjusted models. Years of education significantly influenced associations of openness with HDL cholesterol (β .071 to .042 [p = .02], i.e., 40.9% decrease), triglycerides (β -.036 to -.007 [p = .72], i.e., 80.6% decrease), WC (β -.092 to -.052 [p = .003], i.e., 43.5% decrease), SBP (β -.040 to -.007 [p = .71], i.e., 82.5% decrease) and overall metabolic risk (β -.070 to -.032 [p = .06], i.e., 54.3% decrease). Interactions between personality traits and childhood trauma types in their associations with metabolic risk factors were all non-significant (all p >.05). Sensitivity analyses in which all 166 subjects with CVD or all 485 subjects on lipid-lowering, antidiabetic or antihypertensive medication were excluded yielded largely similar results (data not shown).

8.4 DISCUSSION

In this large study, we most robustly found higher levels of openness to protect people from, and childhood sexual abuse to make people vulnerable to adverse levels of the metabolic CVD risk factors dyslipidemia and abdominal obesity. Our findings were largely independent of the lifestyle factors smoking, alcohol use and physical activity, and of each other. To date, several studies have addressed these relationships,[25,85,279-282,284,289-294] with ambiguous results. More essentially, the current focus on personality as well as on childhood trauma is of great importance as theoretical evidence suggests a bidirectional influence between personality and trauma. Our findings might help identifying persons at increased risk of CVD in the future.

First, we will discuss the most important favorable correlate of metabolic risk factors: openness. More openness was associated with favorable HDL cholesterol, triglyceride and SBP levels, and with a lower WC. One former study also found facets of openness to be related to a lower WC.[277] Other studies did not report specific associations of openness with metabolic risk factors.[282,284] However, our findings are in line with the fact that persons with a high trait of openness have a better physical (including cardiovascular) health.[78] This may be mediated by a higher average intelligence level.[295] Indeed, years of education - as a proxy of intelligence - explained a substantial part of the associations of openness with HDL cholesterol, triglycerides, SBP and WC. The associations with HDL cholesterol and WC remained statistically significant and were therefore not sufficiently explained by education. Other influential factors may be increased interest in adopting physical activities, and more openness to public health recommendations. Although the relationship of openness with lipids and WC was of limited strength, it may explain part of the association between high openness and a lower overall mortality risk.[76]

The most important unfavorable correlate of metabolic risk factors was childhood sexual abuse. People with a history of sexual abuse were prone to abdominal obesity and lower HDL cholesterol levels. People experiencing such childhood trauma might be more prone to an adverse metabolic profile through a lower socioeconomic status[296] and accompanying unhealthy lifestyle habits. However, adjustment for socioeconomic status and lifestyle did not substantially alter associations. Alternatively, traumatic events during childhood might cause epigenetically modified activation of multiple genes involved in abdominal obesity and HDL cholesterol phenotyping. Animal studies have revealed that environmental adversities early in development profoundly affect epigenetic DNA methylation and histone deacetylation processes.[297] An example of epigenetic modification by childhood trauma may be silencing of glucocorticoid receptor gene expression[298] and a corresponding chronic adaptation of the stress system.[273,299] The accompanying higher levels of circulating cortisol[274] could contribute to metabolic alterations like abdominal obesity and lower HDL cholesterol levels.[25,120] However, probably only the accumulated epigenetic modification of multiple genes by childhood sexual abuse could adversely affect obesity and HDL cholesterol levels. Other gene regions that may be involved are those that are part of other pathways for stress regulation like inflammation[300] and autonomic nervous system functioning. Increased depressive symptoms among people who experienced childhood trauma[82,84] might also account for an adverse metabolic profile. Childhood trauma may adversely affect the set points of several endocrine systems and thereby cause among others a persistent elevation of prolactin[301] or thyroid dysregulation.[302] This might subsequently reduce serotonergic neurotransmission[301,303] and thereby cause depressive symptoms. Depression severity, however, did only explain part of the association in the current study. An obesity

tendency among sexually abused people was already found in some – although not all[88] – studies,[87,89,90] and might reduce HDL cholesterol levels.[51] Suggested sequelae of sexual abuse that might lead to adverse metabolic risk factor values are posttraumatic stress disorder,[276] eating disorders,[304] disrupted reproductive hormone regulation and increased feelings of anger.[87] Obesity might also serve as a defense posture that blocks unwanted sexual interest.[305]

Other personality traits and childhood traumas were also related to adverse metabolic risk, although less prominently. Agreeableness was associated with higher levels of triglycerides, neuroticism and emotional neglect were related to a higher blood pressure, and psychological abuse to abdominal obesity. Most of these associations were however significantly determined by an increased amount of depressive symptoms associated with these personality and trauma characteristics in our study,[84,306] which is also well-known from the literature.[307] It is noteworthy that conscientiousness was not associated with metabolic risk factors at all. In another large adult sample, conscientiousness was associated with favorable lipid[278] and abdominal obesity[277] levels. However, within this former study only certain facets of conscientiousness were related to less abdominal obesity. Also, conscientiousness is related to increased physical activity.[308] But physical activity was not taken into account in this former study. This might have attenuated the former associations of conscientiousness with lipid values,[278] as physical activity partly explained these associations in the current study. Theoretically, personality and childhood trauma seem to be bi-directionally connected. However in the current study, associations of metabolic risk factors with personality were not modified by childhood trauma, and vice versa associations of metabolic risk factors with childhood trauma were not modified by personality.

Our analyses have several limitations. First, the cross-sectional design does not allow us to make causal inferences on whether personality and trauma precede metabolic risk factors or vice versa. Second, although the experience of childhood trauma is rather stable, it has been retrospectively reported. This may have introduced recall bias. Third, the exploration of several hypotheses has increased the risk of false positive findings (i.e., type 1 error). Strengths of our study are the large sample size and the extensive assessment of personality, childhood trauma and metabolic risk factors. Another strength is the joint investigation of personality and childhood trauma as correlates of metabolic risk factors.

In conclusion, we found that persons with a low openness trait as well as persons who experienced childhood sexual abuse are at higher risk of adverse metabolic risk factor profiles, especially dyslipidemia and abdominal obesity. Future research is required to verify these results. These could eventually guide the development of CVD prevention and intervention guidelines.

Summary and general discussion

9.1 SUMMARY

Depressive and anxiety disorders as well as cardiovascular disease (CVD) are highly prevalent and their major contribution to the worldwide burden of disease will continue to increase. Substantial evidence implies that depressive and anxiety disorders increase the risk of CVD. There is a growing interest in whether depression and anxiety increase the risk of metabolic adversities as well. Metabolic adversities like dyslipidemia, abdominal and overall obesity, hypertension and hyperglycemia tend to cluster in individuals as the metabolic syndrome. Because these metabolic adversities predict over half of CVD cases, they may help to explain the increased risk of CVD in depression and anxiety. So far, findings on the association of metabolic risk factors for CVD with depressive and anxiety disorders are equivocal.

It was the overarching intend of this thesis to study which characteristics (that is, disorders, severity or dimensions) of depression and anxiety make people prone to certain metabolic risk factors for CVD. The association of antidepressant use with metabolic risk factors was also examined. Moreover, the contribution of biological stress systems and lifestyle to these associations was explored. Additionally, the relationship of personality traits and childhood trauma with metabolic risk was addressed. Studies were based on the Netherlands Study of Depression and Anxiety (NESDA), a large longitudinal cohort study involving 2329 people with lifetime depressive and/or anxiety disorders and 652 healthy controls.

First, we concentrated on the question whether characteristics of depression and anxiety were cross-sectionally associated with metabolic risk factors. In **chapter 2**, it was described that, overall, people with a current major depressive disorder (MDD) and/or an anxiety disorder were not at an increased risk of the metabolic syndrome or its components as compared to controls. However, people with more severe symptoms of depression and to a lesser extent those with more severe symptoms of anxiety were at increased risk of the metabolic syndrome. This increased risk of the metabolic syndrome was driven by a higher prevalence of abdominal obesity, low high-density lipoprotein (HDL) cholesterol and elevated triglycerides. First, these findings illustrated that scales that assess the severity of symptoms of depression or anxiety better reflect individual metabolic derangements than categorical diagnoses. Therefore, severity scales allow determining more precise associations of depression and anxiety with metabolic risk. Second, these findings showed that symptoms of depression and anxiety are not related to an increased risk of the metabolic syndrome as such but to the metabolic risk factors abdominal obesity and dyslipidemia in particular. That especially the components abdominal obesity and dyslipidemia are related to depression and anxiety may explain the mixed findings of previous research on the whole metabolic syndrome in depression or anxiety.

Another finding was that users of tricyclic antidepressants (TCAs) were prone towards abdominal obesity, hypertriglyceridemia and hypertension. This was independent of depressive symptoms, and therefore may reflect TCA-specific side effects.

In **chapter 3** the focus was on the cross-sectional association of dyslipidemia with depression and anxiety. HDL cholesterol levels were lower, and triglyceride levels higher in people with a current MDD than in those with a remitted MDD or controls. People with more severe symptoms of depression had higher levels of total and low-density lipoprotein (LDL) cholesterol and of triglyceride and lower levels of HDL cholesterol and were thus prone towards dyslipidemia.

Whether specific depression and anxiety symptom dimensions of the tripartite theoretical model related specifically to metabolic risk factors was explored in **chapter 4**. Somatic arousal was, independent of lifestyle factors, associated with increased abdominal obesity, triglyceride levels and blood pressure.

Longitudinal associations of depression and anxiety with metabolic risk factors were addressed in **chapter 5**. More severe symptoms of depression and anxiety at baseline predicted a decrease in HDL cholesterol levels and an increase of abdominal obesity over the subsequent 2 years. A reduction of symptoms of depression and anxiety over this time period was not related to amelioration of lipid or abdominal obesity values. This indicated that people who are vulnerable to symptoms of depression or anxiety may display a progression of dyslipidemia and abdominal obesity rather than a decline, even if they have an improvement in mood state. If depression or anxiety were directly related to dyslipidemia and obesity, one would expect that fluctuations in mood state would go together with similar fluctuations in lipid and obesity values. Since such convergence was not objectified, it was concluded that severe symptoms of depression or anxiety may not be directly related to dyslipidemia and abdominal obesity. Rather stable etiological factors – such as sustained smoking, unhealthy diets, inflammation or shared genetic substrates – may connect them.

As described above, people with more severe symptoms of depression and anxiety as well as TCA users were at increased risk of dyslipidemia and of abdominal and overall obesity. Subsequently, it was investigated whether biological stress systems and lifestyle contributed to these cross-sectional associations. Associations of the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis with metabolic risk were portrayed in **Chapter 6**. Increased sympathetic nervous system (SNS) and decreased parasympathetic nervous system (PNS) activity but not basal HPA axis functioning were related to the metabolic syndrome and all of its components. This indicated that ANS dysfunctioning but not HPA axis dysregulation relates to metabolic risk.

In **chapter 7** it was reported that elevated levels of the systemic inflammatory marker C-reactive protein (CRP) as well as smoking

substantially explained the increased prevalence of dyslipidemia and obesity among people with more severe symptoms of depression or anxiety. ANS dysregulations additionally contributed to the metabolic risk among TCA users. ANS dysregulations may be a side effect of TCAs. These findings enhance our understanding of the mechanisms behind the increased risk of dyslipidemia and obesity in depressive and anxiety disorders. Because these putative pathways did not completely explain dyslipidemia or (abdominal) obesity among severely depressed or anxious people, other contributors (e.g., dietary or genetic factors) to these associations remain to be identified.

In **chapter 8** the relation of Big Five personality traits (i.e., extraversion, openness, agreeableness, neuroticism and conscientiousness) and childhood trauma type (i.e., emotional neglect, and psychological, physical or sexual abuse) with metabolic risk factors was additionally studied. Less openness as well as sexual abuse during childhood were independently associated with lower HDL cholesterol and with abdominal obesity. In addition, less openness was related to a higher blood pressure.

Altogether, the findings of chapters 2 through 8 indicate that symptom severity measures of depression and anxiety are more strongly and consistently related to metabolic risk than disorder classifications. Moreover, it was shown that more severe symptoms of depression and anxiety were related to progressive dyslipidemia and obesity but not to hypertension or hyperglycemia. Low-grade systemic inflammation as well as smoking partly contributed to these associations. The use of TCAs was related to an increased risk of dyslipidemia, obesity and hypertension, partly due to enhanced sympathetic and decreased parasympathetic ANS activity. Somatic arousal, childhood sexual abuse and less openness were associated with an increased metabolic risk as well.

If future research confirms these findings, this may help to identify the particular patients who are at a high risk of metabolic adversities and thereby of CVD, and indicate that screening and treatment of metabolic risk factors may be of benefit. Moreover, the factors that contributed to these associations (that is, smoking, inflammation and ANS imbalance) may facilitate the development of new and more fundamental treatment options to reduce CVD risk in patients with depressive or anxiety disorders.

9.2 GENERAL DISCUSSION

In this general discussion the main findings of this thesis will be reviewed, which may contribute to a more comprehensive theory of the role of depression and anxiety in metabolic risk. Also, methodological considerations, and potential implications for future research and clinical practice will be delineated.

9.2.1 THE METABOLIC SYNDROME AND ITS COMPONENTS

The metabolic syndrome has been hypothesized to connect depression and anxiety with CVD. Consequently, several former studies investigated the relationship of depression or anxiety with the whole metabolic syndrome rather than with its individual metabolic components.

However, debate exists whether the metabolic syndrome is a valid concept.[116,309] A first point of criticism is that the metabolic syndrome might be too heterogeneous to define it as a single disorder: combinations of metabolic risk factors vary considerably between individuals. Second, probably no single pathophysiological mechanism underlies the metabolic syndrome. That makes it difficult to develop one treatment that can beneficially affect all components of the metabolic syndrome. A third subject of debate is that the metabolic syndrome does not seem to add to the prediction of CVD beyond the contribution of each individual component. To compare our findings with previous research we studied the metabolic syndrome in relation to depression and anxiety. But because of the questioned validity of the metabolic syndrome concept, we also focused on the relative importance of its individual components.

The findings of this thesis underscore the criticism that the metabolic syndrome may be too heterogeneous to define it as a single disorder. We observed that people with symptoms of depression or anxiety were at increased risk of the metabolic syndrome. However, this increased risk of the metabolic syndrome was driven by a higher prevalence of (abdominal) obesity, low HDL cholesterol and elevated triglycerides (i.e., dyslipidemia) only. Those people were not prone towards hypertension or hyperglycemia. Symptoms of depression and anxiety do thus not necessarily relate to the metabolic syndrome as a whole but only to some specific components. Our findings do not stand alone. Earlier studies that focused on all metabolic syndrome components also mainly reported associations of depression and anxiety with dyslipidemia and obesity,[20-30, 43-46] and more seldom with hypertension[21,27] or hyperglycemia.[22,43,45] Because depression and anxiety are especially related to (abdominal) obesity and dyslipidemia, associations with the whole metabolic syndrome could be weakened. This may explain the mixed findings of previous research on the metabolic syndrome in depression or anxiety.

Why are dyslipidemia and obesity but not hypertension or hyperglycemia associated with depression and anxiety? Maybe etiological factors associated with depression and anxiety such as smoking, inflammation and a sedentary lifestyle mainly affect lipid and obesity

values. Further, core symptoms of depression such as changes in appetite, a loss of energy and reduced initiative (inducing a sedentary lifestyle) may primarily stimulate dyslipidemia and obesity. The other way around, obesity may cause pain in overloaded joints[143] and a lower self-esteem through weight-related prejudices,[310] and therefore induce symptoms of depression.

In sum, compelling evidence exists that symptoms of depression and anxiety are particularly associated with dyslipidemia and obesity rather than with all metabolic syndrome components. As a consequence, we recommend that future studies focus on the individual metabolic risk factors and not (only) on the metabolic syndrome as a whole in relation to depression and anxiety. This approach will clarify the relative importance of individual metabolic risk factors in relation to depression and anxiety.

9.2.2 PSYCHOLOGICAL INDICATORS OF METABOLIC RISK

9.2.2.1.1 Severity of depression and anxiety and metabolic risk

It is invaluable to determine which characteristics of depression and anxiety are most strongly associated with an increased metabolic risk. Subsequently, such information may help to improve prevention and intervention programs.

Various previous studies examined whether depressive or anxiety disorders were related to metabolic risk. Some of these studies reported that depressive or anxiety disorders were related to metabolic adversities, while others did not find such an association. We also did not consistently find that depressive or anxiety disorders were associated with an increased overall metabolic risk. Results of studies on metabolic risk in depressive or anxiety disorders are thus ambiguous.

Patients with a disorder are commonly compared to those without the disorder. Reasons for this approach are that it eases comparability to previous research, that disorder concepts are simplified, and that studies match cut-off points that are used in clinical practice.

However, persons differ in their quantity of symptoms of depression or anxiety. Consequently, symptoms of depressive and anxiety disorders are gradually distributed within the general population without a clear cut-off between people with or without a disorder.[311] By classification into diagnostic groups such variation in symptom severity is not taken into account, which may result in a loss of valuable information.

Considerable methodological literature demonstrates the negative consequences of dichotomizing gradual, continuous variables within scientific research (see for example: [162,312,313]). The loss of variation causes a drop in effect sizes and in power. This increases the risk of not finding a significant result when the effect actually is present (that is, type 2 error). This may explain why studies on metabolic risk that categorize subjects in those with and without dichotomous depressive or anxiety disorders yielded inconsistent results.

In this thesis, associations of metabolic risk with severity of depressive or anxiety symptoms were indeed more consistent and robust than those with diagnosis groups. Likewise, an earlier study reported that severity of depressive symptoms tended to be associated with abdominal obesity and significantly related to lower HDL cholesterol levels. But associations between the presence or absence of a depressed mood and metabolic risk factors were not observed.[25]

The importance to define psychological state as a continuous measure is increasingly recognized. The fact that in developing the new, fifth version of the international Diagnostic and Statistical Manual (DMS-V) of mental disorders, there is high global interest in incorporating a dimensional component into the existing categorical binary classification system underscores this tendency.

A comment should be added to our findings. NESDA participants were recruited from general practices and outpatient mental health care. Patients with the most severe depressive and anxiety disorders who are admitted to inpatient mental health care were therefore not part of our sample. As a result, our findings cannot be generalized to the most severely depressed and anxious patients. It is conceivable that inpatients through more severe and complex psychopathology are more vulnerable to dyslipidemia and (abdominal) obesity than outpatients. Alternatively, inpatients may have a higher risk of weight loss and malnutrition which may reduce body weight and total cholesterol levels. Studies that address these associations among inpatients have however been much more scarcely reported. In an extension of NESDA, inpatients have been recruited.[314] Studies on metabolic risk in depression and anxiety within this sample are underway. These will clarify whether our findings also apply to a more severely depressed and anxious inpatient population.

9.2.2.1.2 The contribution of smoking and inflammation

Understanding mechanisms linking depression and anxiety to dyslipidemia and obesity could provide opportunities for prevention and intervention. What factors may have contributed to the liability towards dyslipidemia and obesity in people with more severe symptoms of depression and anxiety?

First, the tendency towards dyslipidemia in people with more severe symptoms of depression or anxiety was substantially explained by smoking. This might be because they started smoking easier, possibly because of shared (e.g., genetic) etiological factors.[197] Moreover, people with symptoms of depression or anxiety may have had less motivation to quit. This is inherent to the lack of motivation accompanying their disease, but there is also evidence that nicotine has antidepressant effects.[197,198] Smoking is thought to increase total and LDL cholesterol as well as triglyceride levels and to lower HDL cholesterol[75,97] and hence is an important target in the management of dyslipidemia.[17] Moreover, smoking is strongly linked to other adverse lifestyle factors like increased saturated

fat, cholesterol and alcohol intake[315] that may exacerbate dyslipidemia. In sum, smoking importantly relates to depression and anxiety as well as to dyslipidemia. It is thus plausible that smoking partly explained the increased risk of dyslipidemia in people with severe symptoms of depression or anxiety.

Elevated serum levels of the systemic inflammation marker CRP additionally explained the increased risk of dyslipidemia and of obesity in people with more severe depressive or anxiety symptoms. It is known that people with depressive[72] or anxiety disorders[73] display higher levels of inflammatory markers among which CRP. In turn, inflammation may induce dyslipidemia. Inflammatory factors stimulate the release of lipids into the bloodstream to provide energy for host defense. At the same time, inflammation causes a reduction in HDL lipoproteins, resulting in a decreased reverse cholesterol transport.[51] Adipose tissue cells react to these signals by releasing inflammatory markers themselves.[257] Thereby, adipose tissue additionally promotes dyslipidemia in a vicious circle relationship. Elevated CRP levels might also lead to obesity. It is thought that circulating CRP binds to leptin, through which the action of leptin is reduced (which is called 'leptin resistance').[201,202] The hormone leptin controls appetite after eating. Leptin resistance leads to insufficient suppression of appetite and therefore to increased food intake. This may ultimately lead to obesity.

To sum up, inflammation is linked to depression and anxiety on the one hand and to dyslipidemia and obesity on the other hand. It is therefore conceivable that increased inflammation in people with symptoms of depression or anxiety partly explained their vulnerability to dyslipidemia and obesity. Moreover, since smoking substantially raises CRP levels,[260] smoking could have partly induced the increased inflammation in depression and anxiety.

Yet, smoking and inflammation did not fully explain dyslipidemia and obesity among people with more severe symptoms of depression or anxiety. A complexity of factors is eligible as linking mechanism between depression and anxiety on the one hand and lipids and body fat on the other hand. Therefore, probably multiple factors underlie the liability towards dyslipidemia and obesity among people with symptoms of depression and anxiety.

Our longitudinal findings also supported the idea that depression and anxiety were not directly related to dyslipidemia and obesity, but could be due to various underlying factors. If depression or anxiety were directly related to dyslipidemia and obesity, one would expect that fluctuations in mood state over time would go together with similar fluctuations in lipid and obesity values. However, an improvement in mood over time did not coincide with reductions of dyslipidemia or obesity. Dyslipidemia and abdominal obesity even aggravated. This indicates that rather stable etiological factors in people who are vulnerable to symptoms of depression or anxiety cause a progression of dyslipidemia and abdominal obesity,

independent of ameliorations in mood state. From a broader perspective, our longitudinal results are in line with the finding that treatment of depression does not ameliorate the prognosis of existent CVD.[316,317] This observation further stresses the need to gain insight into the mechanisms that are responsible for persistent poor cardiovascular outcomes in depression and anxiety.

Another factor that could further contribute to progressive dyslipidemia and obesity is that people who are vulnerable to depression or anxiety, independent of their current mental state, continue to eat less healthy with more carbohydrates and saturated fat.[118] Persistent unhealthy dietary habits may lead to increases in dyslipidemia and obesity. Moreover, it is possible that symptoms of depression and anxiety share genetic substrates with HDL cholesterol and abdominal obesity. For instance, complex gene-environment interactions may have activated the HPA axis, which subsequently has led to depression as well as to aggravation of obesity. Another possibility is that depressed and anxious people are less healthy in general. In this thesis only CVD and diabetes mellitus were taken into account, and these conditions did not explain the associations found. But several other chronic conditions like renal disease, rheumatoid arthritis and chronic obstructive pulmonary disease are related to depression or anxiety[318-320] as well as to metabolic risk factors.[321-323] Hence, it is conceivable that depression and anxiety are accompanied by a poorer overall health status,[324] which more robustly induces dyslipidemia and obesity.

Research has only just begun to unravel the mechanisms that underlie metabolic risk in depression and anxiety. Besides measurement error and random fluctuations, other factors than smoking and inflammation could account for the unexplained variance in the associations of dyslipidemia and obesity with more severe symptoms of depression and anxiety. However, the precise role of these factors remains to be elucidated by future research. The identification of these factors is essential as these could provide additional leads to better prevent and treat dyslipidemia and obesity in depression and anxiety.

9.2.2.2 TCA use and metabolic risk

Patients who used TCAs were at an increased risk of dyslipidemia, abdominal and overall obesity and hypertension, which could be side effects of TCAs. These findings fit well with the growing evidence of adverse effects of TCAs.[58-63] In secondary care, TCAs are commonly prescribed by psychiatrists. A detailed understanding of their side effects is important to be able to adequately weigh the metabolic risks and the benefits of TCA prescription against alternative treatments. Our findings also stress the importance to monitor for metabolic risk during TCA treatment.

We found that an increased SNS and decreased PNS activity of the ANS as well as increased systemic inflammation partly explained the tendency towards dyslipidemia and obesity in users of TCAs. A higher rate

of smokers among TCA users additionally explained part of their vulnerability towards dyslipidemia. Previous research already indicated such an ANS imbalance and inflammation as TCA side-effects. It has been found that TCAs are agonists for the peripheral α1 adrenergic receptors,[63] which trigger sympathetic activation of the ANS. This sympathetic response may have induced dyslipidemia and obesity, and also vasoconstriction which increases blood pressure. TCAs also have other adverse effects on the cardiovascular system. Their use has also been associated with a decreased parasympathetic control of the heart by the vagus nerve.[62,244] This reduced cardiac vagal control lowers the variability in heart rate. Such beat-to-beat fluctuations in the rhythm of the heart are however essential for good cardiac health. For that reason, reduced heart rate variability (HRV) predicts greater cardiac mortality.[325] Increased systemic inflammation was also observed as a side effect in a former study,[60] although the mechanism that underlies an inflammatory response to TCAs is still poorly understood.

Our findings also showed that higher smoking rates among TCA users explained part of their dyslipidemia. Maybe TCA users initially had a more severe form of depression and were therefore more likely to smoke. This may have confounded their tendency towards dyslipidemia. Depressed NESDA participants on TCAs did not display higher depression severity scores than those free of TCAs, but this is probably attributable to efficacy of TCAs. According to treatment guidelines, TCAs should only be prescribed after unsuccessful administration of SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs).

ANS dysregulation, inflammation and smoking did not entirely explain associations of TCA use with dyslipidemia, obesity or hypertension. Probably other factors are also involved. One such a factor may be antihistaminergic effects of TCAs, which may induce weight gain[58,59] and subsequently dyslipidemia.[131] Another possibility is the abovementioned probability that TCA users initially have more severe and longer lasting symptoms of depression. These severe and prolonged symptoms together with possible side effects of previously used antidepressants may have amplified their metabolic risk.

9.2.3 CAUSAL PATHWAYS OF METABOLIC RISK IN DEPRESSION AND ANXIETY

How can we be sure that depression and anxiety lead to metabolic disturbances? Is there a possibility that this association also runs in the opposite direction? In other words, can metabolic disturbances lead to symptoms of depression or anxiety as well? Insight into cause and consequence of these conditions is still limited. Such knowledge is essential to determine the direction of preventive and therapeutic strategies. Our longitudinal information made it possible to add to the literature on the direction of possible causality.

We assumed that depression preceded dyslipidemia and obesity. The reason for this assumption is that key symptoms of depression are a change in appetite or weight. Moreover, depression and anxiety are often accompanied by unhealthy lifestyle changes. Furthermore, it is thought that depression and anxiety are associated with dysregulated biological stress systems. This could aversely affect lipid levels and body fat. In our longitudinal analyses, more severe symptoms of depression or anxiety at baseline predicted a worsening of dyslipidemia and obesity over time. This finding supports our assumption that depression and anxiety precede dyslipidemia and obesity. Additional evidence for this temporal sequence is derived from meta-analyses that showed that depression preceded obesity.[195,326]

The reverse causal route that dyslipidemia and obesity cause depression or anxiety is plausible as well. Although a genetic study reported that the apolipoprotein E genotype which anchors basal cholesterol levels did not determine depression scores,[40] another study reported that dyslipidemia did predispose to depression.[106] Moreover, a meta-analysis[195] as well as later studies[327,328] showed that obesity increases the risk of future depression. For instance weight-based discrimination[310] could cause feelings of depression. Other evidence for reverse causation comes from a large prospective cohort study which reported that a Mediterranean diet – which is preventive for dyslipidemia and obesity - protects against depression.[247]

Taken together, it is likely that the association of dyslipidemia and obesity with depression and anxiety runs in two directions. Depression and anxiety on the one hand and dyslipidemia and obesity on the other hand might reinforce each other in a vicious cycle.

Because no definite conclusions can be drawn from the relatively scarce studies on longitudinal associations of metabolic risk with depression and anxiety, there lays a major challenge for future research to investigate the possibility of bidirectional causation. In NESDA we studied whether symptoms of depression or anxiety preceded dyslipidemia or obesity. To verify the hypothesis of bidirectionality, it would be compelling to investigate within NESDA data whether lipid or obesity levels predict symptoms of depression or anxiety as well. In addition, replication of longitudinal research on these causal pathways within other longitudinal data collections as well as in treatment trials is warranted.

9.2.4 CLINICAL AND FUTURE RESEARCH IMPLICATIONS

Health research in the past decades has increasingly focused on the interplay between mental and physical health, of which this thesis is an example. This research field more and more indicates that mental difficulties like depression and anxiety are associated with an array of adverse physical outcomes among which diabetes mellitus and CVD. Still, in clinical practice a division exists between the care for mental and physical illnesses. In the care of people with depression or anxiety, there is

not yet a systematic approach to detect and treat co-morbid physical conditions. Within this patient group, physical conditions may therefore progress unnoticed into severe physical ailments. In line with the growing scientific evidence, our findings further stress the need to implement physical care in mental health care. Better awareness in mental care for physical jeopardies could eventually reduce morbidity and mortality rates associated with co-morbid physical conditions such as CVD.

The main finding delineated in this thesis is that severe symptoms of depression and to a lesser extent of anxiety are associated with an increased risk of dyslipidemia and (abdominal) obesity. Because depression and anxiety are among the most common mental disorders, general practitioners (GPs) and especially mental health care professionals regularly treat patients with severe symptoms of depression or anxiety. They could therefore play an important role in reducing the risk of dyslipidemia and obesity and ultimately of CVD among this patient group.

Although weight loss frequently occurs in people with depression, weight gain (with obesity and dyslipidemia as end points) is also regularly observed in patients with depression. Although weight gain might be seen as a normal consequence of depression and of certain antidepressant medication use, clinicians should become more aware of the increased CVD morbidity and mortality associated with weight gain and related dyslipidemia.

In future research, it should be determined whether screening for dyslipidemia and obesity in severely depressed or anxious patients is effective. Severity of depressive and anxiety symptomatology could among others be assessed by the Inventory of Depressive Symptoms (IDS) and the Beck Anxiety Questionnaire (BAI). The IDS and BAI were applied in NESDA and are valid and internationally applied severity scales for depression and anxiety that take little time. We found that people with an IDS score from 49 or a BAI score from 30 displayed a significantly increased risk of dyslipidemia or obesity. Although these thresholds are arbitrary and need to be verified, they provide an indication for cut-off scores for research on dyslipidemia and obesity screening.

When patients report severe symptoms of depression or anxiety higher than the abovementioned threshold, it may be recommendable that GPs and psychiatrists assess their fasting lipid profile and their degree of obesity. The leading dyslipidemia guideline[97] advices dyslipidemia screening in adults at increased risk of CVD at least five-yearly. Overall and abdominal obesity should be assessed during intake and regularly thereafter. A body mass index (BMI [kg/m^2]) of over 25.0,[57] and a waist circumference (WC) of > 102 cm in men or > 88 cm in women[17] are the most widely accepted indicators of overall and abdominal obesity.

If dyslipidemia or obesity is present, diminution of smoking and inflammation might reduce these conditions. Smoking cessation already is generally recommended to reduce dyslipidemia and inflammation,[17, 97] and this general recommendation may facilitate implementation. The most

promising way to reduce smoking dependence within this specific patient group is an integrated behavioral and pharmacological approach combined with psychological counseling of depression or anxiety.[329] Such smoking cessation programs should focus on short-term goals, like building up self-efficacy and motivation to quit, and then stimulating gradual abstinence.[330]

Of course, prevention is the best cure. In severely depressed or anxious patients without obesity or dyslipidemia, clinicians should focus on primary prevention of these conditions, because subsequent weight loss and reduction of dyslipidemia through for example quitting smoking are more difficult to accomplish. This could be achieved by sensitizing patients to the health risks associated with obesity and dyslipidemia and detrimental lifestyle habits like smoking, and through encouraging self-care and self-monitoring in terms of lifestyle and weight.[331]

Future research should determine whether reduction or prevention of smoking and inflammation really reduces the risk of dyslipidemia and obesity among severely depressed or anxious people. If proven effective, screening people with more severe symptoms of depression or anxiety for dyslipidemia and obesity and subsequent prevention and modification strategies could become part of multidisciplinary guidelines and thereby help preventing CVD. Current general[332,333] and mental health care guidelines[334,335] only advice to assess whether or not a depressive or anxiety disorder is present. The assessment of anxiety and depression severity should then be additionally included into these guidelines.

Other strategies could also beneficially affect dyslipidemia and obesity in people with more severe symptoms of depression or anxiety. Physical activity and weight reduction are both recommended to reduce dyslipidemia,[97] obesity[17] and inflammation.[17] Physical activity further has the advantage that it may help to improve mood,[336] at least in the short term.[337] Guided running therapy is therefore already included in international guidelines for treatment of mild to severe depression.[334,338] In the future it should be examined whether for example stimulating physical activity adds to dyslipidemia and obesity management in this specific patient group.

Another finding of this thesis was that TCA users had an increased risk of dyslipidemia, obesity and hypertension. Severity of depression did not explain these results, and so these metabolic disturbances could reflect side effects of TCAs. Therefore, clinicians should be reticent about prescribing TCAs. However, TCAs are usually prescribed after other kinds of antidepressants or psychological interventions have failed to sufficiently relieve symptoms of depression or anxiety. TCA use is thus one of the last resorts, and the few alternatives also have contraindications and side effects.[334] When there are no better alternatives, it should therefore be considered whether, for example based on TCA blood levels, a lowest effective dose can be determined. Furthermore, screening TCA users for

dyslipidemia, obesity and hypertension at the intake and regularly thereafter could be important.

Taken together, the findings in this thesis and related literature underscore that patients reporting severe symptoms of depression or anxiety should be considered as a population at increased risk of dyslipidemia and obesity. The close relationship of depression and anxiety with dyslipidemia and obesity may justify a more integrated clinical approach. Future research should further verify these associations, and whether actions aimed at prevention, detection and management of dyslipidemia and obesity are of benefit. Such actions may ultimately reduce CVD morbidity and mortality in people with depression and anxiety.

9.2.5 METHODOLOGICAL CONSIDERATIONS

Specific limitations of the studies presented in this thesis were already addressed in the corresponding chapters. One of the overarching limitations comprised the limited ability to conclude about causality because of the observational and mainly cross-sectional nature of our studies. A second limitation encompassed the unavailability of additional explanatory information such as information about diet.

In this General discussion, some additional considerations were attended to. A first consideration was that due to attrition the most severely depressed and anxious people were not optimally represented within the NESDA study. As a result, the findings of this thesis are not merely generalizable to those most severely ill. The degree of generalization to this specific population could however be clarified by data of NESDA inpatients.[314] A related restriction is that only adults aged 18 through 65 were included in NESDA. This stands in the way the generalizability of our findings to the elderly. In the future, our findings could be verified in elderly within the Netherlands Study of Depression in Older persons (NESDO)[339], which was designed largely comparable to NESDA.

A final consideration was that the increased metabolic risk among TCA users might not just be a reflection of adverse TCA effects. TCAs are normally prescribed only after unsuccessful treatment with SSRIs and SNRIs. Therefore, TCA users could have been a subgroup with initially more severe and longer lasting symptoms of depression. These severe and prolonged symptoms together with possible side effects of previously used antidepressants may have contributed to their increased metabolic risk.

9.2.7 GENERAL CONCLUSION

The aim of this thesis was to clarify which aspects of depression and anxiety are related to an increased metabolic risk, and which factors contribute to these associations. Taken together, our findings indicate that people with more severe symptoms of depression and anxiety are at particular risk of progressive dyslipidemia and (abdominal) obesity. The higher rates of smoking and systemic inflammation among people with depression or anxiety partially accounted for their adverse metabolic

profile. Dysregulations of the autonomic nervous system partly explained why users of tricyclic antidepressants displayed an increased risk of dyslipidemia and (abdominal) obesity as well, and also of hypertension. These important findings shed light on useful avenues for future research, and on preventive and therapeutic insights and directions.

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List of abbreviations

ANS	Autonomic nervous system
ATC	Anatomical therapeutic chemical
AUCg	Area under the curve with respect to the ground
AUCi	Area under the curve with respect to the increase
AZS	Autonome zenuwstelsel
BAI	Beck Anxiety Inventory
BMI	Body mass index
CAB	Cardiac autonomic balance
CI	Confidence interval
CoAR	Cardiac autonomic regulation
CVD	Cardiovascular disease
CRP	C-reactive protein
DM	Diabetes mellitus
e.g.	Exempli gratia (meaning: for example)
GAD	Generalized anxiety disorder
GP	General practitioner
HDL	High-density lipoprotein / hoge-dichtheid-lipoproteïnen
HPA	Hypothalamic-pituitary-adrenal
HR	Heart rate
HVZ	Hart- en vaatziekten
IDS(-SR)	Inventory of Depressive Symptoms (Self Report)
i.e.	Id est (meaning: that is)
IL-6	Interleukin(IL)-6
LDL	Low-density lipoprotein / lage-dichtheid-lipoproteïnen
MASQ	Mood and Anxiety Symptom Questionnaire
MBP	Mean blood pressure
MCAR	Missing completely at random
MDD	Major depressive disorder
MET	Metabolic equivalent of task
MI	Myocardial infarction
NA	Negative affect
NESDA	Netherlands Study of Depression and Anxiety
PA	Positive affect
PEP	Pre-ejection period
PNS	Parasympathetic nervous system
RSA	Respiratory sinus arrhythmia
SA	Somatic arousal
SNRI	Serotonin-norepinephrine reuptake inhibitor
SNS	Sympathetic nervous system
SSRI	Serotonin re-uptake inhibitor
TCA	Tricyclic antidepressant
TNF-α	Tumor necrosis factor-alpha
WC	Waist circumference

Nederlandse samenvatting

ALGEMENE INTRODUCTIE

Depressieve en angststoornissen komen vaak voor. Bijna twintig procent van de mensen krijgt ooit in het leven een depressieve of angststoornis. Deze aandoeningen komen in meer dan de helft van de gevallen samen voor. Vanwege deze grote samenhang is het belangrijk om ze gezamenlijk te onderzoeken.

Ook hart- en vaatziekten (HVZ) komen veel voor. HVZ zijn zelfs wereldwijd de belangrijkste doodsoorzaak. Zowel depressieve en angststoornissen als HVZ veroorzaken veel ziektelast. Daarnaast brengen zij veel maatschappelijke kosten met zich mee, voornamelijk door arbeidsongeschiktheid.

Er bestaat een opmerkelijke samenhang tussen depressie en angststoornissen enerzijds en HVZ anderzijds. Onderzoek laat zien dat een depressie de kans op het ontwikkelen van HVZ verdubbelt. Angststoornissen verhogen het risico op HVZ met veertig procent. Er is toenemende interesse in de vraag of depressie en angststoornissen ook samenhangen met 'metabole' (= stofwisselings) factoren die de kans op HVZ vergroten. Dit proefschrift haakt hierop in door de vraagstelling te behandelen of bepaalde kenmerken van depressie of angststoornissen ons kwetsbaar maken voor metabole risicofactoren voor HVZ, en waarom.

Metabole risicofactoren voor hart- en vaatziekten (HVZ)

Onder metabole risicofactoren voor HVZ vallen ongunstige cholesterolwaardes in het bloed (ook wel 'dyslipidemie' genoemd), overgewicht, hoge bloeddruk en verhoogde glucosespiegels.

Cholesterol is nodig als bouwstof van lichaamscellen en grondstof voor hormonen. Cholesterol wordt geproduceerd in de lever, maar ook opgenomen via de voeding en beïnvloed door roken, lichamelijke beweging en bepaalde medicatie. Cholesterol wordt verpakt in eiwitbolletjes door het bloed vervoerd. Deze eiwitbolletjes heten 'lipoproteïnen', en de belangrijkste soorten zijn lage-dichtheid-lipoproteïnen (LDL) en hoge-dichtheid-lipoproteïnen (HDL). Een ander belangrijk vet in het lichaam is 'triglyceride'. LDL cholesterol en triglyceriden zetten zich af tegen de vaatwand en veroorzaken daardoor aderverkalking (ook wel 'atherosclerose' genoemd). HDL cholesterol gaat juist aderverkalking tegen door het verwijderen van cholesterol van de vaatwand. Een verhoogde concentratie LDL cholesterol of triglyceriden en/of een verlaagde concentratie HDL cholesterol in het bloed bevordert dus aderverkalking. Dergelijke dyslipidemie is daarom een belangrijke risicofactor voor HVZ.

Bij overgewicht is er sprake van een vergrote hoeveelheid vetweefsel in het lichaam. Overgewicht komt steeds vaker voor, een verschijnsel dat ook wel de 'obesitasepidemie' wordt genoemd. Er wordt vaak een onderscheid gemaakt tussen algemeen overgewicht en vetophoping in de buik. Vooral buikvet maakt bepaalde stoffen aan, zoals ontstekingsfactoren, die het risico op HVZ verhogen.

De bloeddruk is de druk op de bloedvaten die ontstaat doordat het hart bloed de slagaders in pompt. De bloeddruk neemt toe met de leeftijd en door een ongezonde leefstijl, zoals roken en weinig bewegen. Door een

langdurig hoge bloeddruk ontstaan er kleine beschadigingen in de wanden van slagaders. Hierdoor kan cholesterol zich gemakkelijker afzetten tegen de vaatwanden, wat aderverkalking bevordert. Door dit proces worden de vaten nauwer en minder elastisch en moet het hart intensiever pompen om bloed te verspreiden. Hierdoor neemt de bloeddruk verder toe. Een hoge bloeddruk legt een voortdurende druk op het hart en de slagaders en vergroot daardoor het risico op HVZ.

Glucose in het bloed hebben we nodig als brandstof. Normaal gesproken maakt de alvleesklier bij stijgende glucosewaardes het hormoon insuline aan. Insuline zet het teveel aan glucose om in glycogeen, wat wordt opgeslagen in lever en spieren voor later gebruik. Wanneer er een defect is in de opslag van glucose, blijft er te veel van in het bloed achter en stijgen de glucosespiegels. Dit is een belangrijk kenmerk van type 2 diabetes. Verhoogde glucosespiegels veroorzaken via allerlei chemische processen schade aan lichaamscellen, waaronder aan cellen in de bloedvaten.

Dyslipidemie, overgewicht, hoge bloeddruk en verhoogde glucosespiegels komen vaak samen voor en beïnvloeden elkaar over en weer. Bij drie of meer van deze metabole risicofactoren voor HVZ wordt deze clustering 'het metabool syndroom' genoemd. Door hun ongezonde effecten op het hart- en vaatstelsel voorspellen deze metabole risicofactoren samen meer dan de helft van alle gevallen van HVZ.

Depressie en angststoornissen

Een depressieve stoornis wordt gekenmerkt door een sombere stemming en/of interesseverlies die langer dan twee weken aanhoudt. Daarnaast kan er sprake zijn van veranderingen in het slaap- en/of eetpatroon, geremde of juist opgejaagde bewegingen of gedachten, moeheid of lusteloosheid, moeite met concentreren, besluiteloosheid, gevoelens van schuld of waardeloosheid, en terugkerende gedachten over de dood. Om aan de criteria voor een depressieve stoornis te voldoen, moeten minimaal vijf van deze symptomen aanwezig zijn.

Veel voorkomende angststoornissen zijn sociale fobie, paniekstoornis met of zonder agorafobie en de gegeneraliseerde angststoornis. Bij sociale fobie is iemand overmatig bang om zich in sociale situaties op een genante manier te gedragen. Bij een paniekstoornis is er sprake van herhaalde, onverwachte paniekaanvallen. Uit angst voor paniekaanvallen gaat een deel van deze mensen situaties vermijden die daartoe kunnen leiden. In dat geval kan iemand agorafobie (in de volksmond ook wel 'pleinvrees' genoemd) ontwikkelen, waarbij diegene bang is om zich in situaties te begeven van waaruit ontsnappen moeilijk is of waarin geen hulp beschikbaar zou zijn in geval van paniek. De gegeneraliseerde angststoornis wordt gekenmerkt door het zich gedurende langere tijd buitensporig zorgen maken over allerlei alledaagse situaties.

Een diagnose van een depressieve of angststoornis is enkel gericht op het al dan niet voldoen aan een bepaald aantal criteria. Aangezien symptomen van depressie en angst bij iedereen in min of meerdere mate

voorkomen, bieden diagnoses een beperkt inzicht in subtiele individuele verschillen.

Een manier om individuele verschillen in depressie en angst beter in kaart te brengen is door de ernst van symptomen van depressie of angst over een continuüm te bekijken. Ernstvragenlijsten voor depressie en angst registreren het aantal en de mate van symptomen en bieden daardoor informatie over individuele verschillen in ernst, los van of iemand een depressieve of angststoornis heeft.

Een andere continue depressie- en angstmaat, waarmee tegelijkertijd rekening wordt gehouden met de overlap tussen depressie en angst, is het model voor symptoomdimensies. Bij deze relatief nieuwe benadering wordt ervan uitgegaan dat een gebrek aan positieve emoties, waaronder enthousiasme en interesse (zoals samengevat in de positieve affectdimensie), specifiek is voor depressie, symptomen van lichamelijke prikkeling zoals hartkloppingen en zweten (de lichamelijke prikkelingsdimensie) onderscheidend zijn voor angst, en negatieve gevoelens zoals angst en schuld (samengevat in de negatieve affectdimensie) kenmerkend zijn voor zowel depressie als voor angst.

Depressie, angststoornissen en metabole risicofactoren

Omdat metabole risicofactoren voor HVZ meer dan de helft van alle gevallen van HVZ voorspellen, zouden ze deels verantwoordelijk kunnen zijn voor de verhoogde kans op HVZ die depressie en angststoornissen met zich meebrengen. En aangezien metabole risicofactoren relatief eenvoudig op te sporen en te behandelen zijn, zouden dit dankbare aanknopingspunten zijn om het risico op HVZ bij mensen met depressie of angst terug te dringen.

Voorgaande studies naar dit onderwerp onderzochten veelal of metabole risicofactoren vaker voorkwamen bij mensen met een depressie of angststoornis dan bij mensen zonder een dergelijke aandoening. Deze studies leverden tegenstrijdige resultaten op. Een reden hiervoor kan zijn dat het indelen in stoornissen – zoals hiervoor uitgelegd - weinig inzicht geeft in subtiele individuele verschillen in bijvoorbeeld ernst van klachten. Continue maten voor depressie en angst (zoals ernstmaten of symptoomdimensies) geven waarschijnlijk een nauwkeuriger en genuanceerder beeld. Een andere hieraan gerelateerde reden voor tegenstrijdige resultaten van voorgaand onderzoek kan zijn dat een deel van de studies alleen onderzocht of mensen met depressie of angst vaker voldeden aan de algemene criteria voor het metabool syndroom. Omdat er bij deze methode weinig rekening wordt gehouden met individuele verschillen in samenstelling en ernst van metabole risicofactoren, kan dat onduidelijke resultaten hebben opgeleverd.

Omdat er relatief weinig onderzoek is gedaan naar de relatie van continue depressie- en angstmaten met losse continue waarden van metabole risicofactoren, willen we aan de hand van dit proefschrift de kennis hierover vergroten.

Antidepressiva en metabole risicofactoren
Antidepressiva worden aan circa zes procent van de Nederlanders voorgeschreven ter verlichting van zowel depressieve als angstklachten. Twee van de meest gebruikte soorten antidepressiva zijn selectieve serotonine-heropnameremmers (SSRIs) en tricyclische antidepressiva (TCAs). Er zijn aanwijzingen dat TCAs maar ook SSRIs metabole verstoringen zoals dyslipidemie en overgewicht kunnen veroorzaken. Omdat antidepressiva veel worden gebruikt en waarschijnlijk metabole bijwerkingen hebben, zouden zij een deel van het verhoogde metabole risico bij mensen met depressie of angststoornissen kunnen verklaren. Deze mogelijkheid is nog niet grondig onderzocht. Daarom wordt daar in dit proefschrift uitgebreid bij stilgestaan.

Mogelijke oorzaken van metabool risico bij depressie en angst
Behalve dat we wilden onderzoeken of depressie, angst of antidepressivagebruik samenhangen met metabole ontregelingen, wilden we ook weten waarom. Hier is nog maar heel weinig over bekend. Meer kennis over mogelijke verklaringen geeft ons aanknopingspunten over hoe we metabole ontregelingen bij depressie en angststoornissen kunnen voorkomen en genezen. In dit proefschrift werd de rol van biologische stresssystemen en van leefstijl onderzocht.

Biologische stresssystemen
Ons lichaam wordt automatisch actief bij zowel lichamelijk als mentaal stressvolle gebeurtenissen, bijvoorbeeld door het mobiliseren van brandstof zoals cholesterol en glucose, en door het verhogen van bloeddruk en hartslag. Dit zorgt ervoor dat we adequaat op stressvolle situaties kunnen reageren door te 'vechten of vluchten'. Ons lichaam heeft daarnaast ook regelmechanismen die zorgen voor ontspanning en herstel zo gauw de stressvolle situatie voorbij is. Drie belangrijke biologische stresssystemen zijn de hypothalamus-hypofyse-bijnierschors as (HPA as, wat staat voor het Engelse 'hypothalamic-pituitary-adrenal'), het autonome zenuwstelsel (AZS) en de ontstekingsreacties van het immuunsysteem.

De HPA as zorgt ervoor dat in stressvolle situaties de hypothalamus in de hersenen corticotrofine releasing hormoon (CRH) afgeeft in het bloed, wat de afgifte van adrenocorticotroop hormoon (ACTH) door de hypofyseklier stimuleert en vervolgens productie van het stresshormoon cortisol door de bijnierschors in gang zet. Het stresshormoon cortisol zorgt voor het vrijmaken van onder andere glucose en cholesterol om actief te kunnen zijn in tijden van stress. Doordat cortisol als een soort thermostaat de aanmaak van CRH en ACTH remt, komt de stressreactie van de HPA as vanzelf weer tot rust.

Het AZS bestaat uit een sympatisch deel dat het lichaam klaar maakt voor actie door bijvoorbeeld het verhogen van de hartslag en bloeddruk, en een parasympatisch deel dat zorgt voor ontspanning en herstel door het verlagen van hartslag en bloeddruk. Als het sympatische AZS actief is, onderdrukt dit het parasympatische AZS en andersom.

Elke stresssituatie (zowel fysiek als mentaal) activeert ook het immuunsysteem en kan daardoor ontstekingsreacties oproepen. Dit is nodig om voorbereid te zijn op verwondingen die kunnen ontstaan tijdens het vechten of vluchten, en heeft als doel het verwijderen van eventuele infecties en het herstel van schade.

Als een van deze drie biologische stresssystemen langdurig actief is, veroorzaakt dit metabole ontregelingen doordat het lichaam aanhoudend in de actieve stand staat. Zodoende kunnen chronisch verhoogde cholesterolspiegels, glucosewaardes en bloeddruk ontstaan.

Onderzoek laat zien dat ontregelde biologische stresssystemen samenhangen met depressie en angststoornissen. Dat bij mensen met depressie of angst de normale reacties op stress verstoord zijn, kan dus bijdragen aan het verhoogde metabole risico bij depressie en angststoornissen. Of het inderdaad zo is dat overactieve stresssystemen kunnen verklaren dat depressieve en angstige mensen een groter metabool risico lopen is nog niet bekend. Daarom wordt er in dit proefschrift aandacht aan deze mogelijkheid besteed.

Leefstijl

Iets anders wat het metabole risico onder mensen met depressie of angst kan verhogen is leefstijl. Mensen met een depressie of angststoornis hebben de neiging om te gaan roken, meer alcohol te drinken en minder te bewegen. Een dergelijke leefstijl vergroot de kans op metabole ontregelingen zoals een hoge bloeddruk en overgewicht. De rol van een leefstijl is in het verleden nog niet zo grondig onderzocht.

Metabole risicofactoren in relatie tot persoonlijkheid en jeugdtrauma

Hoewel we ons in dit proefschrift vooral richten op depressie en angststoornissen, zijn er ook andere factoren denkbaar die metabole risicofactoren kunnen beïnvloeden. Wij bestudeerden daarom ook de relatie van persoonlijkheid en jeugdtrauma met metabole risicofactoren voor HVZ. Onderzoeksresultaten hierover zijn schaars en tegenstrijdig, en daarom is verder onderzoek hiernaar van belang.

Een gangbare manier om persoonlijkheid in te delen is aan de hand van het Big Five model. Dit model gaat ervan uit dat persoonlijkheid bestaat uit vijf dimensies, namelijk de mate van extraversie (versus introversie), openheid (voor bijvoorbeeld nieuwe ervaringen en ideeën), meegaandheid (tegenover competitiviteit), neuroticisme (versus emotionele stabiliteit) en zorgvuldigheid (tegenover onverschilligheid). Iedereen heeft elk van deze vijf persoonlijkheidstrekken in een bepaalde mate, en de combinatie van deze vijf trekken bepaalt iemands karakter. Deze persoonlijkheidstrekken beïnvloeden onder andere de mate waarin we een gezonde levensstijl belangrijk vinden en naleven, en onze behoefte aan middelengebruik zoals roken of alcoholgebruik. Dit heeft op zijn beurt weer invloed op metabole risicofactoren.

Jeugdtrauma zoals emotionele verwaarlozing, en psychologisch, fysiek of seksueel misbruik hangt samen met een lagere welvaart. Ook vergroot het meemaken van jeugdtrauma de kans op psychische klachten

zoals depressie en angststoornissen. Zowel een lagere welvaart als psychische klachten faciliteren een ongunstige leefstijl, wat het risico op metabole verstoringen kan verhogen.

Doel van dit proefschrift

Samenvattend was het doel van de studies opgenomen in dit proefschrift om te onderzoeken welke kenmerken van depressie en angst (namelijk stoornissen, ernst of symptoomdimensies) mensen kwetsbaar maken voor metabole ontregelingen. De relatie van antidepressivagebruik met metabole risicofactoren werd ook onderzocht. Bovendien namen we de rol die biologische stresssystemen en leefstijl hierin spelen onder de loep. Daarnaast werd gekeken of persoonlijkheidstrekken en jeugdtrauma bijdragen aan metabool risico.

Om dit alles te kunnen onderzoeken, hebben wij dankbaar gebruik gemaakt van gegevens van de Nederlandse Studie naar Depressie en Angst (NESDA). Binnen NESDA worden 2329 volwassenen met een depressie of angststoornis gedurende het leven en 652 gezonde controles (mensen die nooit een dergelijke stoornis hebben gehad) jarenlang gevolgd om het ontstaan, het beloop en de consequenties van depressie en angststoornissen in kaart te brengen.

RESULTATEN

In **hoofdstuk 2** lieten we allereerst zien dat mensen met een huidige depressieve en/of angststoornis niet meer kans hadden op metabole risicofactoren dan mensen die nooit een dergelijke stoornis hadden gehad. Wel bleek dat ernstige depressieve klachten een groter risico gaven op overgewicht en dyslipidemie. Ernstige angstklachten gaven in mindere mate ook een groter risico op overgewicht en dyslipidemie. Deze bevindingen laten zien dat vooral ernstige depressieve en angstklachten, en niet zozeer depressieve of angststoornissen, samenhangen met een verhoogd metabool risico, en met overgewicht en dyslipidemie in het bijzonder.

Ten tweede lieten we zien dat gebruikers van TCAs vatbaar waren voor dyslipidemie, overgewicht en hoge bloeddruk. Mogelijk weerspiegelt dit bijwerkingen van TCAs. Bij behandeling met TCAs kan het belangrijk zijn om deze metabole bijwerkingen in ogenschouw te nemen.

In **hoofdstuk 3** werd beschreven dat mensen met een huidige depressieve stoornis meer kans op dyslipidemie hadden dan mensen met een depressie in het verleden of mensen die nog nooit een dergelijke stoornis gehad hadden. Het lijkt er dus op dat remissie van depressie uiteindelijk leidt tot genormaliseerd gewicht en cholesterol.

Hoe symptoomdimensies van depressie en angst samenhingen met metabool risico werd besproken in **hoofdstuk 4**. Symptomen van lichamelijke prikkeling die bij angst horen (zoals hartkloppingen en zweten) hingen onafhankelijk van leefstijl samen met overgewicht, dyslipidemie en hoge bloeddruk. Dit wijst erop dat vooral lichamelijke symptomen gerelateerd zijn aan metabole ontregelingen.

In **hoofdstuk 5** beschreven we dat ernstige symptomen van depressie of angst bij aanvang van het onderzoek een verergering van dyslipidemie en overgewicht voorspelden over de volgende twee jaar. Over het algemeen namen symptomen van depressie en angst af tijdens die twee jaar. Desalniettemin ging deze algehele verbetering in stemming niet samen met een afname van dyslipidemie of overgewicht. Dit suggereert dat mensen die kwetsbaar zijn voor ernstige symptomen van depressie of angst een verergering van dyslipidemie en overgewicht laten zien over de tijd, zelfs wanneer hun stemming verbetert. Als depressie of angst direct leidt tot dyslipidemie en overgewicht zou je verwachten dat een verbeterde stemming juist samen zou gaan met een verbetering van dyslipidemie en overgewicht. Dat we dat juist niet vonden suggereert dat depressie en angststoornissen op een indirecte manier met dyslipidemie en overgewicht samenhangen. Relatief stabiele factoren onder mensen die kwetsbaar zijn voor depressie of angststoornissen - zoals roken, ongezonde voeding, inflammatie of een genetische kwetsbaarheid – zouden dan dyslipidemie en overgewicht in de hand kunnen werken. Hoe dan ook lijken mensen met ernstige symptomen van depressie en angst langdurig en in toenemende mate kwetsbaar te zijn voor dyslipidemie en overgewicht, en dus voor HVZ.

In **hoofdstuk 6** bestudeerden we de relatie van het AZS en de HPA as met metabool risico. We concludeerden dat een toegenomen activiteit van het sympatische en een afgenomen activiteit van het parasympatische AZS samenhingen met het metabool syndroom en al diens componenten. We vonden geen relatie van de HPA as met metabole risicofactoren.

In **hoofdstuk 7** rapporteerden we dat ontsteking en roken in belangrijke mate bijdroegen aan dyslipidemie en overgewicht bij mensen met ernstiger symptomen van depressie of angst. Daarnaast verklaarden ontregelingen van het AZS (namelijk een verhoogde sympathische AZS en een verminderde parasympatische AZS activiteit) voor een deel de dyslipidemie en het overgewicht bij TCA gebruikers. Zulke AZS ontregelingen zouden een bijwerking van TCAs kunnen zijn. Hoewel ontsteking, roken en het AZS een rol speelden, verklaarden zij niet alles. De rol van andere mogelijke mechanismen – zoals voeding – moet in de toekomst nog bepaald worden. Als toekomstig onderzoek onze resultaten bevestigt, zouden interventies die inflammatie verminderen (zoals stoppen met roken) en AZS activiteit normaliseren (zoals TCA-gebruik staken en vervangen door andere behandeling) dyslipidemie en overgewicht kunnen terugdringen.

In **hoofdstuk 8** bestudeerden we of er een verband is van persoonlijkheidstrekken en jeugdtrauma met metabole risicofactoren voor HVZ. Seksueel misbruik in de jeugd bleek samen te hangen met dyslipidemie en overgewicht. Een verklaring hiervoor kan zijn dat seksueel misbruik een chronisch verhoogde activiteit van het stresssysteem kan veroorzaken. Openheid als persoonlijkheidskenmerk bleek juist beschermend te zijn voor dyslipidemie en overgewicht, en ook voor hoge bloeddruk. Misschien zijn open persoonlijkheden ontvankelijker voor gezondheidsaanbevelingen. Eventueel is deze kennis nuttig bij het ontwikkelen van richtlijnen om metabool risico te verlagen.

SAMENVATTING EN DISCUSSIE

In **hoofdstuk 9** werden alle bevindingen samengevat en bediscussieerd. In het kort laten de resultaten van dit proefschrift zien dat mensen met ernstige depressieve of angstklachten meer kans hebben op dyslipidemie en overgewicht, ook op de langere termijn. Het feit dat deze mensen vaker roken en meer ontstekingsreacties hebben verklaart deze relaties deels, en het aanpakken van deze factoren kan dus een belangrijke methode zijn voor preventie en behandeling van dyslipidemie en overgewicht bij deze groep. Onze resultaten laten ook zien dat het gebruik van TCAs een grotere kans geeft op dyslipidemie, overgewicht en hoge bloeddruk. Dit wordt deels verklaard door ontregelingen van het AZS, wat mogelijk een bijwerking is van TCAs. Dit geeft aan dat behandelaren zich bewust moeten zijn van deze metabole bijwerkingen bij het voorschrijven van TCAs.

Onderzoek richt zich in toenemende mate op het samenspel tussen psychische en lichamelijke gezondheid. Hieruit komt steeds meer naar voren dat psychische problemen zoals depressieve en angststoornissen samengaan met lichamelijke aandoeningen zoals metabole ontregelingen en HVZ.

In de gezondheidszorg bestaat er ondanks de signalen uit onderzoek nog steeds een duidelijke tweedeling tussen geestelijke en lichamelijke gezondheid. Zo is er binnen de zorg voor depressieve en angststoornissen nog geen systematische aanpak van het verhoogde risico op HVZ. Meer bewustzijn in de praktijk van de samenhang die hiertussen bestaat is van grote waarde om dit risico terug te kunnen dringen.

Toekomstig onderzoek moet uitwijzen of preventie, opsporing en behandeling van dyslipidemie en overgewicht onder mensen met ernstige symptomen van depressie of angst effectief is. Zo ja, dan kan dit als onderdeel van multidisciplinaire richtlijnen bijdragen aan preventie van HVZ.

Curriculum vitae

Arianne Klaartje Beraldine van Reedt Dortland, geboren op 10 februari 1981 te Utrecht, behaalde in 1999 haar VWO diploma aan het Keizer Karel College in Amstelveen. Vervolgens studeerde zij in maart 2005 af aan de Vrije Universiteit van Amsterdam, zowel in de Klinische Psychologie als in de Klinische Neuropsychologie. Nadat zij als onderzoeksassistent en coördinator Biologie bij de Nederlandse Studie naar Depressie en Angst (NESDA) en als psycholoog bij GGZinGeest werkzaam was, startte zij in april 2007 als promovenda op de afdeling Psychiatrie van het Leids Universitair Medisch Centrum. Aan de hand van NESDA gegevens onderzocht zij metabole risicofactoren voor hart- en vaatziekten bij mensen met depressieve of angststoornissen, met als resultaat het proefschrift dat nu voor u ligt. Daarnaast voltooide Arianne de masteropleiding Epidemiologie aan het EMGO-insituut. Ook trainde zij hartrevalidanten op het Rijnlands Revalidatie Centrum in stress- en leefstijlmanagement. Sinds februari 2012 is Arianne onderzoekscoördinator en psycholoog bij GGZinGeest/VU Medisch Centrum.

Arianne Klaartje Beraldine van Reedt Dortland, born on the 10th of February 1981 in Utrecht, the Netherlands, graduated from secondary school (Keizer Karel College, Amstelveen) in 1999. By March 2005, she took her Clinical Psychology as well as her Clinical Neuropsychology degree at the VU University of Amsterdam. After she worked as a research assistant and coordinator of Biology at the Netherlands Study of Depression and Anxiety (NESDA) and as a psychologist at GGZinGeest, she began her Ph.D. thesis research at the Leiden University Medical Centre in April 2007. By means of NESDA data she examined metabolic risk in people with depressive or anxiety disorders, which resulted in this dissertation. Moreover, Arianne obtained her masters degree in Epidemiology in 2011. She also trained cardiac patients in stress and lifestyle management. Since February 2012 Arianne has been working as a research coordinator and psychologist at GGZinGeest/VU University Medical Centre.

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