Metabolic disturbances in depression : epidemiological studies on the role of diagnostic approach and treatment setting

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Chapter 1

General introduction

Depression and cardiovascular disease (CVD) are two of the most prevalent health problems in both the Netherlands and across the world, and two of the leading causes of burden of disease worldwide, expressed by the World Health Organisation (WHO) as Disability Adjusted Life-Years (DALYs), "lost healthy-life years". Unipolar depression, now leading cause number three of burden of disease, will soon reach the highest position, while ischemic heart disease, now number four, will be second in rank.[1] Thus depressive disorders and cardiovascular disease (CVD) have a major impact on the public health.

Depression and cardiovascular disease also highly co-occur with reported prevalence rates between 40 to 60%.[2] Therefore, research has increasingly focused on etiological factors, mechanisms of interaction and pathways the two disorders have in common.

The association between depression and adverse cardiovascular outcomes[3] is thought to be mediated by the metabolic syndrome (MetSyn),[4] and other closely related metabolic components, in particular obesity.[5-7] These metabolic changes might be attributable to immuno-inflammatory, autonomic and hypothalamic-pituitary-adrenal (HPA)-axis dysregulations, as well to lifestyle factors such as sedentary lifestyle, unhealthy diet and smoking, which have been suggested to be often present among depressed patients.

In this thesis, the relation between depressive disorders, and MetSyn and related metabolic components is studied with different methodological approaches.

1.1 Depressive disorder

1.1.1 Epidemiology and diagnosis of major depressive disorder (MDD)

Depression is one of the most common psychiatric disorders. Worldwide, lifetime prevalence rates vary from 3% to 20%.[8;9] In the Netherlands, depressive disorders have a lifetime prevalence of about 20%,[10;11] and are about twice as common among females. The Global Burden of Disease 2000 estimates that 5.8% of men and 9.5% of women will experience a depressive episode in a 12-month period.[12]

1.1.2 Diagnosis of major depressive disorder (MDD) and dimensional classification

The presence of depressive symptoms, however, should be distinguished from the presence of a major depressive disorder. The diagnosis of a major depressive disorder (MDD), according to the Diagnostic and Statistical Manual of Mental Disorders (*DSM*) classification is characterised by the presence of at least 5 out of 9 symptoms, for the duration of at least 2 weeks (Table 1). At least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure, the so called "main symptoms". The "accompanying symptoms" are sleep disturbances, impaired concentration, changes in appetite, fatigue, motoric activity, self-worth and/or thoughts of death and suicidal ideation, which can be present in different combinations.

1. **Depressed mood** *most of the day, nearly every day, as indicated either by subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).*
2. *Markedly diminished or* **loss of interest or pleasure** *in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation made by others).*
4. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.

Table 1. Diagnostic criteria of Major Depressive Disorder (MDD), according to the *DSM-IV* criteria. Criteria are present for the duration of at least two weeks. At least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure.

Although the categorical classification is useful for clinical practice, it has several disadvantages. One problem arises when looking at different patients with the same diagnosis. Some will show predominantly anhedonic symptoms, while others suffer especially from fatigue. The categorical classification does not provide information about the most prevalent symptoms. Another problem arises with the presence of more than one disorder at the same time, especially when they show overlapping symptoms. Often it is disputable whether the disorders are truly different clinical entities.

Since depression and anxiety disorders show overlap in symptomatology and show comorbidity rates of 60%,[13] a dimensional approach for mood and anxiety disorders diagnostics has been suggested.[14;15] An example of this approach is the so called 'tripartite model' which discerns three dimensions: "negative affect", reflecting general symptoms of psychological distress such as lack of concentration or pessimism; (lack of) "positive affect", covering anhedonic symptoms typically found in depression; "somatic arousal" reflecting symptoms of hyperarousal such as palpitations, shortness of breath and dizziness, typically found in anxiety disorders. In this thesis the three dimensions of the tripartite model were measured with a 30-item adaptation of the Mood and Anxiety Symptom Questionnaire (MASQ),[16;17] the MASQ-D30.[15;18]

1.1.3. Clinical characteristics of depression and treatment settings

Mental care can be divided into three treatment settings: primary care, secondary care and inpatient care. In the Netherlands the main caregiver in the primary care setting is the general practitioner (GP), and the pharmacological treatment usually consists of selective serotonin reuptake inhibitors (SSRIs). In case of insufficient response or (frequent) recurrence, a GP may refer the patient to a specialized secondary care center, where patients are treated by a psychiatrist. The pharmacological treatment usually consists of a tricyclic antidepressant (TCA). Patients may also be treated with cognitive behavioral therapy, alone or in combination with pharmacotherapy. Ambulant treatment is often sufficient to control one's symptoms and to guide a patient to remission. Again, in case of insufficient response, additional referral to an inpatient facility is needed, where a more intense pharmacological treatment, as well as a safe, controlled and structured environment, can be offered to provide optimal treatment and better monitor and if possible prevent side-effects. The Dutch system thus follows a stepped-care model, according to national guidelines.[19] Following such system implies that with every taken step, the treatment increases in terms of duration and intensity.

However, as many combinations of symptoms may all lead to the same MDD diagnosis, hospitalization seems more likely to be attributable to clinical factors other than the diagnosis, rather than a MDD diagnosis per-se. In fact, the diagnosis of MDD alone does not describe all relevant aspects of the depressed individual, such as the individual burden of disease or the required treatment. Neither does it provides information on factors that account for hospitalisation, such as illness duration, response rate to a certain type of (pharmacological) therapy, the presence of psychotic features, suicidal risk and lack of social support.[20] Despite the fact that several severity scales have been developed in the attempt to specify these relevant aspects by assessing both number and severity of symptoms, the categorical *DSM-IV* classification offers limited information on individual aspects, nor does it provide a subjective description of which difficulties the individual faces or which factors are attributable for hospitalisation.

Inpatients are considered to be the most severely affected patients and tend to show the less favourable prognosis.[21] In addition, depression severity has repeatedly been associated with increased cardiovascular risk. Does this mean that difference in treatment settings are a reflection of a different cardiovascular risk?

1.2 Metabolic syndrome and related metabolic characteristics

A syndrome is a set of characteristics that are often seen in association with each other, with a presumed but not completely known common underlying pathophysiology explaining their reciprocal association. The MetSyn was first described in 1988 as the Syndrome X,[22] intended to identify those at increased risk for cardiovascular disease and diabetes mellitus type 2, with insulin resistance and abdominal obesity as 'key features'. Obesity, in particular

abdominal obesity, has even been described as the central and mediating factor for the origin of several other cardiovascular risk factors.[23;24]

Several definitions of the MetSyn have been proposed, but the latest by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) is the most used:[25] a cluster of three or more of the following criteria: elevated waist circumference, decreased high density lipoprotein cholesterol (HDL-cholesterol), elevated triglycerides, elevated fasting glucose levels and hypertension (Table 2).

Diagnostic criteria for the Metabolic Syndrome		
Waist circumference	Males > 102 cm (> 40 inches) Females > 88 cm (> 35 inches)	
HDL-cholesterol	Males < 1.03 mmol/L (< 40 mg/dL) Females < 1.30 mmol/L (< 50 mg/dL)	
Triglycerides	≥ 1.7 mmol/L (≥ 150 mg/dL)	
Glucose	≥ 6.1 mmol/L (≥ 100 mg/dL)	
Blood pressure	Systolic blood pressure ≥ 130 mm Hg Diastolic blood pressure ≥ 85 mm Hg	and / or

Table 2. MetSyn criteria according to the revised criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III).

Along with the MetSyn components there are closely related metabolic variables such as higher body mass index (BMI) above 25 kg/m² (overweight) but especially above 30 kg/m² (obesity),[26] higher waist-to-hip ratio (WHR > 0.90 in men and > 0.85 in women),[27] and higher low density lipoprotein cholesterol (LDL-cholesterol, > 2.59 mmol/L)[6] which are well-established risk factors for CVD.

1.3 The hypothalamic-pituary-adrenal (HPA) axis

The heterogeneity of the diagnosis MDD induced a quest for a biological marker, intended to help the clinician to assess the severity of the illness, to choose the most effective pharmacological treatment and to predict the course of the disease. This led to extensive

research on the association between cortisol and depression, although the role of cortisol as a biological marker has lost ground.

The hypothalamic-pituary-adrenal (HPA) axis is the main neuroendocrine stress system that is activated in reaction to both physical and psychological stress. Through a cascade initiated in the hypothalamus, cortisol is released from the adrenal cortex which enables the individual to "fight or flight": stored energy is mobilised (glucose levels will increase in the blood stream, fat depositions will be redisposed to offer more energy), immune function is suppressed, and the facilitation of autonomous nervous system functions enables higher mental performance. In an acute stress situation, this response is needed to be able to respond to stress, and has a protective function. But in case of chronic cortisol release, the effects might be adverse by causing sleep and appetite changes, lowered mood,[28] insulin resistance and disturbances in the lipid metabolism.[29;30] These findings suggest an association between HPA-axis and the metabolic syndrome.[6;29]

There is substantial evidence linking HPA-axis disturbances to depression as well. In particular, HPA-hyperactivity, expressed by elevated cortisol levels, and a diminished feedback system, expressed by more non-suppression after the DST, have more prominently been found among more severely depressed patients.[31-33] Although cortisol measurement cannot be seen as a marker, there are several cortisol measures each reflecting a different aspect of the HPA-axis: the cortisol awakening rise (CAR) which reflects the natural increase of cortisol levels within 60 minutes after awakening, indicating whether there is hyper- or hypofunction of the axis; the area under the curve (AUC) with respect to the ground (AUC_g) which reflects the estimation of the total cortisol secretion during the first hour after awakening and is related to the cortisol secretion throughout the day and can be seen as indicator of cortisolemia status; the AUC with respect to the increase (AUC_i) which reflects the dynamics of the HPA-axis emphasizing the expected cortisol increase; evening cortisol measures, the basal resting state of the HPA-axis, and the DST as a reflection of the negative feedback system.

1.4 The Netherlands Study of Depression and Anxiety (NESDA)

The Netherlands Study of Depression and Anxiety (NESDA) is a multi-centre, longitudinal, observational cohort study, designed to describe the long-term course and (public health) consequences of depressive and anxiety disorders, and to integrate their biological and psychosocial paradigms. NESDA was designed to be representative of adults (age 18-65) with mood and anxiety disorders in different outpatient health care treatment settings (community, primary care and secondary care). The baseline study included 2981 participants.

A satellite project was started to additionally examine an inpatient population, recruited from five Dutch mental health care hospitals. The assessments for the included 80 inpatients were identical to the outpatients' assessments, which included at least: a face-

to-face demographic interview, current psychopathology interview, an extensive physical examination, blood draw and saliva sampling. A detailed description of the assessments is described elsewhere.[34]

1.5 Aims and outline of the thesis

In summary, depression has been found to be related to adverse cardiovascular outcomes. This association is thought to be mediated by the metabolic syndrome and related metabolic parameters, in particular overweight and obesity. Disturbances of the HPA-axis in depressed subjects might be an important underlying mechanism and (the role of) the metabolic syndrome and related metabolic parameters are thought to be subject to HPA-axis dysregulations. However, since the "golden standard" categorical diagnostic approach of the diagnosis "depressive disorder" does not completely cover the commonly found differences in presented symptoms, a dimensional approach might show new or different associations between different symptoms and metabolic characteristics. Furthermore, evidence suggests that more severely depressed subjects, such as inpatients, might suffer from more adverse metabolic profiles and show more dysregulations in HPA-axis activity.

The main aim of this thesis was to examine how depressive disorders, in particular major depressive disorders (MDD), are related to the metabolic syndrome and related metabolic parameters, examining if and how this association relates to the diagnostic approach, clinical characteristics of depression, different treatment settings and HPA-axis disturbances. A schematic representation of the thesis' outline is given in Figure 1.

First we examined the association between depression and what is considered to be a "key feature" of metabolic dysregulation: obesity. We did so by means of both a cross-sectional (chapter 2) and a longitudinal meta-analysis (chapter 3) of data published in the literature. In addition, we examined the association between depression (and anxiety) and the MetSyn using a dimensional approach (chapter 4), using data of the ongoing Netherlands Study of Depression and Anxiety (NESDA).

In order to test the assumption that inpatients would show more often and prominent metabolic disturbances, we systematically compared patients with MDD from three different treatment settings (a primary care outpatient, a secondary care outpatient and one inpatient sample), with regard to the MetSyn, individual MetSyn components and related metabolic variables (Chapter 5). The primary and secondary care samples were drawn from the NESDA-study, while the inpatient sample was recruited from five Dutch mental health hospitals.
In chapter 6, we compared HPA-axis activity in MDD across the above mentioned three treatment settings, using several cortisol measures.

In the final chapter (chapter 7) we present the summary of our findings and attempt to put them in a broader view in the general discussion, discussing the main results, their clinical implications and presenting possibilities for future research.

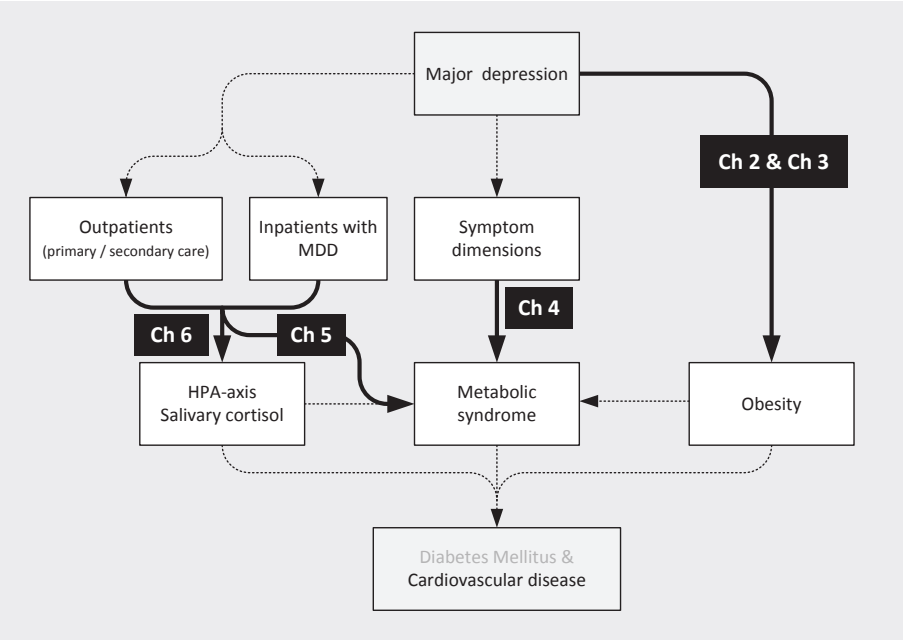

Figure 1. Schematic representation of thesis outline. Ch denotes chapter.

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