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

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Chapter 7

Summary, general discussion and future perspectives

This thesis contains several studies contributing to the examination of the association between depressive disorders, in particular major depressive disorder (MDD), and metabolic factors. In these various studies, the possible roles of diagnostic approach, treatment settings, and hypothalamic-pituitary-adrenal axis (HPA-axis) disturbances were taken into consideration.

7.1 Summary of results

7.1.1 Chapters 2 & 3

In the first two chapters, the association between depression and overweight and obesity was examined first through a meta-analysis of cross-sectional data (chapter 2) followed by a meta-analysis of longitudinal data (chapter 3) (Figure 1).

In the cross-sectional meta-analysis of 17 community-based studies, we found a significant overall association between depression (i.e., depressive symptoms or depressive disorder according to the *DSM-IV* criteria) and obesity (*i.e.*, a body mass index (BMI) ≥ 30 kg/m^2): the overall odds ratio (OR) was 1.26 (95% confidence interval [CI]: 1.17-1.36, p<0.001). The association was not influenced by potential covariates and moderators (i.e., age, continent of residence, year of publication, and differences in measurement methods), except for gender. Subgroup analyses showed that the association with depression was statistically significant among females (OR = 1.32; 95% CI: 1.12-1.34, p≤ 0.001) but not in men (OR = 1.00; 95% CI: 0.76-1.31). A significant association was found for the subgroup with "depressive symptoms" (OR=1.23; 95% CI 1.03-1.47). For the subgroup suffering from "depression disorder" an association was found only among females (OR = 1.29; 95% CI: 1.20-1.39) and not in males (OR= 0.93; 95% CI 0.67-1.30). The heterogeneity of the studies for the different comparisons was high, especially in the male subgroup of studies. In sum, this study showed significant associations between depression and obesity that appear more pronounced among females.

The meta-analysis of longitudinal data included 15 studies, most of which were based on subjects derived from the general population. A bi-directional association was found between depression and obesity in both males and females. Those who were obese at baseline had a 55% increased risk of developing depression over time, whereas those with baseline depression had a 58% increased risk of becoming obese over time. Analyses in subjects who were overweight instead of obese showed attenuated associations. Moreover, the effects of obesity on the development of depression was stronger in studies with North American participants, and was more pronounced among those ultimately receiving a clinical diagnosis of MDD. Remarkably, the studies showed low heterogeneity across studies, additionally emphasizing the strong reciprocal relationships between depression and obesity.

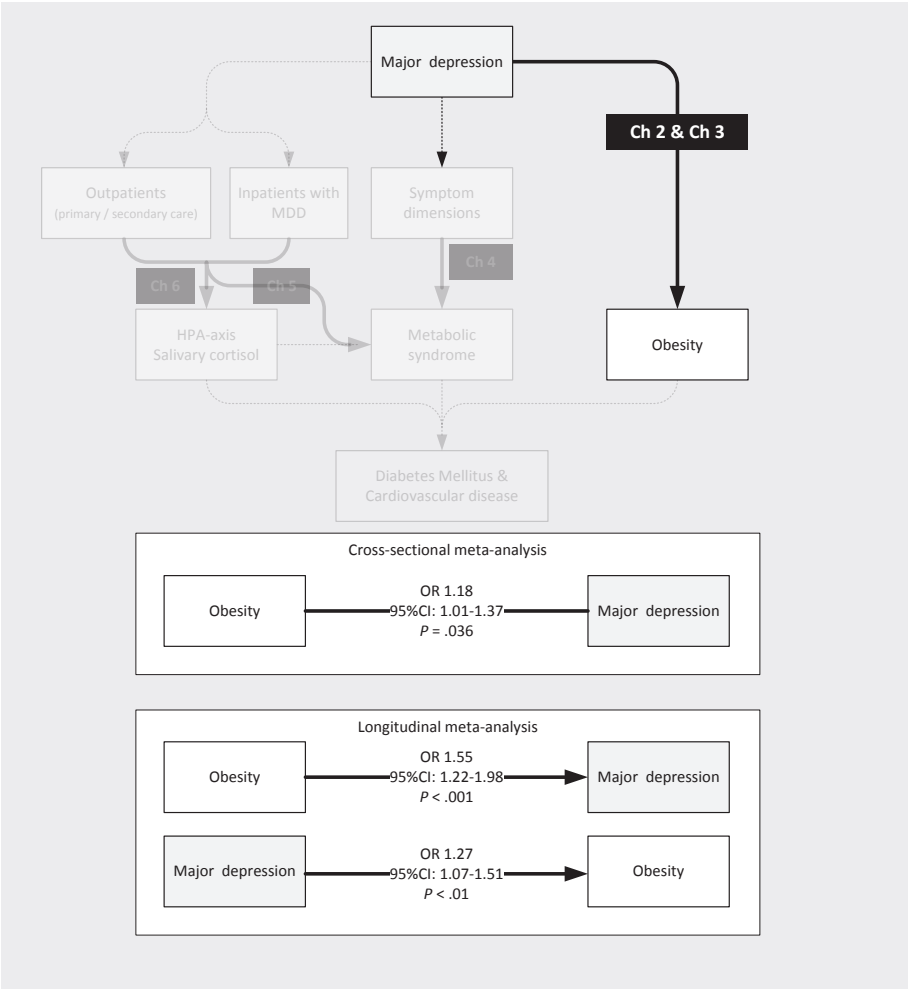

Figure 1. Schematic representation of the major findings of both meta-analyses, expressed as overall odds-ratios (ORs) on the associations between depression and obesity. Ch denotes chapter.

7.1.2 Chapter 4

The next study focussed on symptom dimensions and the metabolic syndrome (MetSyn). This study included 2433 participants from the Netherlands Study of Depression and Anxiety (NESDA). Symptom dimensions of depression and anxiety were assessed using the tripartite model, assessed by the Dutch version of 30 item Mood and Anxiety Symptoms Questionnaire (MASQ-D30). The tripartite model clusters symptoms present in depression and anxiety into three dimensions: “negative affect” (NA), reflecting general symptoms of psychological

distress (*e.g.* lack of concentration or pessimism); (lack of) "positive affect" (PA), covering anhedonic symptoms and "somatic arousal" (SA) reflecting symptoms of hyperarousal (*e.g.* palpitations, shortness of breath and dizziness). Our results demonstrated a significant association between the somatic arousal (SA) dimension and the metabolic syndrome. The association was found for both MetSyn prevalence and most of its individual components (i.e., waist circumference, triglycerides, blood pressure, and total the number of MetSyn components). No association was found between the MetSyn and the dimensions of positive and negative affect. Similarly, the association with the MetSyn was also present when using the Beck Anxiety Inventory (BAI), which in part also represents somatic symptoms of anxiety. These results suggest that not every patient with anxiety or depressive disorders is at an increased metabolic risk, but primarily those with an elevated somatic arousal level.

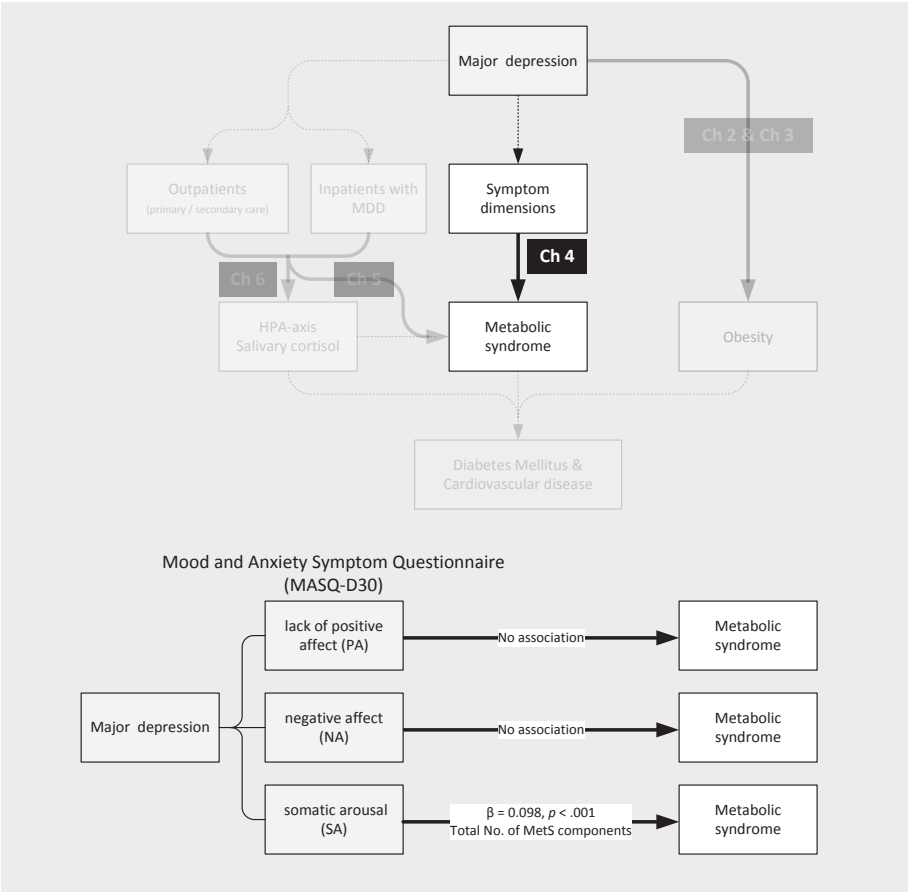

Figure 2. Schematic representation of the associations between symptom dimensions of depression and anxiety on the one hand, and the metabolic syndrome on the other hand. Ch denotes chapter.

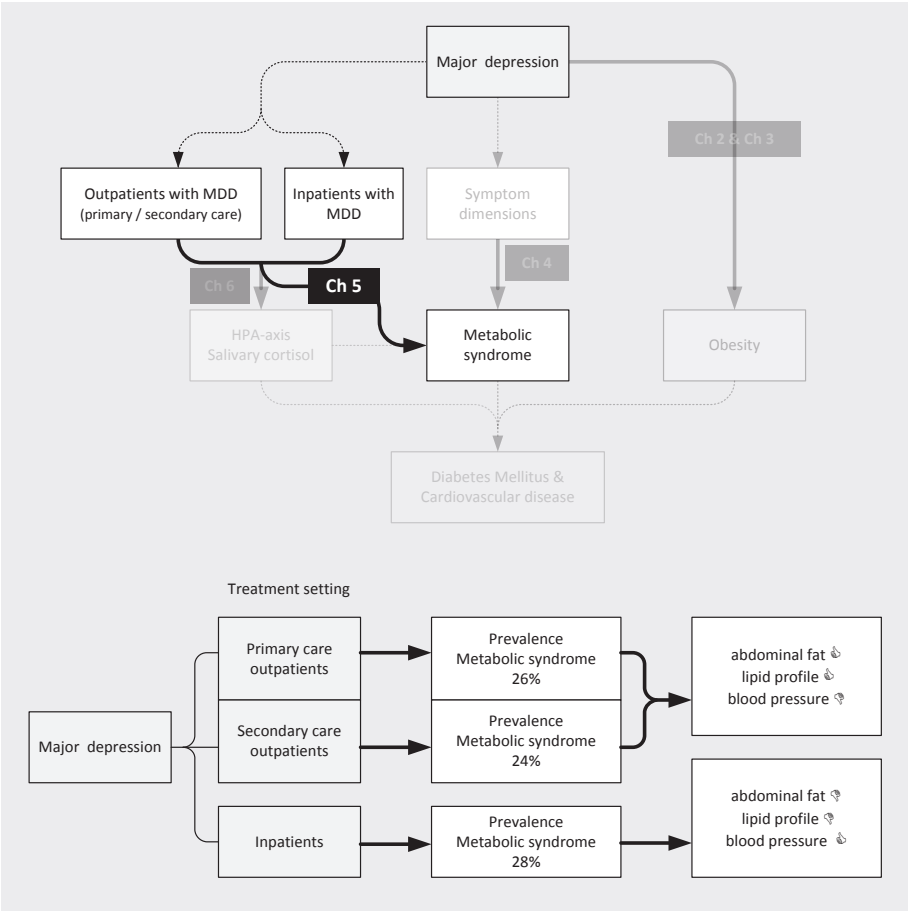

Figure 3. Schematic representation of the comparison of three different treatment settings of MDD patients, with regard to MetSyn prevalence proportions, individual MetSyn components and related metabolic variables. 👍: denotes a more favorable level or profile; 👎: denotes a more unfavorable level or profile. Ch denotes chapter.

7.1.3 Chapter 5

In this study we compared outpatients and inpatients with regard to the MetSyn and related metabolic variables. The three groups in the study comprised 302 primary outpatients, 445 secondary care outpatients, and 80 inpatients, who were all suffering from current MDD (i.e., 1 month diagnosis). We found that the MetSyn prevalence proportions were similar across treatment settings (about 24%). However, significant differences were found for individual metabolic parameters. Compared to outpatients, inpatients had less favourable "fat-profiles" (i.e. less favourable abdominal obesity outcome (waist hip ratio (WHR)), and less favourable

lipid profiles, specifically lower HDL-cholesterol, and higher triglyceride and total cholesterol levels). However, inpatients had a lower average systolic blood pressure (SBP) compared to outpatients. Therefore, these results did not follow the expected syndromal pattern of the MetSyn, supporting earlier mentioned reservations about the concept of the MetSyn in psychiatric patients with affective disorders. Further, we explored the potential mediators of these differences. We found that these metabolic differences across settings could not be explained by clinical characteristics, such as sociodemographic characteristics, the use of psychotropic drugs, or symptom severity. Alternatively, we speculated that a contemporary activation of different biological mechanisms may be involved such as higher activation of the HPA-axis, the autonomous nervous system (ANS), pro-inflammatory pathways in inpatients versus outpatients.

7.1.4 Chapter 6

The study described in this chapter focused on salivary cortisol measurements, as an indicator of HPA-axis functioning. Again, we compared primary care outpatients (n=141), secondary care outpatients (n=199), and inpatients (n=47) with a current diagnosis of MDD. The following salivary cortisol measures were examined: the cortisol awakening rise (CAR), reflecting the natural increase of cortisol levels within 60 minutes after awakening; the area under the curve (AUC) with respect to the ground (AUC_g) and to the increase (AUC_i), measures of different HPA-axis dynamics; evening cortisol levels, reflecting the basal resting state; the dexamethasone suppression test (DST), reflecting the negative feedback of the HPA axis. The included subjects were drawn from the same sample as those in the previous study (chapter 5). The main finding was that inpatients showed higher morning cortisol levels at awakening (T1), higher evening cortisol levels and higher cortisol levels after dexamethasone ingestion (DST). The cortisol suppression ratio and the percentage non-suppressors did not differ across treatment settings, as cortisol levels were increased both before and after dexamethasone ingestion (therefore not affecting mathematical ratios between these two levels). Our results indicate HPA-axis over-activation among MDD inpatients compared to outpatients. Additional subgroup analyses among the inpatients showed that among those with the highest levels of severity, cortisol levels were less elevated than inpatients with a lower severity scores. We found that the inpatients with the highest severity scores showed signs of a blunted CAR, with a less sensitive negative feedback system, as shown by a lower cortisol suppression ratio and a higher percentage of non-suppressors. These findings provided additional support for the hypothesis that in severe MDD may lead to exhaustion of the HPA-axis.

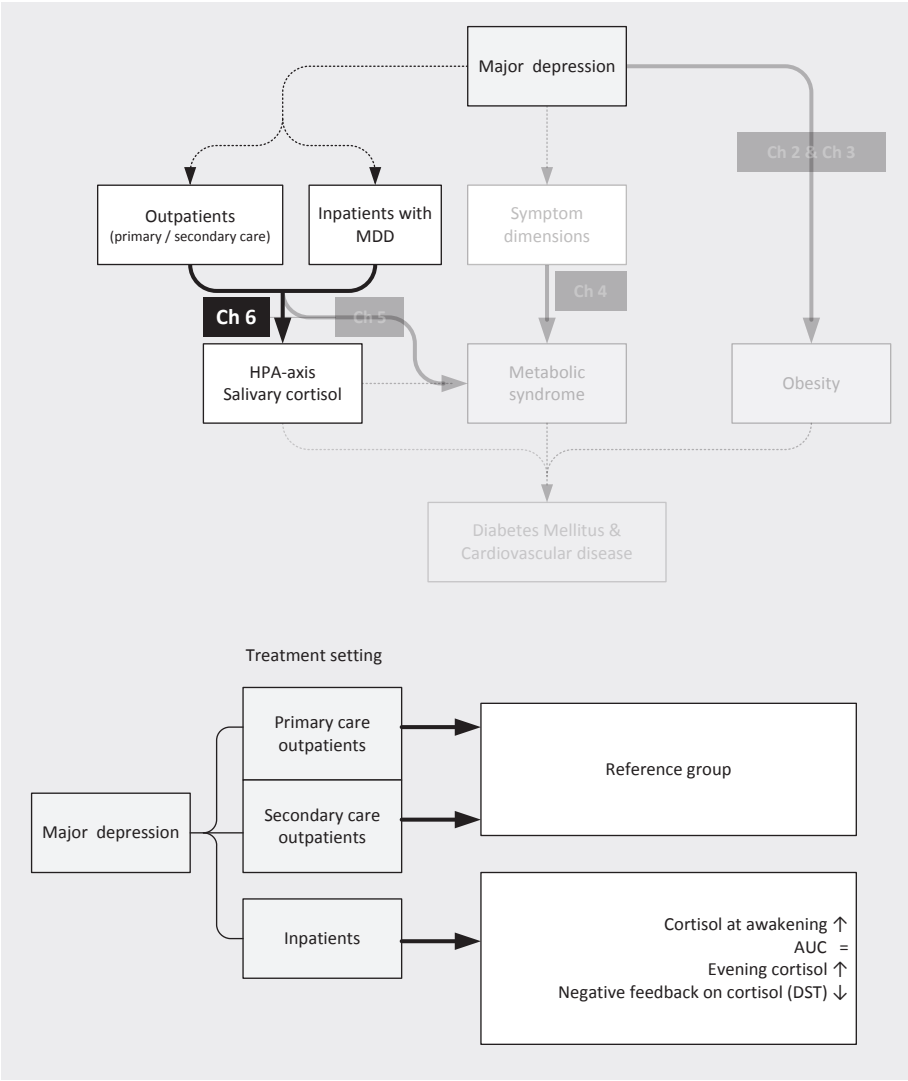

Figure 4. Schematic representation of the comparison of three different treatment settings for MDD patients with regard to salivary cortisol measures. Ch denotes chapter.

7.2 General discussion

The association between depression and adverse cardiovascular outcomes has repeatedly been studied and described. Yet, many inconsistencies have been reported and the origin of the association is not fully understood. Many factors are thought to be (in part) attributable for this association, such as obesity, metabolic syndrome and disturbances of the stress-system.

In this thesis we aimed to examine how depression – in particular MDD – is related to the metabolic risk profile that may increase the risk of cardiovascular disease (CVD) morbidity and mortality, taking into account the presumed roles of diagnostic approach, treatment settings and the stress system. The association between depression and obesity has extensively been studied, mostly by comparative cross-sectional epidemiological studies. Results, however, do not consistently point in the same direction. Therefore a meta-analytic approach was chosen to more objectively study this association, applying both a cross-sectional and a longitudinal design. Studies on the association between depression and metabolic factors, in particular MetSyn mainly report on categorical outcomes. However, there is evidence that specific symptoms or symptom dimensions of depression are more strongly linked to adverse metabolic outcomes. Therefore the association with the MetSyn was studied using a dimensional approach for depression (and anxiety). Further, despite the uniform diagnosis, inpatients and outpatients with MDD showed many differences in clinical characteristics. In order to examine the potential effect of clinical factors, several metabolic outcomes were examined across different treatment settings. Metabolic disturbances in depression have been found to be associated with HPA-axis dysregulations. Since some clinical factors are thought to play a role in determining cortisol levels, and in- and outpatients with MDD differ with regard to clinical characteristics, we also compared several cortisol measures across treatment settings. This general discussion will put the above presented findings in a broader perspective.

7.2.1 Diagnostic approach

7.2.1.1 DSM-IV classification and its limitations

The golden standard to diagnose a MDD is applying the *DSM*-classification. In our studies, we used the *DSM-IV* criteria. Recently, the revised *DSM-V* was introduced, but the criteria for the diagnosis MDD remained unchanged. Although valuable for clinical practice and scientific research, the *DSM*-classification has its limitations.

First, it fails to provide specific and discriminative information on the illness, as two patients that differ in all their symptoms may reach the same diagnosis of MDD. An example may help to explain this notion. Since nearly two months, patient A, a 43 year old female, suffers from a depressed mood. This is not the first time as she experienced this mood state three times before, although in less severe forms. She experienced a complete loss

of appetite, and consequently lost 4 kilograms (kg), while her normal weight was about 60 kg. Further, she complained of loss of energy, insomnia and suicidal ideations. She is convinced that her death will free the world, and these ideations are experienced as very vivid. Therefore she had repeatedly looked for opportunities to put an end to her life. She is not able to undertake any daily activity, and her family, unlike previous times, is worried that she will in fact harm herself. Patient B is a 28 year old male, who since three weeks is unable to experience pleasure in the things he used to enjoy. Although he still goes to work, he also suffers from psychomotoric agitation, experiences loss of energy, feels worthless, and is unable to make even the simplest decisions. Although these complaints never completely fade, they are mostly present in the morning, while by the end of the day he feels better.

Both case vignettes fulfil the *DSM-IV* diagnostic criteria for MDD, but show that disparities can be larger than similarities. These patients differed not only in terms of all of their presented depressive symptoms, but also in terms of symptom duration, recurrence rates, and the presence of psychotic features. These factors are clinically relevant in terms of prognosis, treatment of the current episode and to prevent recurrent episodes.[1-4] The above illustrates the idea that MDD according the *DSM-IV* classification may represent a heterogeneous group of disorders in its essence, which may be of consequence when comparing MDD samples.

A second limitation is the fact that the categorical *DSM-IV* classification does not provide information on the most prevalent symptom(s). From a clinical perspective this is relevant as identification of the most impairing symptoms may remain undetected. In the case of comorbidity, this may additionally lead to insufficient treatment of otherwise important symptoms in terms of remission and prognosis. Depression and anxiety show high comorbidity rates, often leading to the assumption that these conditions are different clinical aspects of the same disorder. Several diagnostic approaches have been proposed to overcome the problems engaged with this overlap.[5] In the attempt to better understand the nature and origin of these overlapping symptoms Hiller et al.,[6] in a sample of 150 outpatients, examined the overlap proportions at different psychopathological levels: a symptom level, a syndrome level and a diagnostic level. They showed that the overlap proportions differed depending on the psychopathological level. In other words, results can be dependant from the chosen approach, a phenomenon that we might call “approach induced heterogeneity”. This may lead to additional insights, and illustrates the possible additional value of using a different approach. More recent work by Lamers et al.[7] showed that different subtypes of depression were associated with different metabolic outcomes suggesting that diagnostic approach may play a role in the found associations.

In our cross-sectional meta-analysis we found an overall association between obesity and depressive symptomatology but not for depressive diagnosis (OR = 1.23; 95% CI: 1.03-1.47 and OR = 1.14; 95% CI: 0.90-1.44 respectively). In the depressive diagnosis group, the association was only present in females. Interestingly, in the longitudinal meta-analysis, we found larger overall pooled effect sizes for obesity and a clinical diagnosis (OR = 2.15; 95%

CI: 1.48-3.12) as compared to depressive symptomatology (OR = 1.36; 95% CI: 1.03-1.80). There are two reasonable explanations. First, time might be an important reinforcing factor of both conditions. Second, "approach induced heterogeneity" may explain the different effect sizes found in the depressive diagnosis groups of both meta-analyses. Using the *DSM-IV* classification, the prevalence proportions of male outpatients with MDD (being roughly 30-35%) are significantly lower compared to inpatients (roughly 50%). Given the fact that both in- and outpatients were included based on a current MDD, and were therefore affected by the same disorder, it is reasonable to assume that the inpatients not only differ from outpatients in terms of severity, but also in terms of symptomatology. Possibly certain symptoms induce a higher burden (for both the patient and/or for the system) leading to an increased need for hospitalisation. These symptomatology differences may result in higher prevalence rates of MDD in inpatients, thus explaining the different effect sizes between depressive disorder and depressive symptomatology depression in relation to obesity. By extension, inconsistencies reported on the association between depression and metabolic outcomes may be the consequence of "approach induced heterogeneity" as well, as most studies used a categorical diagnostic approach.

7.2.1.2 Dimensional approach

A dimensional approach has been suggested to be a feasible alternative for categorical diagnoses, as it is considered to overcome the problems encountered with a categorical approach. An important advantage is that a dimensional approach describes the severity of various psychopathological symptoms, rather than indicate the presence or absence of a psychopathological state. Rather than lumping together disparate symptoms, it enables to study interrelated symptom clusters, thus circumventing the lack of diagnostic specificity within the *DSM-IV* classification. In addition, since dimension scores are continuous rather than categorical, even subtle changes can be detected, which increases discriminative and therefore statistical power.[8;9]

In our study the SA dimension was associated with most MetSyn components. This is in line with previous research where symptom dimensions were associated with somatic outcomes. Especially dimensions reflecting somatic/affective symptoms were more strongly associated with increased cardiovascular risk and poor cardiovascular outcomes.[10;11] Taken the existing literature and our findings together, there is evidence for the existence of a distinct "somatic dimension" related to depression and anxiety. Interestingly, comparable results were found for atypical depression by Lamers et al.[7] In their study melancholic and atypical depressed subject were compared to controls with regard to metabolic and biological outcomes. The sample with atypical depression was found to have significantly higher levels of BMI, WC and triglycerides, and lower HDL-cholesterol compared to melancholic depressed and healthy controls. These results largely overlap our findings. The similarities between our SA dimension and atypical depression can be further explored in future research using a dimensional

subdivision,[12] with atypical depression being a subtype of the somatic dimension. Possibly, the SA dimension and atypical depression share etiological pathways.

The somatic dimension might be the reflection of underlying pathway disturbances caused by an anxious and/or depressed state. There are several pathways that are thought to be involved: inflammatory pathways, HPA-axis and the ANS. Several inflammatory markers, such as C-reactive protein levels, have found to be associated with depression and to be stronger in clinically depressed patient samples compared to community based samples.[13] This association was found to be bi-directional, although stronger for depression as predictor for elevated inflammatory markers.[14] Further, depression has been repeatedly associated with HPA-axis disturbances.[15;16] These disturbances are often revealed by elevated salivary or serum cortisol levels, which in turn might mediate lipid related symptoms such as overweight and abdominal obesity[8;17;18] through altered lipid levels.[17;19] In our final study (chapter 6) we found elevated salivary cortisol levels among inpatients, in particular evening cortisol levels. The more pronounced adverse "fat-profile" found in inpatients gave support to the hypothesis that lipid-related metabolic disturbances are mediated by HPA-axis over-activation. Finally, activation of the ANS might lead to increased blood pressure levels,[20] ultimately resulting in hypertension.[17;20;21] However, inverse directions of causal pathways might explain the link between biological factors and psychopathology as well. For example, elevated inflammatory markers levels may also help to induce a depressive episode,[22] and ongoing metabolic disturbances might lead to (somatic arousal) symptoms of depression and anxiety.[23-27] The results of our longitudinal meta-analysis tend to support the presence of both hypothetical mechanisms, as obesity in depression-free subjects seems of predictive value for the onset of depression over time, and vice versa.

Many inconsistencies have been described regarding the association between metabolic disturbances and depressive disorders. Not every sample of depressed patients has been found to be at increased cardiovascular risk. The presence of a somatic dimension might be the key feature in the association between depression/anxiety and somatic outcomes, explaining these inconsistencies and showing the additional value of a dimensional approach.

7.2.2 Treatment settings: clinical and metabolic differences

In the Netherlands, mental care can be divided into three treatment settings: primary outpatient care, secondary outpatient care and inpatient care. In the primary care, the general practitioner (GP) is the main caregiver. Selective serotonin reuptake inhibitor (SSRI) is the most prescribed class of antidepressant drugs in this treatment setting. Secondary care is characterised by an outpatient setting as well. Here, not the GP but the psychiatrist is the main caregiver. The pharmacological treatment usually includes the use of SSRIs, selective serotonin and noradrenalin reuptake inhibitor (SNRIs), tricyclic antidepressants (TCA's), or a combination of different (classes) antidepressants. Due to the complexity or severity of the illness, in some cases inpatient treatment is required. During admission (initiation of) a more

intensive (pharmacological) treatment, sometimes even electroconvulsive therapy (ECT), can be offered. In other words, treatment options increase in terms of (pharmacotherapeutical) intensity, weight and duration, with upscaling of the treatment setting.

There are several factors contributing to hospitalisation, distinguishing inpatients from outpatients. Some have a social character, such as marital status or (the absence of) a social support system, others a clinical one: e.g. a severely impaired cognitive state, serious comorbidity, psychotic features, suicidality, therapy resistance and chronicity. These clinical factors have been suggested to reflect increased severity and psychopathological complexity.[28-34]

To our knowledge, no literature is available regarding metabolic differences across different treatment settings comprising subjects all suffering from the same diagnosis. Most studies on this topic included outpatient samples.[34;35] Those considering inpatients were either (small) case-control studies[36-40] or examined metabolic factors within an inpatient sample alone.[41-45] There are only a few studies comparing inpatients to outpatients, one of which focused on the MetSyn.[40] However, this study compared an inpatient sample with MDD with a primary care sample without psychopathology. There are studies comparing depressed inpatients to depressed outpatients, although their focus lies on clinical differences rather than metabolic ones. Depression severity and comorbidity were found to be important predictors for the duration and recurrence of the illness.[31] Inpatients differed from outpatients not only with regard to the severity of current psychosocial stressors and hospitalization rates[46] but showed significantly decreased levels of functioning and work ability as well, thus negatively influencing the prognostic outcomes.[46;47]

With regard to metabolic outcomes, we found inpatients to have more adverse fat-profiles and lower mean blood pressure levels compared to primary and secondary care outpatients. Several factors may have contributed to these differences, such as clinical, biological and behavioural factors. One of the most relevant clinical factors is depression severity. Although it has been suggested to play a role in the association with metabolic disturbances,[34;48] Byerly et al*.,* who compared inpatients, outpatients and healthy subjects with regard to depression severity measures,[49] did not find the depressed samples to differ in terms of severity. This is in line with both previous literature[50] and our own findings in chapters 5 and 6, where we found that "treatment setting" better explained differences across settings (metabolic differences in chapter 5 and cortisol level differences in chapter 6) than depression severity, although the CIDI-scores were on average higher in inpatients than outpatients. The findings from the two studies presented in chapters 5 and 6 included inpatients and outpatients both with a current MDD according to the *DSM-IV* classification, but showed many clinical, metabolic and biological differences, which additionally supports the notion of the importance of treatment setting.

Our inpatients showed relatively low comorbidity of anxiety disorders as compared to outpatients. Yet, in previous studies, comorbidity has been positively associated with severity

of symptoms,[31] which in turn has been described to affect metabolic outcomes.[34] Our results are not necessarily in line with these findings, since the average CIDI-score was significantly higher in inpatients compared to the two outpatients samples. Inpatients therefore likely suffered from a more severe but more pure form of MDD, which may be clinically different from that of outpatients. Also in line with the hypothesis that in- and outpatients differ in terms of symptom dimensions is our finding that inpatients showed lower mean blood pressure levels, while we showed in chapter 5 that elevated blood pressure levels were associated with elevated somatic arousal symptomatology.

The role of medication should be considered as well. An extensive meta-analysis[51] examined how the several antidepressant classes affected individual MetSyn components. Roughly, SSRI's are MetSyn "neutral" meaning that they do not significantly affect any of the MetSyn components. A significant effect was seen for TCA's and mirtazapine, which in general had adverse effects on several MetSyn components. We reported in chapter 5 that TCA's and the group of "other AD", which included mirtazapine, had some influence on metabolic parameters, especially on "fat-profile" components. Because inpatients more often used TCA's and "other AD", and tend to have a longer medical and pharmacological history, they may have a more vulnerable metabolic blueprint.

Metabolic differences across treatment settings might be (in part) explained by biological factors, such as differences in the HPA-axis, the ANS and inflammatory pathways. Elevated stress levels, as found in depression, induce a neuro-endocrinological cascade initiated in the hypothalamus, resulting in the secretion of cortisol by the adrenal cortex. Cortisol levels have generally found to be more elevated in depressed subjects,[52] and especially in inpatients.[50] Hypercortisolism, especially in the presence of insulin, inhibits lipid mobilizing enzymes,[53] inducing several homeostatic changes leading to insulin resistance, changes in fat storage, visceral adiposity and disturbances in the lipid metabolism,[19;54;55] in part explaining the adverse "fat-profiles" in inpatients. Together with our finding of a more adverse "fat-profile" in inpatients versus outpatients, it supports the idea of a causal relationship between HPA-axis over-activation and disturbances in lipid metabolism and fat distribution.

Although we did not examine the possible influence of other systems such as the ANS or inflammatory pathways, they too may play a role in the differences across treatment settings. Activation of the ANS has been associated with being overweight and depression[22;56], but it is mainly thought to increase blood pressure.[55;57] The use of TCAs is considered to increase blood pressure as well.[51] We found lower blood pressure levels in inpatients, despite the more frequent TCA use. Exhaustion of the ANS system in the most severe form of depression[58;59] might explain these findings.

Elevated stress levels have been associated with an increased inflammatory state.[60] A state of mild but chronic inflammation has suggested to link depression and "fat-profile" elements, in particular body weight, WC and body mass index.[50;61] The higher cortisol levels in inpatients can be considered to reflect an increased and more chronic state of psychological

stress. This may lead to activation of inflammatory pathways thus inducing "fat-profile" disturbances. It is therefore arguable that inflammatory pathways (at least in part) influence metabolic profiles among depressed subjects.

Finally, due to a more impaired cognitive state, behavioural factors such as a sedentary life-style and dietary habits may adversely affect metabolic outcomes. These behavioural problems are common among depressed subjects,[62] as many depressive symptoms such as anhedonia, appetite loss or extreme fatigue will not encourage the depressed individual to follow a healthy life-style. Although these life-style and behavioral factors were not assessed in our inpatient sample, the clinical impression and observation during baseline assessments, justifies the assumption that this group in general was physically inactive and not engaged to pay attention to a healthy diet. Since these factors are associated with adverse metabolic outcomes,[63;64] the metabolic differences may in part be explained by sedentary life-style or adverse dietary habits.

7.2.3 Depression and metabolic disturbances

Cardiac mortality and morbidity among depressed individuals[65] are thought to be mediated by metabolic dysregulations, which have been reported to be in fact more pronounced among depressed subjects.[17;66;67] This thesis focused on the association between depression and metabolic disturbances. The presented results indicate that depression is associated with several metabolic disturbances.

7.2.3.1 Depression and obesity: potential mediating mechanisms

Within the broad scale of metabolic disturbances ultimately leading to CVD, there is a growing belief that (abdominal) obesity forms a key feature in the onset of other metabolic disturbances.[68-70] There are several anthropometric adiposity measures to assess abdominal obesity, such as BMI, WC and WHR. Despite the discussion which parameter has the strongest association with CVD,[71] BMI is one of the most frequently used.

In the first two chapters our results showed a significant association between depression and obesity, which had both a cross-sectional and longitudinal, and have a mutual character. Although evidence of a biological link between overweight, obesity and depression is not definitive,[72-75] there are several mechanism that are considered to be involved in this association. First, through activation of inflammatory pathways, often seen in case of weight gain,[76;77] obesity might be considered to be an inflammatory state, which in turn has repeatedly been associated with depression.[22;56;78] Second, HPA-axis dysregulation, often seen in depression,[79;80] is considered as a possible mediating mechanism as well. Third, a surplus of adipose tissue alters neuropeptide secretion levels, and induces a state of hypercortisolism. Both neuropeptides and cortisol affect HPA-axis functioning, thus leading to a depressed state.[81] Fourth, obesity is closely related to the onset of diabetes and increased insulin resistance.[82] Through its angiopathic characteristics, hyperglycaemia could induce

alterations in the brain[83] and increase the risk of depression.[84] Fifth, psychological distress induces by overweight or body weight perception, may lead to increased body dissatisfaction and decrease self-esteem, both well-known risk factors for depression.[85] Finally, disturbed eating patterns and eating disorders, as well as experiencing physical complaints as direct consequence of obesity, are risk factors for depression as well.[86;87]

7.2.3.2 Depression and the Metabolic Syndrome

In the context of metabolic disturbances as mediating factors for the onset of CVD in depressed subjects, the MetSyn has long been seen a central feature. The MetSyn has repeatedly been associated with depression, both cross-sectional and longitudinally.[34;88;89] However, results on this association remain inconsistent.

These inconsistencies might in part be explained by the nature of the concept of the MetSyn. First, the diagnosis is quite heterogeneous: numerous combinations of metabolic disturbances are possible all leading to the same diagnosis. Second, its pathophysiological concept is based on the presence of insulin resistance and glucose impairment.[90-92] However, the pathophysiological mechanisms of the other components are not necessarily similar. Non-insulin dependent diabetes mellitus is a significant cardiovascular risk factor as well, but a causal relation with the other MetSyn components has not consistently been found, and the independent contribution of an hyperglycaemic state of type 2 diabetes to cardiovascular risk is rather weak.[70] More important, due to the heterogeneous presentation, the MetSyn may be present in the absence of its "key feature" insulin resistance. In fact, within the MetSyn, the most consistent evidence is found for the relationship between depression and obesity-related components (abdominal obesity, low HDL-cholesterol, hypertriglyceridemia),[26;40;93-95] while associations with hyperglycemia and hypertension were less often found.[96] This led to criticism on the concept of the MetSyn.[97;98]

Our findings are in line with literature. We consistently found an association between depression and (abdominal) obesity and lipid parameters. Moreover, the finding that BMI showed a temporal and bidirectional association with depression (chapter 3) seems to even further underline its central role for the onset of the MetSyn, especially when put against the recent meta-analysis of Pan et al.,[88] who showed a temporal and bi-directional association between MetSyn and depression as well. Inconsistent results were found for blood pressure, whereas no association was found with glucose levels. Our results show associations between metabolic parameters and depression that do not follow the expected patterns based on the pathophysiological concept of the MetSyn. Instead, our results suggest the presence of distinct metabolic profiles among depressed subjects.

The association between depression and adverse "fat-profiles" has been suggested to be in part the consequence of activated inflammatory pathways, as seen in overweight and depression.[22;56;78] Since dyslipidaemia is common among subjects with overweight and obesity, it is reasonable to argue that inflammation is associated with adverse lipid profiles

as well. There is substantial evidence for involvement of HPA-axis disturbances as well. HPA-axis disturbances in depression often result in elevated cortisol levels,[99;100] and are known to act on fat-storage and lipid-metabolism, thus mediating the association between depression and altered lipid levels.[39;101;102] In fact, associations between hypercortisolemia and adverse lipid outcomes have been reported before,[54] such as elevated total cholesterol,[103] elevated triglycerides and decreased HDL-cholesterol levels.[101;104] The finding that cortisol secretion was found to be prospectively and positively associated with cardiovascular morbidity and mortality[105] adds to the hypothesis that metabolic disturbances mediate the association between depression and adverse cardiovascular outcomes through increased HPA-axis activity. This is supported by our finding that inpatients presented more adverse "fat-profiles" and higher cortisol levels compared to outpatients.

Although some studies argue a positive association between depression and elevated blood pressure levels,[106;107] others report lower blood pressure levels in depression.[57;108] In chapter 4 we found a positive association between SA and blood pressure. A more pronounced somatic arousal dimension, specific for anxiety,[109] might be associated with increased blood pressure levels through activation of sympathetic nervous system.[20] Since the inpatients showed less comorbid anxiety levels, it is arguable that the blood pressure elevating effect due to elevated arousal levels in those with anxiety/arousal symptoms was therefore less present in inpatients, thus explaining the finding that inpatients showed lower blood pressure levels compared to outpatients. An additional argument for the inconsistencies reported within the association between depression and the MetSyn may lie in the diagnostic approach of both. A continuous dimensional factor as we and others[110] used may be more informative that a categorical classification.

7.2.3.3 HPA-axis in depression

Hyperactivity of the HPA-axis in depression is considered one of the more reliable findings in biological psychiatry. A meta-analysis on this topic reported that approximately 73% of depressed individuals showed increased cortisol levels.[111]

On the one hand, depression may induce HPA-axis disturbances. The stress, induced by the depressive state, is perceived by the cerebral cortex and transmitted to deeper cerebral structures, the hypothalamus and the pituary gland, leading to excessive activation of the HPA-axis, thus resulting in an inappropriate release of cortisol into the blood.[99;100] On the other hand, HPA-axis hyperactivity may result in neurobiological changes that enhance the vulnerability to depression, including epigenetic modification of the glucocorticoid receptor and cortisol-mediated abnormalities in neurogenesis, neuroplasticity, and/or neurotoxicity, particularly in the hippocampus, which is implicated in the pathogenesis of depression.[112;113] Further, there are parallels between some aspects of the stress response, severe depression, and the effects of centrally administered CRF, such as increased arousal and vigilance, loss of appetite and increased heart rate and blood pressure.[100;114] This has led to the proposal

that a hyperactive HPA-axis may contribute to depression not only through hypercortisolism, but also via enhanced CRF transmission in the hypothalamus and other brain regions that are innervated by these neurons. Finally, since cortisol is a counterregulatory hormone, with prolonged exposure it will induce visceral/central adiposity, insulin resistance, dyslipidemia, and hypertension, rather than protect the subject from adverse outcomes.54 These hypercortisolemia induced metabolic changes, in particular insulin resistance, could induce alterations in the brain[25] (ref) and increase the risk of depression.[23]

Many studies have examined cortisol levels among depressed samples. Morning cortisol values have generally be found to be elevated among depressed subjects,[115-117] evening cortisol levels have been found to be higher in (remitted) depressed subjects and inpatients as well,[16;118] and, quite consistently, more higher DST levels and more non-suppression is described in those with more severe forms of depression, such as those with psychotic features and inpatients.[111;119-122]

Our results showed that inpatients had higher mean morning cortisol levels at awakening (T1), higher evening cortisol levels and higher cortisol levels after dexamethasone ingestion (DST levels) compared to primary and secondary care outpatients. All in all the findings of higher cortisol levels in inpatients might be explained by several factors. First, sleeping disturbances may result in earlier HPA-axis activation,[123;124] and earlier extinction of the CAR. As a consequence, higher cortisol levels might be no longer detectable at regular waking times. Second, the higher evening cortisol levels might be attributable to hospitalization, in reaction to hospitalization-related stress.[50] Also sleeping disturbances contribute to an elevated basal resting state of the HPA-axis,[123] as well as postponing ones normal bedtime.[125] However, it has also been argued that higher evening cortisol levels may also in part reflect genetic vulnerability or represent a specific endophenotype of depression.[126]

Our additional analyses showed signs of a blunted CAR, consistent with previous findings, where exhaustion of the HPA-axis has been described in the most severe forms of depression.[8;127;128] Contrary to most findings, we found no effect for the presence of psychotic features. This is interesting since the presence of psychotic features is considered to be an important aspect of depression severity, often contributing to hospitalization. In fact, we did not find an association with depression severity, but with treatment setting. This is in line with the results of the meta-analysis performed by Stetler & Miller.[111] Although they found a positive association with symptom severity, the association between cortisol levels was fully accounted for by hospitalization status. In other words, they found the association with elevated cortisol levels to be strongest in a group of inpatients, independently from depression severity. One of the consequences of hospitalization is a certain loss of independence: inpatients have to follow times and rules of the ward, do not always have the freedom to meet family and friends at their own terms, and are in a way submitted to the treatment policy inducted by their physician. The patient may experience this as social isolation and a loss of individual control, thus inducing psychological distress. In addition,

hospitalization may induce changes in circadian rhythms as a consequence of the imposed institutional demands, and therefore affect ones cortisol values.

7.3 Limitations

The methodological limitations of this thesis have been described throughout the previous chapters. However, a short summary of the main limitations will be presented in the current paragraph.

One of the main limitations is the cross-sectional design of most of the studies in this thesis. Therefore no conclusions can be drawn regarding the causality of the examined associations. Another important limitation is the lack of information about some of the possible confounders. Apart from the confounders for which we adjusted, there are other factors known to be related to adverse metabolic outcomes, such as diet patterns and physical activity. In addition, we lacked detailed information on sleeping patterns, which might give additional information on the observed cortisol levels.

Some additional limitations need to be mentioned as well. First, the number of included studies in both meta-analyses was relatively small, the samples mainly consisted of community-based samples. The heterogeneity of the samples was high and did not provide a broad scale of covariates consistent over studies. Ideally, included samples would be more comparable, taking into account more covariates so that their effects could not have confounded the individual effect estimates. Second, the tripartite model is a rather simple dimensional model, not differentiating in additional or potentially more relevant sub-dimensions. Further, the dimensional approach was applied only to the diagnosis of the included sample. Approaching the dependent metabolic outcomes as continua as well could offer additional insights on both the association with depression and their interrelationship. The dimensional approach should not be limited to the MetSyn and to a sample of healthy controls and outpatients, but should add other important metabolic variables and inpatients. In addition, the limited discriminative capacity of the CIDI- score, likely contributed to a low reliability, since it forms a crude proxy measure of severity. Therefore, we were not able to examine possible associations with depression sub-types such as melancholic or atypical depression. Finally, non-linear associations have been suggested with the highest severity levels. Our inpatient sample, however, most likely failed to include most severe inpatients. Therefore we could not assess the effect of “very severe depression” on metabolic and biological outcomes.

7.4 Clinical implications and future perspectives

Despite the above mentioned limitations, this thesis offers relevant implications for clinical practice, as it provides evidence for a significant association between depression and

adverse metabolic outcomes. First, the association between depression and obesity has a longitudinal character. Both conditions can be seen as a late consequence of one another. This finding is of clinical relevance in terms of prevention. Early detection and treatment of both conditions may help to prevent the other. It urges mental and somatic health care practitioners to collaborate closely. Second, this thesis shows that symptoms of somatic arousal are closely related to adverse metabolic outcomes, in particular "fat-profile". When aiming a holistic treatment approach, regular attention should be paid to depressed patients showing anxious arousal. Given the finding that metabolic disturbances are qualitatively more present in inpatients, this group should be monitored for the presence of somatic arousal. Finally, the results might contribute to future adaptation of the diagnostic approach, by implementing dimensionality in the already existing categorical approach, resulting in an optimal discriminative view of the patient's condition. By doing so, prevention and treatment of mood and metabolic disorders may be optimized, possibly leading to a reduced burden of disease of depression and cardiovascular disease.

Future research should replicate and extend our findings. Longitudinal aspects of the associations between depression and other metabolic outcomes should be further explored. Extended insight into these associations will enable the development of optimal prevention and treatment strategies. Further, given the additional value of a metabolic and HPA axis measurements should be examined in relation to symptom dimensions, also in inpatients. These insights may subsequently lead to the design of better preventative strategies against the detrimental cycle in which depression and CVD might impact on each other.

7.5 General conclusions

Depression is closely related to several adverse metabolic outcomes. The nature of this association is complex. The association between depression and obesity was found to be bi-directional, and is likely to play a central role in the onset of an adverse "fat-profile", rather than insulin resistance or glucose impairment. When exploring this association with a dimensional approach, the symptom dimension of somatic arousal resulted to be associated with unfavourable metabolic outcomes. These findings may help to better explain the link between depression and the increased cardiovascular mortality. Moreover, "treatment setting" seems to be an important independent variable in the association with adverse metabolic outcomes through treatment-setting-related characteristics, such as illness duration, recurrence, comorbidity, medication use, life-style and psychosocial stress. In order to offer optimal prevention and treatment strategies, future longitudinal research is warranted. In the meantime, health care providers should monitor both "fat-profile" and mood.

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