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Summary

Depression is a common mental disorder which causes high burden for both the community and the individual. According to the World Health Organization depression ranks high in the top ten of diseases with the highest disease burden due to a marked loss in quality of life. Also high in this top ten is cardiovascular disease. Depressed persons have approximately a two-fold increased risk of having or developing cardiovascular disease. Further, after a cardiovascular event the risk of onset of depression is increased, resulting in poorer cardiovascular outcome. Mechanisms underlying this comorbidity between depression and cardiovascular disease are still largely unknown. The metabolic syndrome, a constellation of cardiovascular risk factors including (abdominal) obesity, hypertension, dyslipidemia and hyperglycemia, has been suggested to be one possible pathway linking depression and cardiovascular disease. Evidence exists that metabolic disturbances might occur more frequently in depressed persons. Disturbed functioning of one of the most important stress systems of the human body, the hypothalamic-pituitary-adrenal (HPA)-axis, might underlie the association between depression and metabolic syndrome. Evidence for these hypotheses is largely confined to cross-sectional research and to investigation of individual as opposed to the combination of metabolic disturbances. Therefore, the general aim of this thesis is to examine whether depressive disorders or symptoms are associated with, predict or follow metabolic disturbances, such as present in metabolic syndrome. In addition, a possible mediating role of the HPA-axis in the relationship between depression on the one hand and metabolic syndrome and cardiovascular disease on the other hand is examined. Knowledge to be gained by this thesis could increase our understanding of pathophysiological processes linking depression and cardiovascular disease, which might be very useful for prevention and treatment of both conditions. To study these research questions data from several large prospective cohort studies are used. Focus is given to older populations as both depressive symptoms and cardiovascular conditions are highly prevalent among the aged. After the theoretical background and research model is presented in **Chapter 1**, Chapters 2 through 9 report on research outcomes.

First, the cross-sectional association between depression and metabolic syndrome is investigated. **Chapter 2** reports on data from the Health, Aging and Body Composition (ABC) study and examines the cross-sectional relationship between several psychosocial risk factors (depressive and anxiety symptoms, negative life events, and inadequate emotional support) and metabolic syndrome in a community-based sample of black and white older persons (N = 2917). All examined psychosocial risk factors were (modestly) associated with metabolic syndrome, although depressive symptoms only in white persons and anxiety symptoms only in men. A combined psychosocial risk index showed the strongest association with metabolic syndrome, which was not confined to a specific component of the metabolic syndrome. **Chapter 3** presents results from the InCHIANTI study among 867 persons aged 65 years and older. Also in this study, depressive symptoms and metabolic syndrome were associated. Findings from the Longitudinal Aging Study Amsterdam (LASA), including 1212 participants aged 65 years and older, are described in **Chapter 4**. However, results of this study did not show significantly increased odds of metabolic syndrome in

persons with major depressive disorder. Persons with subthreshold depressive symptoms even had a decreased odds of metabolic syndrome.

Next, a possible role of the HPA-axis in the association between depression and the metabolic syndrome is examined. Cortisol levels, from urine or blood, provide an index of HPA-axis activity. In **Chapter 3**, based on the InCHIANTI study, a profound role of cortisol is uncovered. The reported cross-sectional association between depressive symptoms and metabolic syndrome largely disappeared after appropriate adjustment for urinary cortisol levels. This indicates a mediating role of high cortisol levels in the association between depression and metabolic syndrome. Moreover, it was found that only those depressed persons that presented with hypercortisolemia were at increased odds of having metabolic syndrome. In particular, high levels of cortisol were associated with a large waist circumference, high triglyceride levels and low high-density lipoprotein cholesterol levels in depressed persons. Although no positive association was found between depression and metabolic syndrome in LASA (**Chapter 4**), results from this study did show that serum cortisol levels are associated with metabolic syndrome. This again suggests that when depressed persons present with hypercortisolemia, odds of metabolic syndrome are increased.

Subsequently, the temporal direction of associations between depression and metabolic syndrome is examined using longitudinal designs. Special focus is given to (abdominal) obesity as this is a central component in metabolic syndrome. **Chapter 5** examines whether depressive symptoms predict an increase in abdominal obesity using 5-year follow-up data from 2088 participants of the Health ABC study. This study showed that having depressive symptoms was followed by an increase in abdominal obesity, specifically visceral fat. This increase was independent of overall obesity, suggesting that there may be specific pathophysiological mechanisms that link depression with visceral fat accumulation. In **Chapter 6** the reverse direction is investigated in the Health ABC study, namely whether (abdominal) obesity increases the risk of onset of significant depressive symptoms in 2547 persons without depression at baseline. Both overall and abdominal obesity predicted onset of depressive symptoms over 5 years of follow-up in men, but not in women. When examined simultaneously, only the effect of visceral fat, but not overall obesity, was an independent predictor of depressive symptoms onset. Stronger associations were found for the onset of depressive symptoms that persisted. **Chapter 7** examines whether metabolic syndrome and its components are associated with both the onset and the chronicity of depressive symptoms using data from 823 participants of the InCHIANTI study. Higher waist circumference, but no other metabolic syndrome component, increased odds of depressive symptoms onset after 3 or 6 years in initially non-depressed persons. Among depressed persons, metabolic syndrome was associated with an almost 3-fold increased odds of persistence of depressive symptoms. Findings suggest that a vicious cycle between depression and visceral fat accumulation might eventually result in a chronic depressive subtype, characterized by metabolic disturbances ('metabolic depression').

Lastly, to make the research model complete, presumed associations between both HPA-axis hyperactivity and depression with cardiovascular disease are tested. HPA-axis activity has been linked to several cardiovascular risk factors, but its effect on clinical cardiovascular endpoints has hardly been examined. **Chapter 8** again uses data from the InCHIANTI study to examine whether urinary cortisol levels predict all-cause and cardiovascular mortality over 6 years of follow-up among 900 participants. Persons having urinary cortisol levels in the top tertile had an almost 3-fold increased risk of dying of cardiovascular disease within 6 years. Risk of all-cause mortality was not increased. These findings confirm that high cortisol levels might be particularly damaging to the cardiovascular system. **Chapter 9** investigates whether the frequently reported association between depression and cardiovascular disease extends to a psychopathology-based sample, as evidence for this association almost exclusively comes from studies among heart patients or the general population. In addition, anxiety disorders are taken into account as they are often comorbid to depression. Data are from 2807 persons with current or remitted depressive or anxiety disorders and healthy controls of the Netherlands Study of Depression and Anxiety. Results show that persons with a current anxiety disorder were approximately three-fold more likely to have coronary heart disease. Increased prevalence of coronary heart disease among depressed persons was largely owing to comorbid anxiety.

The thesis ends with a general discussion (**Chapter 10**) of the findings of Chapters 2 through 9. Taken together, this thesis suggests that in older persons the association between depression and metabolic syndrome might be restricted to a specific subgroup of depressive patients, those that present with hyperactivity of the HPA-axis. In a longitudinal perspective, depressive symptoms and abdominal obesity appear to have a two-directional relationship. When both conditions are present, additional metabolic disturbances might promote a chronic character of the depressive symptoms. These results are suggestive of a vicious cycle and are indicative of the existence of a specific condition, which might be labeled as metabolic depression. Awareness of and appropriate monitoring of comorbid metabolic disturbances in depressed patients might improve their somatic health status and could possibly prevent subsequent cardiovascular disease. Whether treatment of metabolic disturbances could improve depression prognosis needs to be examined.

