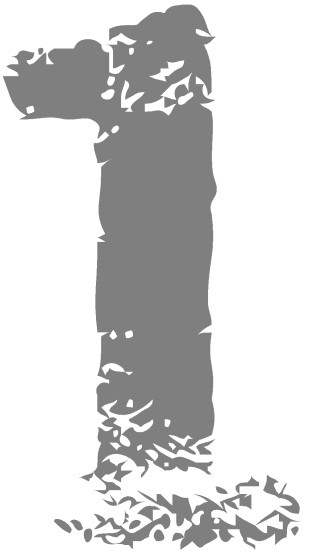
General introduction



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