1. General introduction

For it happens in this, as the physicians say it happens in hectic fever, that in the beginning of the malady it is easy to cure but difficult to detect, but in the course of time, not having been either detected or treated in the beginning, it becomes easy to detect but difficult to cure.

Nicolo Machiavelli (1469-1527)

Depressive and anxiety disorders are associated with excess cardiovascular morbidity, and vice versa, cardiovascular disease (CVD) patients often encounter depressive and anxiety complaints. These conditions of poor mental or cardiovascular health are highly prevalent, highly disabling and attended with enormous costs (e.g. health care, productivity loss). Taking to heart the information above has resulted in this report – the yield of a quest for insight into the associations between depression, anxiety and early cardiovascular disease.

Depression and anxiety: common mental disorders

According to World Health Organization (WHO), mental health is not just the absence of mental disorder, but "a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community." Everyone gets stressed or feels down or frightened every now and then. However, some people experience those feelings of distress more often or for longer periods of time, or even develop a diagnosable illness that significantly interferes with one's cognitive, emotional and/or social ability. Two of the most common mental disorders are depressive disorders and anxiety disorders, which are also highly concurrent [1, 2]. These clusters of disorders (i.e. major depressive disorder, dysthymia, general anxiety disorder, panic disorder, agoraphobia, social phobia) will be the primary focus of this thesis, but some additional attention will be given to mental health in general (i.e. psychological distress). In the general Dutch population, the abovementioned depressive and anxiety disorders have a lifetime prevalence of 20.0% and 18.5%, respectively [3].

Depressive disorders

Major depressive disorder is characterized by the presence of five or more symptoms for at least a two week period; one of the symptoms is either depressed mood or loss of interest or pleasure. Other depressive symptoms include, amongst others, feelings of worthlessness, fatigue, poor concentration, recurrent thoughts of death, changes in weight/appetite, and insomnia/hypersomnia. Lifetime prevalence of major depressive disorder is 18.7% [3].

Dysthymia is a chronic state of depression, characterized by the presence of depressed mood for more days than not during at least two years. This is accompanied by two or more other symptoms which are never absent longer than 2 consecutive months. Lifetime prevalence of dysthymic disorder is 1.3% [3].

Anxiety disorders

Generalized anxiety disorder encompasses feelings of anxiety and excessive worry about everyday things which are difficult to control, together with 3 or more other symptoms (such as muscle tension, restlessness, being easily fatigued, etc.) for at least 6 months. The lifetime prevalence of general anxiety disorder is 4.5% [3].

The essential characteristic of a panic disorder is a panic attack, defined as a sensation of intense fear or distress that develops suddenly and increases within ten minutes after the onset. This attack is accompanied by at least 4 other symptoms, such as accelerated heart rate, chest pain, dizziness, and fear of going crazy. The individual fulfils criteria of a panic disorder if there are two or more panic attacks, at least one of which is followed by persistent concern about having additional attacks, worry about the implications of the attack or its consequences, and a significant attack-related change in behaviour. Lifetime prevalence of panic disorder 3.8%, in 35-65% of cases accompanied by agoraphobia [3];

Agoraphobia is marked by anxiety about being in places or situations from which escape might be difficult or embarrassing. Agoraphobic fears typically involve situations that include being outside the home alone; being in a crowd, or standing in a line; being on a bridge; and travelling in a bus, train, or automobile. These situations are avoided, are endured with marked distress, or require the presence of a companion. Lifetime prevalence of agoraphobia without comorbid panic disorder is 0.9% [3].

A persistent fear of social or performance situations characterizes the social phobia. The individual suffering from this type of anxiety disorder fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing, although the fear is recognized as being excessive or unreasonable. The feared social or performance situations are avoided or endured with intense distress, which interferes significantly with the individual's normal routine or occupational / social functioning. Lifetime prevalence of social phobia is 9.3% [3].

(Subclinical) cardiovascular disease

CVD is referring to those conditions that affect the heart and blood vessels, including amongst others coronary heart disease, cerebrovascular disease, peripheral artery disease, and hypertension. According to the WHO, cardiovascular disease is the primary cause of death around the world. For the Netherlands, this means that about one-third of mortality rates (women 31%; men 29%) are attributable to CVD [4].

Arteries: function and structure

The arterial tree has a conduit and a cushioning function. The first refers to its delivery of oxygenized blood to bodily organs and tissue, and the second to the converting of an intermittent, pulsatile flow to a more continuous blood flow. With respect to the composition of the arterial wall, three layers (tunica) can be distinguished from the inside to the outside: the intima, the media, and the adventitia [5]. The tunica intima is made up of endothelial cells and subendothelial connective tissue. The endothelium (being in direct contact with the blood flow) forms a permeability barrier and thrombo-resistant lining, thereby supporting the artery's conduit function. The tunica media is a thick layer that predominantly consists of elastic fibers and smooth muscle cells. These components are essential for elasticity and contractility, the characteristics needed for cushioning. The adventitia, the outer layer of the arterial wall, is composed of supportive and nutritive tissue, including collagen (a protein that makes up connective tissue) bundles, fibroblasts, and small blood vessels.

Disease processes

Although changes in the structure and function of arterial walls to some extent reflect adaptive processes that are related to age and blood pressure, they also mark

pathophysiological processes that lead to CVD [6, 7]. Two separate, but often overlapping conditions that affect medium and large arteries are atherosclerosis and arteriosclerosis [8, 9]. Atherosclerosis primarily compromises the conduit functioning of an artery, but is also associated with increased stiffness. Arteriosclerosis impairs the cushioning function, and along the line increases the risk of endothelial damage, i.e. atherosclerosis [10, 11]. Atherosclerosis starts in the intima and includes focal thickening, the formation of athērōmata (literally: tumors full gruel-like matter). Those atheromatous plaques are built up from fatty substances, cholesterol, cellular waste products, calcium and fibrin, and cause the arteries to narrow and be less flexible. Atherosclerosis therefore can (partially) block the oxygen-rich blood supply, leading to ischemic events. Arteriosclerosis, or hardening of the arteries, starts in the media en includes decreasing levels of elastin and increased amounts of collagen and calcium, which leads to arterial stiffening.

Indicators of subclinical cardiovascular disease

Considering Machiavelli's remark dating back almost 500 years, it now has become much easier to detect subclinical disease thanks to the emergence of modern imaging techniques. Detailed information about CVD burden in different arterial beds can be obtained using non-invasive methods. Surrogate markers that have been used for this thesis are ankle-brachial index, carotid intima-media thickness and plaque, coronary artery calcification, and both carotid and central arterial stiffness.

Doppler ultrasonography blood flow detection can be used to calculate the ankle-brachial index (ABI). ABI is based on potential differences between systolic pressures in arteries of the lower legs and the arms. This measure is used to screen for peripheral arterial disease. A low ABI (≤0.90) has also been recognized as an indicator of systemic atherosclerosis [12], and as such of increased risk of subsequent mortality, coronary heart disease and stroke [13].

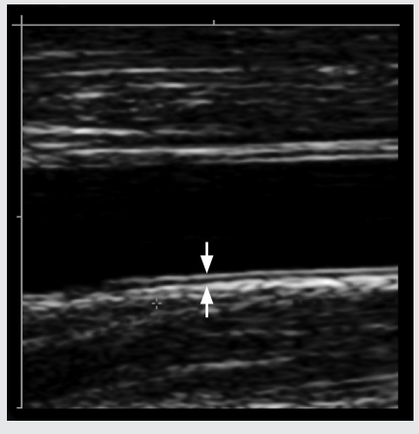

FIGURE 1. Common carotid intima-media thickness

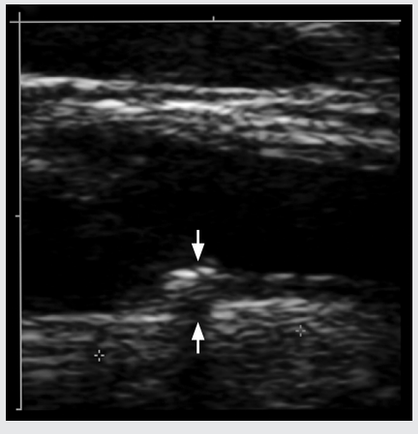

FIGURE 2. Plaque in carotid bifurcation

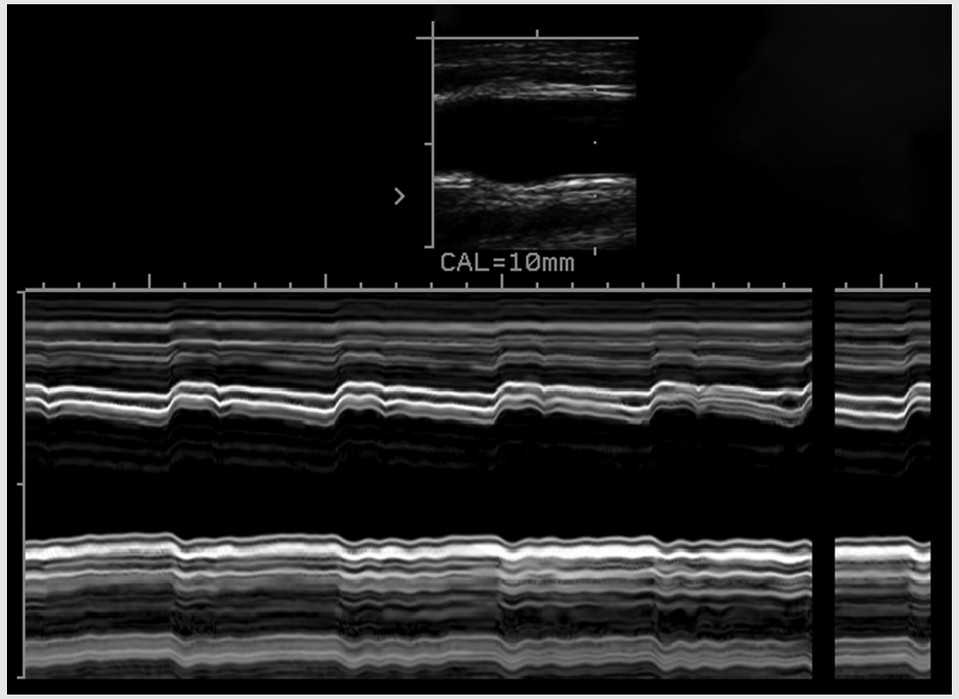

FIGURE 3. M-mode ultrasonography for measuring carotid distensibility coefficient

B (brightness)-mode ultrasonography visualizes internal body structures by directing ultrasonic waves into the tissues and recording the backward waves that reflect changes in density. Using this method, information can be obtained on carotid intima-media thickness (CIMT; **Figure 1**) and plaque presence (**Figure 2**), which are both early markers of atherosclerosis [14, 15] and predictors of future CVD events [16, 17].

Electron beam computed tomography gives 3D images of the heart and is used to identify coronary artery calcification (CAC). Coronary calcification scanning is an accurate method to detect patients with early CVD [18]. Besides, there is strong evidence for the prognostic value of CAC. A meta-analysis by Greenland and colleagues reveals a summary relative risk ratio of 4.3 for any measurable calcium to experience coronary events over 3 to 5 years of observation as compared with a low-risk CAC [19].

In this thesis, two methods have been used for measuring arterial stiffness. Central stiffness is indicated by the central augmentation index, which has been calculated based on pulse wave analysis. Local carotid stiffness is indicated by the carotid distensibility coefficient, obtained by M (motion)-mode ultrasonography (**Figure 3**). Both central and local (carotid) stiffness are predictive of future CVD events [20].

Depression, anxiety and subclinical cardiovascular disease

Depression almost doubles the risk of coronary heart disease in healthy subjects and of future events in coronary patients [21]. Likewise, anxiety disorders have shown to increase the risk of cardiovascular events [22, 23]. These and other findings (e.g. [24]) have given rise

to the now common belief that psychological distress plays a role in the pathophysiology of CVD. Based on this belief, associations between depression or anxiety and subclinical CVD are a logical expectation, and as such, have been studied previously with several surrogate markers. However, those investigations have yielded mixed results: some studies have found positive associations (ABI [25]; CIMT/plaque [26, 27]; CAC [28]; stiffness [29, 30]), but other studies did not find a significant relationship (ABI [31]; CIMT/plaque [32, 33]; CAC [34]). Factors that could have been responsible for the diverging findings are the often small sample sizes and the large differences in populations (with respect to age, disease status, etc), both of which raise questions as to the generalizability of the observations. Besides, associations between anxiety (disorders) and subclinical CVD until now have sparsely been studied.

Why this topic is important

Based on projections models, by 2030 depressive disorders and ischemic heart disease will be the second- and third-largest health burden on society throughout the world [35]. The existing evidence of their interconnectivity makes them even more interesting and important subjects of study. In this respect, anxiety disorders should not be passed, since these are also stress-related conditions and as such risk factors for CVD, plus depressive and anxiety disorders are highly co-existent.

For many individuals the first warning of CVD is a major event, such as a heart attack, stroke, and for some even cardiac death. At the same time, it is known that atherosclerosis and arterial stiffening already begin early in life [36]. This opens up opportunities to identifying asymptomatic individuals at risk. Besides, early detection of CVD can already provide us with information on underlying pathophysiological mechanisms. Both risk factors of and mechanisms involved in CVD need to be illuminated in order to interrupt or slow down the progression of atherosclerosis and arteriosclerosis and (finally) prevent cardiovascular events. The knowledge to be gained by this thesis contributes to this exercise, since depressive and anxiety disorders have great potential as influenceable risk factors: they are highly prevalent in the community at large and especially in medical settings [37]; can be easily measured; are eminently modifiable, once diagnosed [38].

Studies used in this thesis

Netherlands Study of Depression and Anxiety (NESDA)

NESDA is an ongoing longitudinal cohort study to examine the prevalence, course and consequences of depressive and anxiety disorders [39]. In order to represent various health care settings and stages of psychopathology, participants were recruited from community, primary care and outpatient psychiatric clinics. At the baseline assessment in 2004-2007, participants were 2981 men and women, aged 18-65 years. The baseline interview included assessment of demographic and health and lifestyle characteristics, a standardized diagnostic psychiatric interview, and a medical assessment. 2596 (87.1%) of the baseline participants took part in the 2-year follow-up.

NESDA – cardiovascular extension

A subsample of participants of the NESDA 2-year assessment was recruited for additional cardiovascular measurements (June 2007 to July 2009; median of 68 days after 2-year follow-up). This cardiovascular sample included 650 participants, aged 20-66 years. Apart from investigation on potentially important changes since the regular 2-year assessment (e.g. regarding medication use or weight), an electrocardiogram was obtained, blood pressure was measured, and carotid ultrasound scanning and radial pulse wave analysis were carried out.

Heart Scan Study

Whitehall II is an ongoing longitudinal cohort study, which started in 1985 among British civil servants to examine demographic, psychosocial and biological risk factors for coronary heart disease [40]. A subsample of Whitehall II participants was recruited into the Heart Scan Study. Criteria for entry into the Heart Scan (2006 to 2008) included no history or objective signs of CHD, no previous diagnosis or treatment for hypertension, diabetes, inflammatory diseases, or allergies. Participants with a history of major depression or using antidepressant medication in the 12 months prior to the testing were also excluded. The total Heart Scan sample included 543 men and women, aged 53-76 years. Each participant underwent a laboratory session during which biological responses to standardized stress tests were assessed, questionnaires (e.g. on chronic life stress, psychological state) were completed, and coronary calcification was measured.

Aims and hypotheses

The main objective of this thesis is to find possible explanations for the excess cardiovascular risk associated with depression and anxiety. In order to do so, associations between depressive and anxiety disorders and subclinical cardiovascular disease in several parts of the arterial tree are examined. To enhance the understanding of potential relationships, we also use the wealth of data that NESDA provides on clinical characteristics of depressive and anxiety disorders, i.e. subtype of disorder, symptom severity and duration, age of onset, use of antidepressant medication. Additional objectives are to examine a possible relationship between psychological distress and atherosclerotic burden; to explore the role of lifestyle and hypothalamic-pituitary-adrenal (HPA) axis reactivity in associations between mental and cardiovascular health; to assess depressive or anxiety disorders in association with clinical CVD.

We hypothesize that people diagnosed with either a depression or an anxiety disorder will show atherosclerosis and arterial stiffness to a larger amount than do healthy controls; that associations with subclinical CVD will be more pronounced for those with a higher severity and duration of depressive and anxiety symptoms; and that part of the associations between depressive or anxiety disorders and subclinical CVD may be explained by unhealthy lifestyle. Additionally, we expect that people with long-term psychological distress will show increased risk of subclinical atherosclerosis; and that clinical CVD will be found more often in depressed and anxious subjects than in healthy controls.

Outline of this thesis

The studies are summarized in **Figure 4**.

- Chapter 2 describes associations between subclinical peripheral arterial disease (measured by the ankle-brachial index) and depressive or anxiety disorders and characteristics. Analyses are based on the total NESDA baseline sample, after exclusion of CVD cases.
- Chapter 3 investigates whether carotid atherosclerosis (intima-media thickness and plaque presence) is associated with depressive or anxiety disorders – in general or according to specific psychiatric characteristics. Here, data from the NESDA baseline and 2-year assessments are combined with additional measurements from the cardiovascular extension study.
- Chapter 4 is based on the same cardiovascular extension-subsample of NESDA. This chapter studies whether depressive or anxiety disorders are associated with increased arterial stiffness, as measured by either central augmentation index or carotid distensibility coefficient. In addition, associations between psychiatric characteristics and arterial stiffness indicators are assessed.
- Chapter 5 also uses data from this NESDA subsample in order to investigate specific vulnerability traits which are related to depressive or anxiety disorders, i.e. cognitive reactivity to sadness or to bodily sensations, are associated with markers of early cardiovascular disease.
- Chapter 6 is based on data from the Heart Scan Study and examines whether current or long-term psychological distress is associated with subclinical coronary artery calcification. Besides, cortisol reactivity is examined as a factor to explain (mediate) or further refine (moderate) the association between psychological distress and coronary calcium.
- Chapter 7 examines whether clinical cardiovascular disease is more prevalent among depressed or anxious subjects as compared with controls. In addition, the role of clinical characteristics of depressive or anxiety disorders is assessed. Analyses are based on the total NESDA baseline sample.
- Finally, Chapter 8 summarizes and discusses the main findings of the studies included in this thesis.

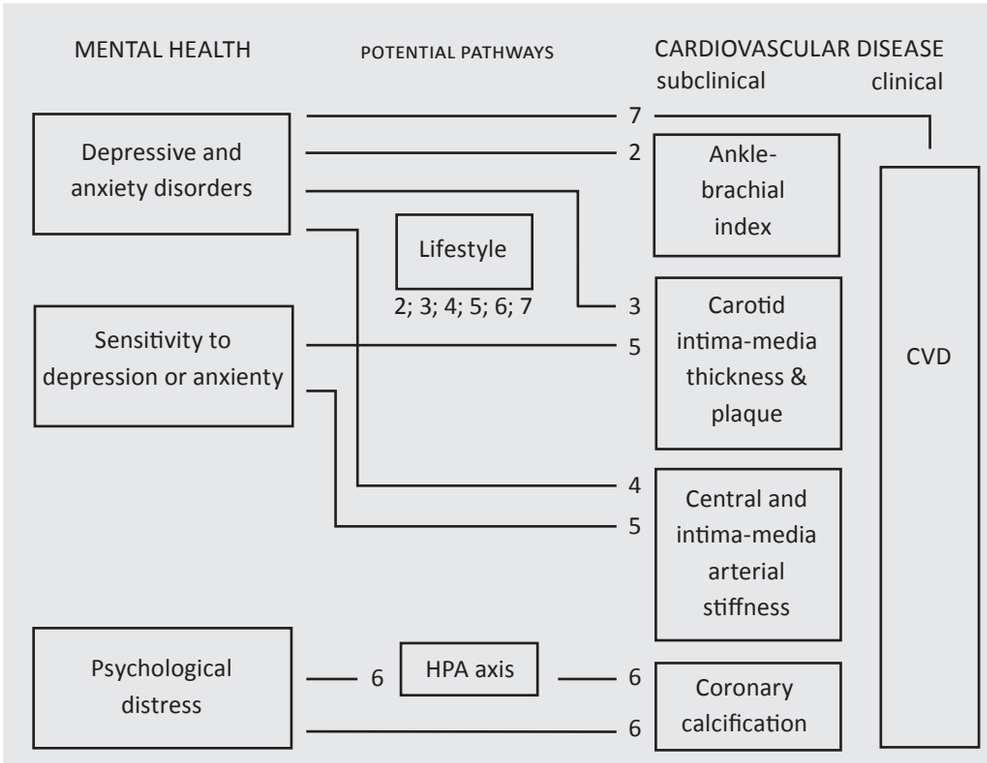

FIGURE 4. Schematic overview of studies in this thesis

numbers indicate chapters
CVD = cardiovascular disease; HPA axis = hypothalamic-pituitary-adrenal axis

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