

Summary

General introduction

Depression and anxiety are common mental disorders which cause high disease burden. They also are considered risk factors for cardiovascular disease (CVD). CVD carries a high disease burden too, due to loss of quality of life and reduction of life expectancy. The existing evidence of the interconnectivity of mental and vascular health makes them even more interesting and important subjects of study. For many individuals the first warning of CVD is a major event, such as a heart attack, stroke, or cardiac death. At the same time, it is known that changes in arterial structure and function can be measured already on an early, subclinical level. Various markers of (subclinical) CVD can be distinguished, based on e.g. the vascular bed concerned (central or more peripheral) and the underlying pathophysiological process. As to the latter, athero- and arteriosclerosis are two separate but often overlapping conditions that affect medium and large arteries. Atherosclerosis or narrowing of the arteries is the process by which fatty substances, calcium particles and waste products build up along the (damaged) linings of arterial walls. As a consequence, increasingly less blood – and therefore less nutrition and oxygen – is able to reach the bodily organs and tissue. Arteriosclerosis or arterial stiffening refers to the progressive loss of elasticity of the arterial wall, due to which the risk of endothelial damage increases and the heart is hindered to supply sufficient blood flow. Both atherosclerosis and arteriosclerosis have been shown to predict cardiovascular events.

Previous studies regarding depression or anxiety and subclinical cardiovascular disease have yielded inconsistent results. A lot of studies were also based on small samples and therefore could not adequately adjust for potential confounders, nor study the influence of specific psychiatric characteristics. Besides, associations between anxiety (disorders) and subclinical cardiovascular disease until now have sparsely been studied. Further, as depression and anxiety are often found to be co-morbid, it would be important to study the association of depression and anxiety with subclinical cardiovascular disease in concert.

The aim of this thesis is to contribute to knowledge on the association between depression, anxiety and subclinical CVD. The primary research question is: Are depressive or anxiety disorders, or specific psychiatric characteristics, associated with increased atherosclerosis or arterial stiffness? Additionally, it is investigated whether psychological distress is associated with atherosclerosis; whether lifestyle or hypothalamic-pituitary-adrenal axis reactivity may play a role in potential associations between mental and vascular health; and whether depressive or anxiety disorders are associated with (clinical) CVD.

Current depression and/or anxiety disorder and peripheral arterial disease

In Chapter 2 we compared the presence of peripheral atherosclerosis between people with or without depressive or anxiety disorders. We used data from 2717 participants of the baseline measurement of the Netherlands Study of Depression and Anxiety (NESDA). Participants for the current study were aged 18 through 65 years and had no history of CVD. Peripheral atherosclerosis was measured using the ankle-brachial index. This index is based on the systolic blood pressure measured in the ankle and the arm. When the ankle

pressure is lower than that of the arm (ankle-brachial index ≤ 0.9), this is evidence for decreased blood flow in the legs due to atherosclerosis. 1619 participants had a depressive and/or anxiety disorder in the year prior to the measurement (current), and 496 participants had been depressed or anxious ever before (remitted). We additionally had a group of 602 healthy controls, without a history of depressive or anxiety disorders.

As compared with healthy controls, participants with a current depression or anxiety disorder almost 3-times more often had peripheral atherosclerosis. Within this group with current psychopathology, the severity and duration of depressive or anxiety symptoms was not of influence, nor was the use of antidepressant medication. No increased risk was found for those with remitted diagnoses of depression or anxiety disorders. This might be explained by the retrospectively obtained diagnoses (which are less reliable). Another possibility is that the group with psychopathology also includes the more chronically depressed or anxious subjects. Our observations suggest that both depression and anxiety disorders are associated with increased risk of atherosclerosis.

Late-onset depression and thickness of the carotid arterial wall

In Chapter 3 we investigated whether the arterial wall of people with a depression or anxiety disorder was more increased than that of healthy controls. Thickened layers in the arterial wall, e.g. damaged endothelium where cholesterol, platelets and calcium can start to build up, can cause narrowing or other trouble after part of the 'plaque' gets loose and ends up travelling in the blood stream. The carotid arteries were visualized using ultrasonography in 649 participants of the NESDA 2-year assessment. The thickness of the carotid arterial wall (i.e. intima-media thickness) was calculated and the presence of local protrusive areas (plaques) was registered.

In general, no difference was found between the 470 participants with a current or remitted depression or anxiety disorders and 179 controls with respect to arterial wall thickness. In the group with psychopathology, increased severity or duration of symptoms was not associated with carotid atherosclerosis either. However, among those who ever had a depressive disorder, the age of the first depression onset did matter. The later the age of first depression onset, the likelier the probability one showed an increased intima-media thickness and plaque presence. Because atherosclerosis is a process taking decennia, these findings better suit the hypothesis that (subclinical) CVD can cause depression than vice versa. Based on existing knowledge, we think this might be caused by plaques in particular brain areas that are responsible for emotion regulation. Our results thus suggest that poor vascular health might contribute to someone's vulnerability to develop a depression.

Current depression and/or anxiety disorder and arterial stiffness

In Chapter 4 we investigated whether depression or anxiety disorders, or specific psychiatric characteristics, were associated with arterial stiffness. Arterial stiffness increases the risk of endothelial damage and causes the heart to work harder. Local elasticity of the carotid arteries (distensibility-coefficient) was measured using ultrasonography; aortic stiffness (central augmentation index) was estimated based on radial artery waveforms recorded with an applanation tonometer and a transfer function. The analyses were based on 618

participants of the NESDA 2-year assessment, with 29% having a current (last month) diagnosis of depressive or anxiety disorder, 44% having remitted depression or anxiety and 27% without a diagnosis of depressive / anxiety disorder ever (controls).

In general, participants with a current depression or anxiety disorder showed an increased augmentation index as compared with controls. People who had suffered from a depressed or anxious episode in the past but were currently recovered, did not differ from controls with respect to central arterial stiffness. It therefore can be suggested that arterial stiffening might be a state effect, which returns to normal when depressed or anxious episodes fade away. We further observed that subjects who were longer or more severely exposed to anxiety or depressive symptoms showed increased stiffness, fitting into a dose-response relationship. Regarding carotid distensibility coefficient, no significant differences were found between depressive/anxious subjects and healthy controls. This could be due to heterogeneity in aging of different arterial regions (the aorta might be more prone to vascular stiffening than peripheral arteries).

Anxiety sensitivity, carotid atherosclerosis and arterial stiffness

Chapter 5 describes a study on whether cognitive vulnerability ('sensitivity') to depression or anxiety is associated with subclinical CVD. Depressive and anxiety disorders often co-occur and partially include the same symptoms. Since previous studies investigating cardiovascular risk mostly have focused on either depression or anxiety disorders, it is not clear yet what exactly drives CVD risk in depressed or anxious subjects. We therefore investigated associations with subclinical CVD at the level of trait-like, cognitive vulnerability to depression or anxiety, using data from 635 participants of the NESDA 2-year assessment. Depression sensitivity measures the extent to which dysfunctional cognitions (e.g. hopelessness, aggression, rumination) are triggered during normal mood, that is cognitive reactivity to sadness. Anxiety sensitivity assesses the degree to which one is concerned about possible negative consequences of bodily, cognitive or publicly observable sensations (e.g. increased heart rate, concentration problems, blushing). Carotid bifurcation intima-media thickness, presence of carotid plaques and central augmentation index were taken to be indicators of subclinical CVD.

Apart from a tendency of higher aggression reactivity to be associated with carotid plaque, no significant associations were found for any of the depression sensitivity measures. However, subjects scoring higher on anxiety sensitivity both had a higher likelihood of plaque presence and showed increased arterial stiffness. These findings suggest that cognitive vulnerability to anxiety, rather than depression sensitivity, is associated with indicators of increased cardiovascular risk. The current study further stresses the importance of including anxiety disorders among the potential CVD risk factors.

Psychological distress and coronary calcification

In Chapter 6 we studied psychological distress (current or long-term) in association with subclinical coronary artery calcification. Additionally, we investigated whether someone's hormonal reactivity to stress could play a role in this association. We analysed data from the Heart Scan Study (London, Great Britain), which is based on the Whitehall II cohort. 527 healthy men and women (aged 53-76) without a history of CVD or depression came for an extra laboratory visit. A heart scan was made in order to measure coronary calcification and salivary cortisol was measured before and after stress-tasks. Participants also completed a questionnaire (Mental Health Index; MHI-5) about how they had felt (nervous, down in dumps, calm, happy, low) over the past month. Long-term distress was based on the averaged scores of six assessments over the 15 preceding years.

The more chronic psychological distress people had, the higher was their likelihood of having severe coronary calcification. No significant associations were found between current distress and calcification. Psychological distress in general was not associated with increased cortisol stress-responses. However, people who both reported chronic distress and showed increased hormonal stress responses had the highest risk of severe coronary calcification; these 'hypercortisolemically distressed' were 8-times more likely of having severe calcification as compared with people who for a long time had been 'happy in one's skin' and didn't show a large cortisol peak following stress tasks. Long-term psychological distress was not associated with mild/moderate coronary calcification. This could imply that exposure to psychological distress speeds up the progression of atherosclerosis, rather than brings about its initial development.

Current anxiety disorders (and depression) and cardiovascular disease

In Chapter 7, data from the NESDA baseline assessment were analyzed in order to investigate whether CVD was more often found in people with a depression and/or anxiety disorder as compared with controls. Besides, we studied specific psychiatric characteristics in association with CVD. The presence of CVD was based on self-report and medication use and subsequently categorized as stroke and coronary heart disease (angina pectoris, myocardial infarction, coronary angioplasty and coronary artery bypass grafting). Participants were 2315 subjects with a depression or anxiety disorder in the year prior to assessment (current) or earlier in life (remitted) and 492 healthy controls. Several clinical characteristics were measured, such as comorbidity, severity and duration of symptoms, and use of psychotropic medication.

People with a current anxiety disorder about 3-times more often had coronary heart disease. The odds were 2.7 for subjects who only had a diagnosis of anxiety disorder, and 3.5 for those who also had a comorbid depressive disorder. No significant association was found between depression or anxiety and stroke. Likewise, no associations with CVD were found for people with a current depression only, or with remitted depression or anxiety. Severity of depressive or anxiety symptoms was associated with coronary heart disease in a dose-response manner. This study among people with depression and/or anxiety shows that those with anxiety disorders carry increased risk of coronary heart disease.

General discussion

Briefly, the results presented in this thesis show that both depressive and anxiety disorders are correlates of subclinical CVD. More specifically, peripheral atherosclerosis and increased central arterial stiffness are more often found in people with current depression or anxiety as compared with controls. Clinical CVD is more often found in subjects with a current anxiety disorder, but comorbid depression increases the odds even further. Besides, some evidence was found in favor of a dose-response relationship between depression, anxiety and CVD risk: the more depression/anxiety symptoms or long-term psychological distress reported, the more increased the central arterial stiffness, the likelihood of subclinical coronary calcification or clinical coronary heart disease. The associations between mental and vascular health were not exactly the same along the arterial tree, since no significant associations were found between depression, anxiety and (sub-/)clinical CVD in the cerebrovascular bed (i.e. carotid atherosclerosis, carotid stiffness, stroke). However, late-onset depression was associated with carotid atherosclerosis. It is not likely that an unhealthy lifestyle directly explains the subclinical CVD in depressed or anxious participants. Although lifestyle factors separately were associated with CVD outcomes, they hardly changed the associations found when included as covariates.

Because of the primarily cross-sectional character of the studies described in this thesis, no conclusions can be drawn about the causality of the associations between mental and vascular health. Despite that, our observations seem to imply that monitoring the cardiovascular risk of depressed and anxious patients is no frivolous luxury: they appear to be a high-risk population with respect to both increased atherosclerosis and arterial stiffness.