General discussion

8.

Gladness of the heart is the life of man, and joyfulness of a man prolongeth his days.

Ecclesiasticus (± 180 BC)

The overarching purpose of this thesis was to investigate whether depressive and anxiety disorders are related to indicators of subclinical cardiovascular disease (CVD). Further objectives were: to examine associations between psychological distress and atherosclerotic burden; to explore the influence of lifestyle and HPA axis reactivity on these associations; and to assess the impact of depressive or anxiety disorders on the occurrence of clinical CVD.

Various samples and indicators of CVD have been used throughout this paper. Baseline data of the Netherlands Study of Depression and Anxiety (NESDA) were used for the analyses on ankle-brachial index (ABI) and clinical CVD in Chapters 2 and 7. Participants were 2981 men and women (18-65 years), with or without depressive or anxiety disorders.

- ABI is based on potential differences between systolic pressures in arteries of the lower legs and the arms and calculated using Doppler ultrasound blood flow detection. Subclinical CVD was defined as the presence of an ABI score associated with increased cardiovascular risk (below or above 1.11-1.40; [1]). A low ABI (≤0.90) is considered an indicator of systemic atherosclerosis, whereas a high ABI (>1.40) probably reflects poor arterial compliance due to arteriosclerosis, i.e. arterial stiffness.
- CVD included stroke, angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty and coronary artery bypass grafting and was adjudicated using standardized algorithms considering self-report and medication use.

Data from a subsample (n=650) of the NESDA 2-yr follow-up were used for the analyses on carotid atherosclerosis and arterial stiffness in Chapters 3, 4 and 5.

- Information on carotid atherosclerosis (intima-media thickness, CIMT; plaque) was obtained using B (brightness)-mode ultrasonography. Both increased CIMT and the presence of carotid plaque are considered markers of atherosclerosis [2, 3].
- Central arterial stiffness was indicated by the central augmentation index, which has been calculated based on radial pulse wave analysis and a transfer function. Local arterial stiffness was indicated by the carotid distensibility coefficient, obtained by M (motion)-mode ultrasonography. Both central and local (carotid) stiffness are predictive of future CVD events [4].

Data from the Heart Scan Study, a subsample of the Whitehall II cohort, was used for the analyses of coronary artery calcification (CAC) in Chapter 6. Participants were 527 healthy, older (age: 53-76 years) men and women, without a history of coronary heart disease or depression.

- CAC was identified using electron beam computed tomography. CAC scanning is considered an accurate method to detect patients with early CVD [5].

In this chapter, we present the main findings of the studies described in the individual chapters of thesis, and discuss these in the context of the current scientific evidence. In addition, we address methodological considerations, review possible implications and propose suggestions for future research.

Main findings

The results from the entire thesis are summarized in the **table 1** below.

Depression and anxiety

Depressive and anxiety disorders are very often comorbid conditions [6, 7]. Indeed, out of the participants of the NESDA cardiovascular subpopulation (n=650) with a lifetime diagnosis of anxiety disorder, 80% also had a depressive disorder once in their life, and vice versa, of those with a lifetime depressive disorder, 76% had a lifetime anxiety disorder as well. So far the majority of studies that investigated subclinical CVD in association with depression or anxiety had examined either of these psychiatric conditions only - thereby mainly focusing on depression. Positive relationships frequently have been reported of (subclinical) CVD and depression as well as anxiety. However, it remained uncertain which of the two associated best with increased cardiovascular risk. A strong point of this thesis, therefore, is the fact that depressive and anxiety disorders were diagnosed according to DSM-IV criteria, a large amount of psychiatric characteristics was collected, and both conditions were studied simultaneously with respect to CVD risk.

The studies described in Chapters 2 and 4 have investigated the hypothesis that depressed and anxious subjects have a higher risk of subclinical CVD (atherosclerosis and arterial stiffness, respectively). In Chapter 2 we studied the presence of a deviant ABI. Compared with healthy controls, subjects with a current diagnosis of depressive, anxiety, or comorbid depressive and anxiety disorder had a significantly increased likelihood of low ABI (2.8-times, 3.1-times, or 2.7-times, respectively). Our observations are in line with a previous study which showed that high levels of depressive symptoms increased the risk of incident peripheral arterial disease in a middle-aged population based cohort [8]. In contrast, two studies found no significant association between depression and low ABI [9, 10], which could have been due to the relatively small sample size (n=167) in one [9] and the relatively low prevalence (3%) of depressive disorder in the other study [10]. One small-sized study (n<50) previously assessed ABI in subjects with anxiety disorders and controls, and found no significant association [11]. However, continuous ABI was used instead of categories – which may be problematic since ABI is shown to have a non-linear, U-shaped association with CVD risk. In Chapter 4 we tested the hypothesis that participants with a current diagnosis of depressive or anxiety disorders showed increased arterial stiffness as compared with healthy controls, using data from the NESDA cardiovascular subpopulation. Indeed, as in Chapter 2, both depression and anxiety (both established diagnoses and symptoms) were associated with a higher central augmentation index, which indicates early wave reflection due to arterial stiffness. Since this sample initially also included subjects with CVD, we additionally excluded all subjects with known or suspected (diabetes, use of antihypertensive or lipid-modifying medication) major cardiovascular health problems.

		Atherosclerosis			Arterial stiffness		Clinical CVD	
		Peripheral low ABI (≤0.9)	*Carotid* IMT & plaque	*Coronary* CAC	*Carotid* DC	*Aorta* AIx75	*Cerebral* Stroke	*Coronary* CHD
Depressive disorder	**current**	+	/		/	+	/	/
	remitted	/	/		/	/	/	/
	characteristics	/	+ later onset		/	+ severity, duration, comorbidity		+ comorbid dep
	sensitivity		/			/		
Anxiety disorder	**current**	+	/		/	+	/	+
	remitted	/	/		/	/	/	/
	characteristics	/	/		/	+ severity, duration, comorbidity		/
	sensitivity		+ (plaque)			+		
Psychol. distress	**current**			/				
	long-term			+ (severe) moderated by cortisol reactivity				

TABLE 1. The associations of depression, anxiety and subclinical CVD

Abbreviations: ABI = ankle-brachial index; AIx75 = heart rate corrected augmentation index. CAC = coronary artery calcification; CHD = coronary heart disease; CVD= cardiovascular disease; DC = distensibility coefficient; IMT= intima-media thickness.
Explanation of marks: /, no significant association; +, significant positive association.

However, this did not change the fore-mentioned significant associations. Although previous literature on this topic is sparse [11,12], and the available studies may be biased by a relatively small sample size (N<50; [11-17]), the inclusion of elderly individuals (over 60 years of age; [11, 12, 15, 18, 19]) and those with comorbid conditions, collectively the available evidence was in line with our findings. Given the large sample size of our NESDA cardiovascular cohort, the careful assessment of the psychiatric disorders and the state-of-the-art measurement of indicators of arterial stiffness, our findings may be regarded as an important contribution to this field.

Chapter 5 was based on the premise that heterogeneity exists in depressive and anxiety disorders, which complicates the sorting out of the respective contribution, of anxiety versus depression, to the development of CVD. We examined associations of sensitivity - or psychological vulnerability – to depression or anxiety and subclinical CVD (carotid atherosclerosis, central arterial stiffness). The sensitivity measures detect dysfunctional cognitions that are thought to be involved in the development and maintenance of particularly depressive (Leiden Index of Depression Sensitivity [20]) or anxiety (Anxiety Sensitivity Index [21]) disorders. Carotid plaque presence and central arterial stiffness were especially increased in subjects who tend to be highly fearful of anxiety-related bodily sensations. Anxiety sensitivity therefore, to a greater extend than depression sensitivity, might constitute a CVD risk factor.

In Chapter 7 the prevalence of clinical CVD was studied in the NESDA baseline sample, including subjects with and without lifetime depressive or anxiety disorders. CVD was more prevalent in subjects who were currently depressed as compared with controls. Likewise, subjects with a current anxiety disorder had a higher likelihood of CVD. When combining the presence or absence of a depressive or anxiety disorder in one variable, however, the increased likelihood of CVD was only observed in those with a current anxiety disorder with or without comorbid depression, but not in subjects with a current depressive disorder only. The results of Chapters 5 and 7 are in line with a recently published large prospective study that found anxiety disorders but not depressive disorders predictive of future (37-yrs follow-up) coronary heart disease [22].

As stated earlier, relatively few studies have examined the link between anxiety and cardiovascular outcomes, when compared to those investigating the association between depression and cardiovascular risk. Taking together the observations as described in Chapters 2, 4, 5 and 7, the focus of research and clinical practice, which is traditionally on depression and CVD, should perhaps be widened to include anxiety as well.

Current versus remitted disorder

When focusing on associations between clinical diagnoses of depressive or anxiety disorder and cardiovascular health, one consistent result throughout this thesis is the lack of significant findings for remitted disorders. Subjects with a current depressive or anxiety disorder, however, repeatedly showed to be at increased CV risk. As described in Chapter 2, a low ABI (i.e. subclinical atherosclerosis) was about 3-times more often found in currently depressed or anxious people than in healthy controls, whereas remitted cases were not significantly different from controls with respect to the occurrence of deviant

ABI. In Chapter 4, increased aortic stiffness was found in those with a current depression or anxiety disorder, but those with remitted disorders showed no significant differences in arterial stiffness as compared with controls. In Chapter 7 we found that clinical CVD was more prevalent in subjects with a current (depressive or) anxiety disorder as compared with controls. Again, those with remitted disorders showed no significantly increased likelihood of CVD. There may be several reasons for the divergence in results of current and remitted disorders.

Assessment of remitted psychopathology has been done retrospectively and might thus suffer from decreased reliability [23]. In other words, this group of subjects with remitted diagnoses of depression or anxiety probably is contaminated with those who actually are healthy controls. However, this bias less likely occurred in the analyses of arterial stiffness, since 45% of the remitted cases in that subsample had a current diagnosis at the NESDA baseline assessment.

Furthermore, the current psychopathology diagnosis might function as a measure of chronicity. This group of subjects with current diagnoses in fact also includes those who frequently relapse into - or even are chronically affected by - depressive or anxious episodes. The remitted status then indicates increasingly less severe exposure to stress experience over time. Thus the divergence of CV risk between current and remitted disorders could be the reflection of a dose-response relationship. For central arterial stiffness and coronary heart disease (Chapters 4 and 7, respectively), the validity of this interpretation was supported by significant positive associations between depression and anxiety comorbidity and severity and CVD. Our findings result of an association between long-term psychological distress, but not with distress that was reported once (i.e. concurrently), and severe coronary artery calcification also emphasizes the importance of the duration of poor mental health (Chapter 6).

Besides, the lack of associations between remitted diagnoses of depression or anxiety and CV markers could imply that arterial status returns to normal when people recover from their depressive / anxious episode. At least, this might be thinkable for arterial stiffness, which is a more dynamic process than atherosclerosis. Evidence for such a state-effect has been advanced by a study that showed how severely depressed women showed increased arterial stiffness as compared with controls, whereas this difference disappeared after successful antidepressant treatment [14].

Late-onset depression

In Chapter 4, we examined whether depressive or anxiety disorders - in general or according to specific psychiatric characteristics – were associated with the presence of carotid atherosclerosis. The disorders in general were not significantly associated with higher atherosclerosis burden. However, within the group of subjects with a lifetime diagnosis of depressive disorder, a later age of onset was positively related to carotid atherosclerosis. These observations not only confirm results of a previous study [24], but also expand the evidence by a) performing careful state-of-the-art CIMT measurements, b) studying carotid plaque instead of using CIMT in the common carotid artery only, and c) additionally comparing depressed cases with controls. As compared with controls, we found no

significant differences for total CIMT or plaques, but still for bifurcation CIMT in late-onset (onset ≥ 40 years) cases. One study did find significantly increased total CIMT as compared with controls [25], probably due to the older age of their sample (mean age: over 70 years vs. 46 years in our study). Since especially bifurcations are atherosclerosis progression-prone segments, it was not surprising that we found more distinct and significant bifurcation CIMT differences between groups. The idea that age of first depression onset may help to stratify for CVD risk has also received support from a genetic perspective. Data from the Swedish Twin Registry have shown that early-onset depression was found to be linked to a familial burden of depression, but late-onset depression to a familial burden of vascular disease [26]. Hence, late-onset as compared with early-onset depression probably has a different pathophysiology that includes a vascular component. In other words, atherosclerosis could make a subject vulnerable to develop depression. This fits into the 'Vascular Depression' hypothesis, which states that cerebrovascular disease might predispose or perpetuate some depressive syndromes later in life [27].

Differences between outcome measures

Some discrepancies are found when comparing associations of clinically diagnosed depression or anxiety across the various outcome measures. As described earlier, the presence of a depressive or anxiety disorder increases the likelihood of subclinical and clinical CVD, but this did not hold true for atherosclerosis and arterial stiffness in the carotid arteries (Chapters 3 and 4, respectively), nor for stroke (Chapter 7), which showed no significant associations.

An explanation for the discrepancies regarding the association of psychopathology and the various surrogate measures of subclinical vascular damage could be the relatively young population of NESDA (range: 18-66 years). At a younger age, the range of aberrant values is not very wide and, as a consequence, associations are hard to be detected. Linked to this point, a differential impact (i.e. rate and severity) of aging across the arterial tree might also partially explain the seemingly discrepant findings. It has been demonstrated that subclinical atherosclerosis probably does not affect all arterial beds in a uniform and contemporaneous manner [28]. This may due to a differential composition of the vascular wall, i.e. so-called elastic (e.g. large central arteries such as the carotid artery) versus muscular arteries (e.g. femoral artery) as well as the location of the arteries in the body. This might explain why we found associations between depressive or anxiety disorders and CVD markers for some (aortic, coronary, peripheral/femoral), but not for other (carotid, cerebral) vascular beds.

Besides, CIMT has been criticized as a marker of atherosclerosis. In as much a thickening of the intimal-medial layer of arterial walls to some extent is a reactive adjustment to higher blood pressure and shear stress changes, it indeed not necessarily be the consequence of frank atherogenesis [29]. On the one hand, this would explain why we did not find differences in CIMT between controls and depressed or anxious cases in Chapter 3. On the other hand, beyond a certain thickness CIMT more likely represents atherosclerosis [30], but a clear cut-off value is still lacking. The presence of carotid plaque, which is thought to represent more advanced atherosclerosis, was also studied in Chapter 3. Although our plaque definition was

an 'area of focal increased thickness ≥ 1.10mm', we still did not find anxiety or depression (overall) to be associated with a higher prevalence of carotid atherosclerosis.

Potential pathways

Several causal models can been applied to associations between depression, anxiety and subclinical CVD. A common underlying factor could predispose to poor mental as well as poor vascular health. According to the vulnerability-stress model [31], the presence of predisposing factors combined with a certain amount of stress (e.g. depression and anxiety), via behavioral and physiological pathways could lead to the development of CVD. Or, in case of reverse causality, subclinical CVD may render individuals susceptible to depression. These causality models should not be considered mutually exclusive, but complementary - together accounting for the pathophysiology. A schematic representation of the biopsychosocial interactions between depression, anxiety and CVD is given in **Figure 1.**

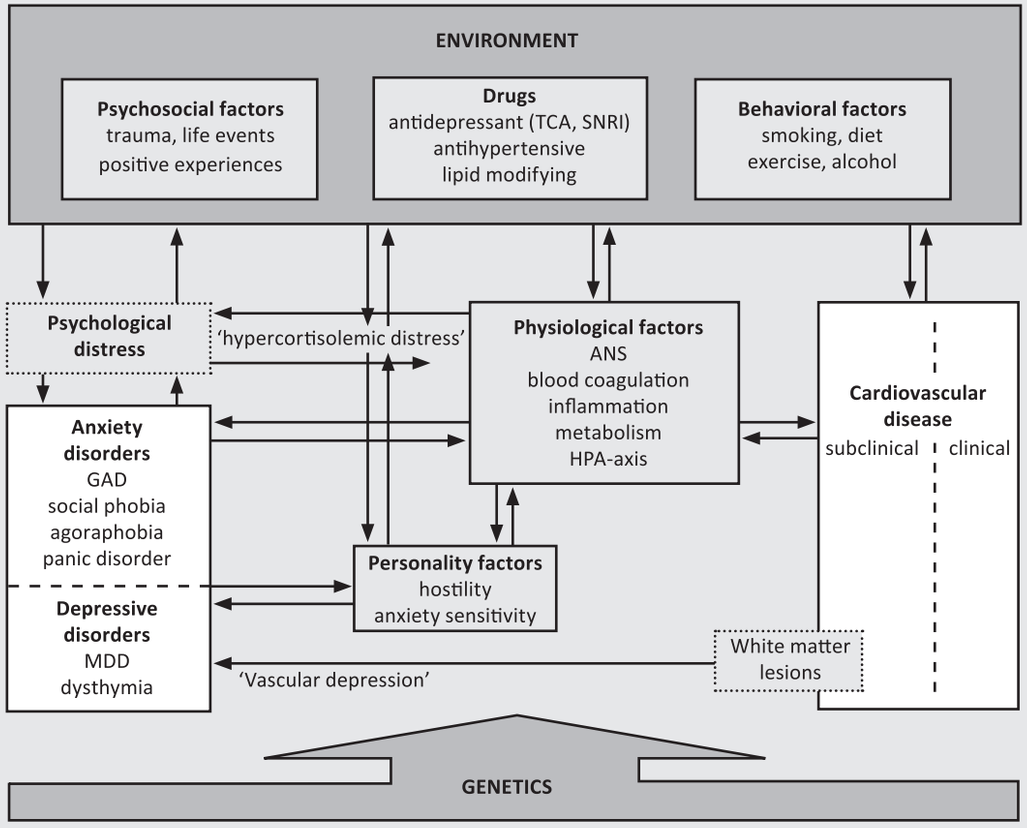

FIGURE 1. Biopsychosocial model of depression, anxiety and (subclinical) CVD

ANS= autonomic nervous system; GAD= generalized anxiety disorder; HPA=hypothalamic-pituitary-adrenal; MDD= major depressive disorder; TCA= tricyclic antidepressant; SNRI= serotonin-noradrenalin reuptake inhibitor.

The common underlying factor for example could constitute a genetic basis. According to this model, associations between depression, anxiety and subclinical CVD as found in this thesis could be a form of 'pleiotropy', i.e. a single gene brings about several phenotypes. Since depression, anxiety and CVD are disorders that 'run in families', they are expected to have a considerable genetic component [32-34] and therefore could share certain vulnerability genes [35, 36]. A twin study indeed has shown that genes related to inflammation or serotonin explain about 20% of the variability in depressive symptoms and coronary artery disease[37].

In this thesis, special attention was paid to the role of health behaviors and the main neuroendocrine stress system. Several lifestyle factors, such as smoking, lack of physical activity, or unhealthy diet, have been associated both with poor mental and vascular health [38]. In all studies, we have corrected for risk-promoting behaviors in order to investigate whether increased CVD burden in psychopathology cases was explained by unhealthy lifestyle. **Table 2** shows how lifestyle factors are associated with the surrogate measures of vascular damage within the NESDA samples. These data support the established evidence that obesity and smoking is associated with harm to arteries, whereas a physically active life and (limited) consumption of alcoholic beverages might confer benefit. However, the associations between current psychopathology and CVD outcomes (Chapters 2,4,7) remained significant and even hardly changed after correction for these lifestyle factors. These observations appear to contradict evidence from the Heart and Soul Study [39], which has shown that lifestyle largely explained the increased risk of cardiovascular events associated with depression – though in coronary heart patients. Health behaviors may still be important when it comes to subclinical CVD, but the associations we found for current depression or anxiety were not completely explained by lifestyle.

In addition, the role of the physiological stress systems is of interest, since depressive and anxiety disorders are considered stress related conditions. Hypercortisolemia due to hypothalamic-pituitary-adrenal (HPA) axis activation in response to stress, can point to additional hyper-reactivity of this system. This hypercortisolemia has been associated with atherosclerosis [40-42], and has been found in depressed subjects [43] – although blunted cortisol responses have also been reported [44, 45]. Whether HPA axis dysfunction in depressed or anxious NESDA participants [46, 47] partly explains the increased prevalence of (subclinical) CVD as described in Chapters 2, 4, and 7, remains to be studied. However, data from the Heart Scan Study that consisted of a sample of healthy, older individuals (age: 53-76 years; n=527), indicate that increased cortisol reactivity indeed contributed to the association between psychological distress and coronary artery calcification (Chapter 6). Cortisol stress-responders had doubled odds of the presence of high coronary calcification scores and subjects in the highest quartile of long-term – but not of concurrent – distress had a 3-times higher risk. Although psychological distress was not significantly associated with cortisol stress responses (which excludes the possibility of mediation), subjects with both long-term distress and cortisol reactivity showed an even 8-times higher likelihood of severe CAC. Individuals with 'hypercortisolemic psychological distress' in particular might be at high cardiovascular risk, like previously was shown for high diurnal cortisol levels combined with depressive symptoms [48].

	NESDA total sample		Subsample NESDA		
	Low ABI (≤0.9)	**$CIMT_{total}$**	**$CIMT_{bifurcation}$**	**Carotid plaque**	**$Stiffness_{AIx}$**
BMI, kg/m^2	/	↑ *p*=.003	↑ *p*=.07	/	/
Smoking status					
never (ref)					
former	/	↑ *p*=.07	/	↑ *p*=.11	↑ *p*=.003
current	/	/	/	↑ *p*=.01	↑ *p*<.001
Alcohol consumption					
< 1 per week (ref)					
1-14 per week	/	/	↓ *p*=.04	↓ *p*=.10	↓ *p*=.01
> 14 per week	/	/	↓ *p*=.04	↓ *p*=.07	↓ *p*=.02
Physical activity level					
low (ref)					
medium	↓ *p*=.10	/	/	/	↓ *p*=.01
high	↓ *p*=.01	/	/	/	↓ *p*=.08

*TABLE 2. Multivariate associations between lifestyle factors and subclinical CVD in NESDA**

Abbreviations: ABI = ankle-brachial index; AIx = augmentation index; BMI = body mass index; CIMT = carotid intima-media thickness; DC = distensibility coefficient; ref = reference value.

Explanation of marks: / associations with p >.15; ↓ negative association; ↑ positive association.

** using linear (CIMT; stiffness) or logistic (ABI; plaque) regression analyses adjusted for age, sex, education, blood pressure.*

Other mechanisms underlying the increased prevalence of subclinical CVD in currently depressed or anxious cases could include proatherogenic metabolic abnormalities [49, 50], blood coagulation [51], immune system responses (i.e. inflammation) [52 53] and imbalance of the autonomic nervous system [54]. Yet, existing prospective evidence on the latter two as potential mediators in the association between depression and CVD does not look very promising: inflammation [39, 55, 56] and autonomic function [55] explain only a small part of the predictive power of depression. Besides, previous studies within NESDA were not able to consistently provide evidence for an association between autonomic changes – increased sympathetic ('fight or flight') tone and decreased parasympathetic ('rest and digest') tone – and psychopathology in general. It appears, though, that some antidepressants (tricyclic antidepressants, TCAs; serotonin-noradrenalin reuptake inhibitors, SNRIs) have an unfavourable effect on autonomic balance [57-59]. Data from the Scottish Health Survey recently have confirmed that TCA users had increased risk of incident CVD [60]. In the same population, the use of TCAs was associated with systemic inflammation [61]. However, apart from some evidence of increased arterial stiffness among participants using TCAs or SNRIs in Chapter 4 – which in fact could also have been due to a higher depression/

anxiety severity – we found no evidence that this association was mediated by the use of antidepressant medication.

This thesis was mainly written in the context of a vulnerability-stress model in which poor mental health leads to CVD, but data regarding carotid atherosclerosis did not confirm this model. Chapter 3 indirectly supports the idea of the existence of vascular depression and as such of reverse causality. Frontostriatal and frontolimbic impairment has been proposed as a causal process [62]. Cerebral white matter lesions, which have been associated with CVD [63] and carotid atherosclerosis [64], could result in cerebral ischemia in those regions concerned with mood regulation [65-67]. Although the vascular depression hypothesis originally is based on data from geriatric populations and the cut-off for the typical late first onset of vascular depression was set at 65 years [26], we state that a cut-off at 40 years of age in a relatively young sample can be tenable, since atherosclerotic as well as white matter lesions in general appear as of the fourth decade of life [68, 69]. If in the late 30s compromised cardiovascular health can be observed, from then on lesions can be invoked that cause (vulnerability to) depression.

Methodological considerations

Throughout the previous chapters, several methodological issues already have been addressed. The most important considerations with respect to the validity of our observations are (re)considered below.

Construct validity: Do the measures reflect the intended concepts?

The primary focus of this thesis was on the association of psychiatric syndromes, i.e. depressive and anxiety disorders, and CVD. Good diagnostic tools for the assessment of the former conditions are essential, since depressive or anxiety symptoms not necessarily indicate the primary presence of a psychiatric disorder; they may also be secondary to drug use, medical conditions or other psychiatric diagnoses. The presence or absence of depressive or anxiety disorders was established during a standardized interview by specially trained staff. Diagnoses were obtained by using the DSM-IV based Composite International Diagnostic Interview (CIDI), which has a high validity for depressive and anxiety disorders [70]. Using clinical diagnostics and taking both disorders into account in analyses improve the construct validity of depressive and anxious psychopathology.

How well is a subclinical marker able to predict major CVD events? Predictive validity is a way to test whether surrogate markers of subclinical CVD indeed reflect pathophysiological processes leading to CVD. All subclinical markers used for this thesis have proven to be successful in predicting CVD morbidity and mortality in various populations [1, 4, 71-73]. Although CIMT to a certain extent can reflect the influence of hemodynamic forces on the arterial wall [30], we additionally used the presence of carotid plaques as surrogate marker of carotid atherosclerosis. Augmentation index is not a direct measure of arterial stiffness. It estimates the amount of aortic stiffness based on the timing of the reflection wave as obtained by radial tonometry. The use of aortic pulse wave velocity, the 'gold standard' measure of arterial stiffness, would improve construct validity.

Conclusion validity: Is there a relationship?

Erroneous conclusions can be a consequence of violated assumptions of statistical tests. We have conducted regression analyses to study whether poor mental health is associated with poor vascular health. In order to be suitable for linear regression analyses, outcome variables should be normally distributed. We therefore pre-examined the data on this aspect before conducting the analyses. The stiffness measures and CIMT in general showed a normal distribution but a few outliers were noted. We therefore have truncated the upper or lower percentile of the data that included the outliers. Because the CAC data remained positively skewed even after log-transformation, we have used multinomial logistic regression analyses instead. Multinomial logistic regression analyses were also the appropriate technique for ABI, because of its U-shaped association with CVD risk.

Statistical power is needed to detect an existing relationship. One of the strengths of our studies, therefore, is the large sample size – an essential element of good statistical power. The NESDA baseline data enabled us to study ABI in a relatively young population (n=2717), while abnormal ABI is generally, although not exclusively, found in subjects aged 50 years and older [74]. Also, we have strengthened the existing evidence (often based on n<50; [11-15, 17]) of an association between current psychopathology and arterial stiffness in our cardiovascular subsample (n=618). In this subsample, however, no significant differences were found on carotid atherosclerosis for depressive or anxiety disorders in general versus controls. In spite of the large sample size (n=649), a relatively low amount of subjects (14.6%) had carotid plaque, which might have suppressed the significance of the raised odds found for psychopathology.

A lack of reliability in measurements is another form of noise that obscures the ability to see a relationship. With respect to the psychopathology measures, it should be mentioned that diagnoses of disorders occurring long before baseline were retrospectively obtained and may therefore be less reliable. This may have influenced the findings for remitted psychopathology. Regarding vascular measures, both ABI and CAC data include a systematic error of underreporting peripheral and coronary atherosclerosis, respectively. ABI was measured in only one leg and electron beam computed tomography only detects calcified plaques, whereas stenosis can be caused by non-calcified plaques as well. The CVD risk associated with current depression or anxiety (ABI) and with long-term psychological distress (CAC) could thus be even higher. The lack of a significant relationship between psychopathology and carotid atherosclerosis could have been due to unreliable measurement. However, this is not likely for three reasons. First, the measures were associated with well-known cardiovascular risk factors, amongst which age and blood pressure were the most cardinal contributors. Second, all scans were performed and analyzed by one trained and certified sonographer [AS] thereby preventing an important source of error to occur, i.e. intersonographer variability. Third, intra-sonographer, intra-analyst and inter-analyst (compared with experienced reader of the Department of Vascular Medicine, Academic Medical Centre, Amsterdam) correlations were high: ρ= 0.98, ρ= 0.99, and ρ=0.93, respectively.

Internal validity: Is the relationship causal?

In order to establish the existence of a causal relationship between two variables, it first has to be proven that those variables are associated. We have met this requirement by showing that current depression/anxiety, late-onset depression, and long-term psychological distress indeed are positively associated with subclinical CVD. It should be noted, however, that observational studies do not lend themselves to prove causality. This is the inevitable 'flaw' of naturalistic cohort studies – the best available design for psychiatric research.

Most importantly, there is the second point of temporal precedence: the causal factor should precede the effect. This, however, could not be confirmed in our studies, because both variables were measured cross-sectionally. We a posteriori have argued in favour of poor mental health causing subclinical CVD, or vice versa. In the NESDA baseline sample, almost 80% of the currently depressed or anxious cases had their first disease onset before the age of 30, that is, long before the ABI assessment. Depression or anxiety as a consequence of subclinical atherosclerosis is therefore less likely. Besides, prospective evidence exists that support the premise that depressive symptoms precede peripheral arterial disease [8]. Likewise, longitudinal observations support the idea of increased arterial stiffness as a state-effect of depression [14]. Our observations that remitted cases show no increased stiffness and that the amount of depression or anxiety severity gets along with the level of arterial stiffness can be seen as indirect evidence for the temporal precedence of psychopathology. Although the Heart Scan Study included longitudinal data on psychological distress, CAC was only measured once and could have been present at baseline as well. This, however, is unlikely, because none of the participants were symptomatic after 15 years of follow-up. Besides, if CAC had caused psychological distress, we would have expected to find an association with concurrent distress as well (which lacked). For carotid atherosclerosis we only found significant associations with age of depression onset: the later the first onset, the less likely depression has preceded atherosclerosis. Reverse causality therefore seems an appropriate interpretation, which also has received support from genetic perspective [26].

A third requirement is that no other (spurious) variable should explain why the cause is related to the outcome. In regression analyses, the plausibility of alternative explanations can be minimized by adjusting for possible confounders. For that reason, we have corrected all associations for sociodemographic factors and traditional cardiovascular risk factors. Because existing cardiovascular health problems could complicate associations, we also carried out sensitivity analyses from which subjects with known CVD, diabetes, hypertension or hyperlipidemia were excluded. In adjusted analyses as well as sensitivity analyses, associations between psychopathology and subclinical CVD remained significant.

External validity: Can the observations be generalized?

The broad recruitment of participants in NESDA and the broad age-range are to the credit of the generalizability of our findings concerning depressive and anxiety disorders. The baseline sample included subjects between 18 and 65 years, from different health care settings (community, primary care practice and outpatient clinics), and in different stages of the disorders (no, high familial risk, subthreshold disorders, first and recurrent episodes) [75]. However, very severely depressed or anxious subject probably are underrepresented in

the NESDA sample and – as was shown, even more – in the cardiovascular subsample. Although it is expected that these people in particular would show increased subclinical CVD (they have a current diagnosis, high severity, and supposed comorbidity and chronicity), we cannot be sure if our findings apply to them as well. Besides, not all depressive and anxiety disorders were studied and a diagnosis of bipolar disorder, obsessive-compulsive disorder or post-traumatic stress disorder (PTSD) even was an exclusion criterion for entry. However, previously found associations of PTSD with arterial stiffness and CVD risk [76], but also with anxiety sensitivity [77, 78], directly and indirectly suggest that our findings could also apply to this subtype of anxiety disorder. The Heart Scan sample is a subpopulation (aged 53-76 years) of the Whitehall II cohort. Criteria for entry into this sample included no history or objective signs of CHD, no diagnosis or treatment of hypertension, diabetes, inflammatory diseases or major depression. As a consequence, healthy and carefully selected older participants were enrolled in the Heart Scan Study, which may affect the extent to which findings apply to the general population (i.e. that also includes e.g. less healthy and younger people). Also, both cohorts predominantly consist of white European participants, limiting extrapolation to other ethnic and racial groups.

Possible implications

Based on the associations found between depression, anxiety and subclinical CVD, high-risk groups could be identified for future prevention and/or treatment. We have found current depression or anxiety, high severity of symptoms, depression and anxiety comorbidity, and a late first onset of depression to be indicators of increased CVD risk. The first thing that has become clear from this thesis is that research in this field needs to pay attention not only to depression, but to anxiety as well. The two disorders rival each other in terms of high CVD burden.

For the knowledge of high-risk characteristics to be implemented, health care first of all needs to embrace an interdisciplinary approach. Primary health care need to deal properly with signs of poor mental health (stress, depression, anxiety) and mental health care should monitor cardiovascular risk in their patients. In general practice, this starts at the point of recognition of psychological complaints. Although the time of a consultation is short, some interview characteristics could improve the recognition of mental health issues, such as an empathetic style, asking psychologically oriented questions early in the interview, maintaining eye contact and responding to non-verbal cues [79, 80]. An early recognition of depressive and anxious complaints could prevent the development of a full-blown disorder. Several non-drug approaches could be considered helpful for poor mental health and accompanying physiological stress reactions, such as stress management techniques [81] and cognitive-behavioural therapy, e.g. for those highly fearful to anxiety-related sensation [82]. In turn, psychiatrists should as a matter of standard practice incorporate regular measurements of blood pressure, cholesterol and glucose levels, and give extra attention to life style in treatment for depressive and anxiety disorders.

We do not know yet how the associations between depression, anxiety and subclinical CVD came about in terms of physiological pathways. Until a better insight is gained into the underlying mechanisms, the best advice appears to be to focus on general cardiovascular risk reduction in high-risk populations. As to the primary target of risk intervention, the American Heart Associations has stated that "adoption of healthy life habits remains the cornerstone of primary prevention, including the avoidance of tobacco (including second-hand smoke), healthy dietary patterns, weight control, and regular, appropriate exercise. An important role of healthcare providers is to support and reinforce these public health recommendations for all patients" [83]. Based on this thesis, this supporting and reinforcing role would also fit professionals in psychiatry, since a population at increased cardiovascular risk has been committed to their charge. Although risk-promoting behaviour not likely explained the associations with subclinical CVD in our studies, lifestyle remains a good candidate for intervention. The latest prospective evidence with respect to exercise suggests that physical activity may reduce the risk of CVD events (partly by improving metabolic and inflammatory risk markers) [84] and also positively influences mental complaints [85 86].

With respect to a pharmacological approach in primary prevention, recent promising evidence of the polypill suggests itself. Twelve weeks use of a daily 4-in-1 combination pill of aspirin and agents to lower blood pressure and cholesterol has shown to halve cardiovascular risk in subjects with raised CVD risk, who did not necessarily have high blood pressure or cholesterol [87]. Although it now is still too early to decide on preventive cardiovascular medication in specific depression or anxiety subgroups, it is not unthinkable that prospective research confirming the causal role of psychopathology in subclinical disease and specifying who carry the highest risk will turn the scale.

Apart from promoting a general awareness that depression and anxiety tend to co-occur with poor vascular health, it more concretely can be considered whether subclinical measurements should be integrated in medical check-ups. It has already been shown that subclinical data can help doctors in making treatment decisions [88]. Other studies have proven that information on CIMT or carotid plaque add to CVD risk identification independent from the Framingham risk scores [89, 90]. A few issues would need to be settled before these now merely research measures can be used in everyday practice. First, whereas ABI≤0.9 is a generally accepted cut-off that is also used for decisions about treatment, other subclinical measures lack a clear cut-off value (central augmentation index and CIMT) or are not yet indicative for action (plaque). Second, the cost-effectiveness of investigating subclinical CVD in primary care patients of this age-group is doubtful, since the prevalence is not that high - low ABI < 3/100 and carotid plaque < 13/100 in CVD-free NESDA (sub-)population.

Future directions

This thesis aimed to provide insight into the links between depression, anxiety and subclinical CVD. Although this work indeed has yielded some clarification, the psycho-physiological field remains to be complicated. The refrain of this thesis therefore is a call for further research.

- Future studies intended to narrow down the definition of high-risk associated with depression and anxiety should include participants aged 35 and higher, thereby increasing the probability to detect subclinical CVD (84% of low ABI and 100% of carotid plaque in NESDA) and – as a consequence – increasing statistical power.
- Within NESDA, it soon will be possible to investigate associations between both depressive or anxiety disorders and 4-, 6- or 8-year CVD incidence, and to study the role of physiological mechanisms (e.g. inflammation, HPA axis functioning, metabolic abnormalities), and the predictive value of one's prior subclinical CVD status. Most of the subclinical measures described in this thesis are not yet scheduled to be measured again within NESDA, as a result of which the next two issues regarding carotid atherosclerosis and arterial stiffness probably will not be sorted out.
- As for now, most evidence about the predictive value of CIMT is for the cross-sectional assessment, and not for CIMT change [91]. In spite of this, performing repeated measurements of carotid atherosclerosis in a psychiatry-based sample would be of interest in order to determine whether psychopathology or related features, such as anxiety sensitivity, actually influence the disease progression.
- Whether arterial stiffness indeed is a reversible state-effect of current psychopathology, could be studied in a prospective way by which the use of aortic pulse wave velocity would be preferable.
- As for the generalizability of our results, additional studies examining depressed inpatients or inclusion of other anxiety disorders such as PTSD would be informative.
- In addition, the pathophysiologies of early-onset and late-onset depression should be further unravelled. In this thesis, it has been suggested that the traditional cut-off of a first onset at 65 years for vascular depression might be too strict. Trials with life style changes and/or cardiovascular medication for subjects with a late-onset depression and raised cardiovascular risk are needed to test whether this approach will be able to fight depression along with CVD.

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