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Depression, Vascular Conditions and Chronicity

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1. Introduction

In recent years, the association between depression and cardiovascular disease has been studied extensively (Nicholson *et al.* 2006; Van der Kooy *et al.* 2007). Cardiovascular disease (CVD) refers to those conditions that affect the heart and blood vessels, including amongst others coronary heart disease, cerebrovascular disease, and peripheral artery disease. According to the World Health Organisation, cardiovascular disease now is the primary cause of death around the world. Depressive disorders enhance the development of CVD by both behavioural and biological pathways. They may contribute to unhealthy lifestyle habits that increase cardiovascular risk, such as smoking, low physical activity, and unhealthy diet. Also, this psychiatric condition is associated with activation of the immune system, blood coagulation, hyperactivity of the physiological stress system (e.g. hypothalamic pituitary adrenal axis), and other biological mechanisms which are thought to be involved in de development and progression of CVD. As these behavioural and biological factors are more continuously present in persons with chronic depression, it can be assumed that the risk of developing CVD is even higher in chronically depressed subjects, although this has not been clearly demonstrated yet. The first aim of this Chapter is to summarize what is known about the association between depression and vascular conditions. An overview of the literature will be given and a more detailed description of recent findings from a large Dutch cohort study on depression and anxiety (Seldenrijk *et al.* 2010; Seldenrijk *et al.* 2011b; Vogelzangs *et al.* 2010) will be presented. The second aim is to discuss the relevance of reviewed findings for chronic depression.

2. Depression and vascular comorbidity

2.1. Existing evidence on association between depression and CVD

A recent meta-analysis (Nicholson *et al.* 2006) has reviewed prospective cohort studies that reported on the association between depression and coronary outcomes in healthy

populations and in coronary heart patients. Twenty-one studies in healthy populations were identified that investigated the incidence of myocardial infarction or fatal coronary heart disease over a mean follow-up period of 10.8 years. It was shown that depression was associated with an 81% increased risk of new coronary events. Studies using clinical measures of depression reported a higher risk than those using symptom scales. Another meta-analysis (Van der Kooy *et al.* 2007), which additionally included cerebrovascular disease outcomes, has shown an even more distinct difference between the effect sizes of clinical depression versus depressive symptoms in association with subsequent CVD (risk ratio of 2.54 versus 1.39, respectively). The authors suggest that this difference may indicate a dose-response relationship between depressed mood and the development of CVD. The meta-analysis by Nicholson and colleagues also identified thirty-four prognostic studies that investigated the association between depression and coronary or all cause mortality in coronary heart patients over a mean follow-up period of 3.2 years (Nicholson *et al.* 2006). Crude results indicated that depressed patients had an 80% higher risk to die during the follow-up compared with non-depressed patients. Results from studies that also adjusted for confounding indicate that 88% of the associations were independent from major coronary risk factors. Although the high risk estimates may be inflated due to incomplete and biased reporting of adjustment, these meta-analytic data provide evidence for depression as a risk factor in the development and course of CVD. In addition, (Carney & Freedland, 2009) have reviewed the literature in order to identify subtypes of depression which are associated with the highest risk of cardiac events in coronary heart patients. They discuss existing evidence from several large clinical trials, such as ENRICHD, MIND-IT, and SADHART. The authors conclude that in particular patients who are unsuccessfully treated for depression following an acute coronary syndrome were found to be at risk for cardiac morbidity or mortality.

This paragraph has illustrated the now large body of literature relating depression to clinical end-points of CVD based on e.g. general practice or hospitalization records. However, the emergence of modern imaging techniques has enabled to study pre- or subclinical cardiovascular outcomes. By examination of subclinical CVD, the temporal sequence and the pathophysiological pathways of the associations might be better understood.

2.2. Arteries and subclinical CVD

Detailed information on different aspects of the cardiovascular burden throughout the body can be obtained using non-invasive methods. Before an overview is given of the research regarding depression and subclinical CVD markers, we will first give some background information on the function and structure of human arteries, and the changes that reflect subclinical disease.

2.2.1. Function and structure of arteries

The arterial tree has a conduit and a cushioning function. The first refers to its delivery of oxygenated 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 or 'tunica' can be distinguished from the inside

to the outside: the intima, the media, and the adventitia (Zarins & Glagov, 2004). 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 fibres 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.

2.2.2. Vascular 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 'subclinical' pathophysiological processes which lead to CVD. Two separate, but overlapping conditions that affect medium and large arteries are *athero*sclerosis and *arterio*sclerosis (Mackey *et al.* 2007). Atherosclerosis primarily compromises the conduit functioning of an artery, but is also associated with increased stiffness. 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, impairs the cushioning function, and along the line increases the risk of endothelial damage, i.e. atherosclerosis. Arteriosclerosis starts in the media en includes decreasing levels of elastin and increased amounts of collagen and calcium, which leads to arterial stiffening.

2.2.3. Subclinical CVD markers

One of the ways to measure subclinical atherosclerosis is by calculating the ankle-brachial index (ABI). The 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, but a low ABI (≤0.90; indicative of limited blood flow to the legs) has also been recognized as an indicator of systemic atherosclerosis (Newman *et al.* 1993). Other markers of subclinical atherosclerosis are carotid intima-media thickness (CIMT) and coronary or aortic calcification. CIMT can be measured after visualizing the innermost two layers of the arterial wall by using ultrasonography. Calcification of the coronary arteries or aorta can be identified in 3D images of the heart using electron beam computed tomography. These atherosclerosis markers have shown a predictive value for future incident cardiovascular events (Fowkes *et al.* 2008; Greenland *et al.* 2007; Lorenz *et al.* 2007). Arteriosclerosis also can be detected using various markers of arterial stiffness or endothelial dysfunction (Anderson, 2006). Arterial stiffness can be locally measured using ultrasonography, e.g. by calculating the carotid distensibility coefficient (DC). The DC gives the relative change in cross-sectional area (diameter) per unit of pressure. A measure to estimate aortic stiffness is to analyze

pulse waves or contours, derived by applanation tonometry. The arterial pressure waveform consists of a forward wave which is created by ejection and a backward wave caused by reflection (e.g. at bifurcations). The central augmentation index (AIx) estimates the percentage of augmented late systolic pressure due to arterial stiffness. Indicators of arterial stiffness have shown capable of predicting future cardiovascular events (Adji *et al.* 2011; Laurent *et al.* 2006).

2.3. Existing evidence on association between depression and subclinical CVD

Studies investigating the association between depression and the ABI have yielded conflicting results. One prospective study used low ABI amongst other measures to define incident peripheral arterial disease in a middle-aged population and found moderate or high levels of depressive symptoms to be associated with an 20% and 44% increased risk (Wattanakit *et al.* 2005). In contrast, two studies found no association between depressed mood and low ABI among older men and women. This lack of a significant association might have been due to a low prevalence of depressive disorder (3%) in the population-based Rotterdam Study (Tiemeier *et al.* 2004) or to a relatively small sample size (n=167) in the other study which was carried out in patients with peripheral arterial disease and controls (Arseven *et al.* 2001). Literature on the association between depression and other markers of subclinical atherosclerosis shows a similar inconclusiveness as the ABI research. Some studies – based on middle-aged or older individuals – have shown a positive association between depression and CIMT(Chen *et al.* 2006; Elovainio *et al.* 2005; Paterniti *et al.* 2001; Stewart *et al.* 2007; Tiemeier *et al.* 2004; Whipple *et al.* 2009), whereas other studies have found no association (Jones *et al.* 2003; Matthews *et al.* 1998; Narita *et al.* 2008; Rice *et al.* 2009; Seldenrijk *et al.* 2011a; Spitzer *et al.* 2008). Likewise, depression has been associated with coronary or aortic calcification in some (Agatisa *et al.* 2005; Hamer *et al.* 2010; Matthews *et al.* 2010; Tiemeier *et al.* 2004), but not in other (Diez Roux *et al.* 2006; O'Malley *et al.* 2000) studies. An interesting observation with respect to chronicity of depression is that the positive findings for depression and calcification were particularly found for long-term poor mental health as indicated by recurrent depressive episodes or repeatedly measured depressive symptoms.

Studies investigating the association between depression and arteriosclerosis have used a variety of indexes for vascular function (Lavoie *et al.* 2010; Oulis *et al.* 2010; Paranthaman *et al.* 2010; Rajagopalan *et al.* 2001; Rybakowski *et al.* 2006; Sherwood *et al.* 2005; Tiemeier *et al.* 2003). Irrespective of these different outcome measures, all studies unanimously have shown depressed individuals to have impaired endothelial function or increased arterial stiffness. The association may be influenced by psychiatric characteristics, such as chronicity of symptoms, but evidence for this idea is still meager. In older diabetic women, recurrent but not single episode depression was associated with endothelial dysfunction (Wagner *et al.* 2009). In initially severely depressed women, successful antidepressant treatment was followed by a restoration of vascular function (Oulis *et al.* 2010). Additionally, preliminary evidence from a case-control study (Paranthaman *et al.* 2012) suggests that non-response to antidepressant monotherapy in late-life is related to increased endothelial dysfunction (n=31) and CIMT (n=45).

These observations are indicative of an association between depression and subclinical CVD. However, for both atherosclerosis and arteriosclerosis, there are still doubts on the generalizability of the observations since sample sizes of existing studies often were small, and many studies were performed in older or diseased populations. In a large Dutch cohort study some of these limitations could be overcome. This study addresses both depression and anxiety, since these are highly concurrent disorders (Kessler *et al.* 2005) with partially overlapping symptoms (Hiller *et al.* 1989).

## 2.4. Netherlands Study of Depression and Anxiety (NESDA)

2.4.1. Sample

NESDA is an ongoing longitudinal cohort study to examine the prevalence, course and consequences of depressive and anxiety disorders. In order to represent various health care settings and stages of psychopathology, participants were recruited from community (19%), primary care (54%) and outpatient psychiatric clinics (27%). Participants were men and women, aged 18-65 years at the baseline assessment in 2004-2007. Individuals with remitted and current depressive or anxiety disorders, as well as healthy controls were included. Details of the study rationale, recruitment strategy and methods are described elsewhere (Penninx *et al.* 2008). Based on NESDA baseline and 2-year follow up data, associations between depression, anxiety and several vascular conditions have been investigated in large samples (see flow chart, figure 1). The methods and results of three publications (Seldenrijk *et al.* 2010; Seldenrijk *et al.* 2011b; Vogelzangs *et al.* 2010) are being described below.

2.4.2. Methods

The assessment included amongst others a blood draw, a medical examination, administration of several written questionnaires concerning, e.g., mood state, lifestyle, and medical history, a psychiatric interview, and an interview regarding somatic health aspects. Diagnoses of depressive disorders (major depression, dysthymia) and anxiety disorders (generalized anxiety disorder, panic disorder, agoraphobia, social phobia) were established using the DSM-IV based Composite International Diagnostic Interview. In addition, clinical characteristics of these disorders were assessed. Severity of symptoms was measured with the 30-item Inventory of Depressive Symptomatology self-report version and the 21-item Beck Anxiety Inventory. Duration of symptoms was assessed using the Life Chart method (Lyketsos *et al.* 1994), after which the percentage of time with symptoms during the past few years was computed. Psychoactive medication use was assessed based on drug container inspection of all drugs used in the past month and classified according to the WHO Anatomical Therapeutic Chemical classification. Psychoactive medication included selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), other antidepressants and benzodiazepines.

The presence of CVD at the baseline assessment was adjudicated using standardized algorithms considering self-report and medication use based on drug container inspection.

CVD included stroke and coronary heart disease, i.e. angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty and coronary artery bypass grafting. Cardiovascular surgery was based on self-report alone, whereas other reported CVD conditions were only considered present when self-report was supported by the use of medication. Subclinical atherosclerosis was indicated by the ABI, measured using a Doppler ultrasound at the baseline assessment. In line with recommendations from the Ankle Brachial Index Collaboration, three groups of increased cardiovascular risk were distinguished: low ABI (0.90 or less) and mildly low ABI (ranging 0.90 to 1.11), but also high ABI (greater than 1.40) (Fowkes *et al.* 2008). ABI analyses were conducted in subjects without known CVD. Two year after baseline, 87.1% of the NESDA sample took part in a follow-up visit. A subsample of these participants was then recruited for additional cardiovascular measurements, including two different indicators of arterial stiffness (Seldenrijk *et al.* 2011b). The carotid DC was measured using M-mode ultrasound scanning. In addition, the central AIx was estimated by using radial pulse wave analysis.
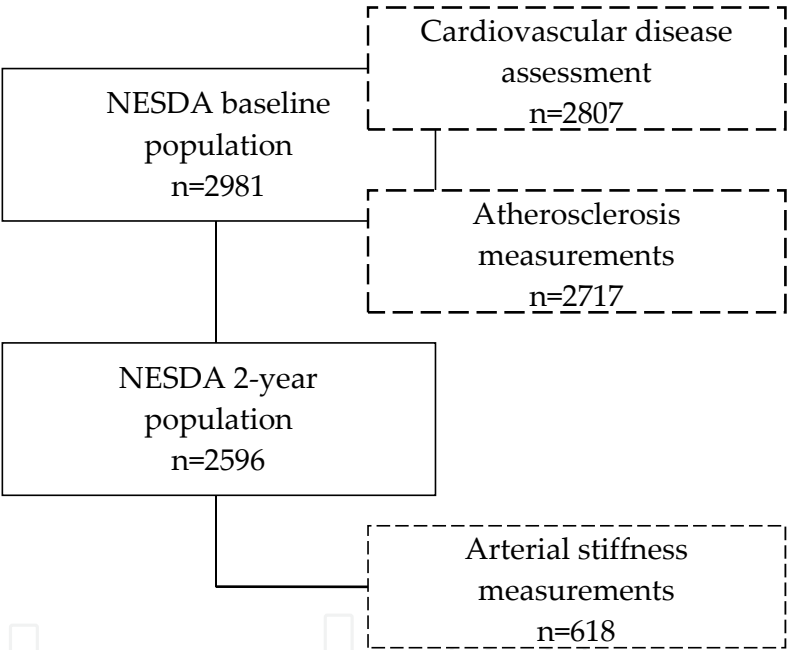

Figure 1. Flow chart of study population per vascular outcome

2.4.3. Results

The prevalence of CVD in the NESDA baseline population was 5.6%. First, depressive and anxiety disorders were analyzed separately. After adjustment for sociodemographics and lifestyle factors, people with a current depression (odds ratio of 1.6) and those with a current anxiety disorder (odds ratio of 2.2) showed increased likelihood of having CVD as compared with those who never had a depressive or anxious episode. When combining the presence or absence of both psychiatric conditions in one categorical variable, only people with a current anxiety disorder with or without co-morbid depression more often had coronary heart disease. The adjusted odds were 2.7 for subjects who only had a diagnosis of anxiety disorder and 3.5 for those who also had a co-morbid depressive disorder. No

significant association was found between depression or anxiety and stroke, nor between remitted diagnoses and CVD. Of the psychiatric characteristics, severity of depressive or anxiety symptoms was positively associated with coronary heart disease in a dose-response manner. No significant associations were found for duration of psychiatric symptoms prior to baseline or use of psychotropic medication.

The prevalence of a low ABI was 2.2% in the CVD-free baseline population. People with a current diagnosis of depression or anxiety disorder almost 3-times more often had a low ABI as compared with controls. This increased likelihood in currently depressed or anxious was independent of sociodemographic factors, hypertension, diabetes and lifestyle factors. No increased risk was found for those with remitted diagnoses of depression or anxiety disorders. Possible explanations for this are decreased reliability of remitted diagnoses because of their retrospective character and that they indicate less severe exposure to psychological distress, the current group more frequently including chronic and relapsing cases. Psychiatric characteristics, such as severity and duration of depressive or anxiety symptoms prior to baseline, or the use of antidepressant medication, did not further differentiate the risk of low ABI in depressed and anxious subjects. No association was found between depression or anxiety and mildly low (prevalence 35.7%) or high (prevalence 2.5%) ABI.
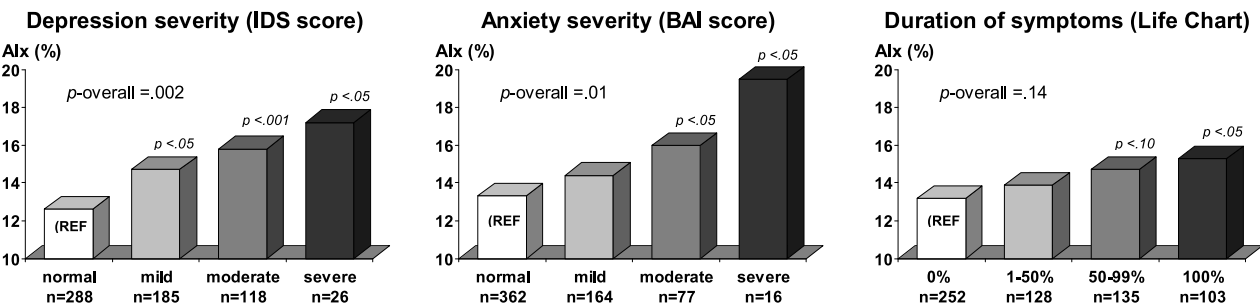
Figure 2. Association between symptom severity or duration and central arterial stiffness (AIx in %)

People with a current depressive or anxiety disorder at the NESDA 2-year assessment showed an increased central arterial stiffness as compared with controls. Again, those who had suffered from a depressed or anxious episode in the past but were currently recovered, did not differ from controls with respect to arterial stiffness. In addition to earlier mentioned explanations (i.e. reliability, chronicity), this could also imply that arterial status returns to normal when people recover from depression or anxiety. Evidence for a dose-response relationship was provided in our observations of an increased AIx in subjects who were longer or more severely exposed to depressive or anxiety symptoms over time (see fig. 2). No significant associations were found for carotid DC, although the duration of depressive and anxiety symptoms tended to be associated with a higher carotid artery stiffness. To rule out the possibility that observed associations were driven by subjects with known CVD or diabetes, or using antihypertensive or lipid-modifying medication, analyses were repeated without those cases and results remained similar. After exclusion of participants with suspected cardiovascular health, those using TCAs or combined serotonin/noradrenaline reuptake inhibitors (SNRIs) showed significantly increased AIx.

3. Summary and relevance for chronic depression

At this point in time there is a paucity of research that directly compares chronic versus non-chronic depression in association with the development of CVD. This paragraph summarizes the evidence regarding an association between depression and vascular conditions as presented above. In addition, inferences are made on the relevance of the reviewed evidence for a chronically depressed population.

Meta-analytic data have shown that depression increases one's risk to develop CVD (Nicholson *et al.* 2006; Van der Kooy *et al.* 2007) and to have an unfavourable course of CVD with more cardiac events and higher mortality rates (Nicholson *et al.* 2006) (see paragraph 2.1). Included studies that investigated clinical depression showed larger effect sizes than those using symptom lists. This may suggest that a more sustained exposure to psychological distress results in a dose-response effect on cardiovascular outcomes. Although the studies in these meta-analyses had no primary focus on chronic depression, it can thus be argued that chronically depressed patients have a particularly increased cardiovascular risk. A literature review of studies in coronary heart patients has supported this idea for depression as a prognostic factor: patients with treatment resistant depression more than responders were at risk for an unfavourable course of CVD (Carney & Freedland, 2009).

The mostly cross-sectional studies that investigated depression in relation to subclinical atherosclerosis are still inconclusive (see paragraph 2.3). Some studies failed to provide evidence for a higher cardiovascular risk in depression. However, other studies did find significant associations for either subclinical atherosclerosis or arteriosclerosis. Certain observations are of special interest, since they seem to point out that people suffering from long-lasting or treatment resistant depression constitute a distinctly high-risk group. Studies that demonstrated depression to be associated with a higher prevalence of aortic or coronary calcification found this either in participants who repeatedly reported high depressive symptoms (Hamer *et al.* 2010), or in those with recurrent depressive episodes (Agatisa *et al.* 2005; Matthews *et al.* 2010). Also with respect to CIMT and endothelial function, a gradient has been shown across groups, with non-depressed control subjects having the best vascular structure or function, antidepressant non-responders worse and responders in-between (Paranthaman *et al.* 2012).

Based on our studies (Seldenrijk *et al.* 2010; Seldenrijk *et al.* 2011b; Vogelzangs *et al.* 2010), it can be concluded that people with a current depressive or anxiety disorder have a higher likelihood of coronary heart disease and peripheral atherosclerosis and increased central arterial stiffness (see paragraph 2.4.3). No significant associations were found for remitted disorders. Psychiatric characteristics that in some way differentiated the CVD risk were severity of symptoms (coronary disease, central arterial stiffness) and duration of symptoms (arterial stiffness). In all three studies, a current diagnosis of depression or anxiety was associated with an increased likelihood of vascular conditions. No significant associations were found for subjects with remitted disorders. Since emotional distress likely exerts its effects on the arteries in a cumulative manner, people who chronically suffer from a

psychiatric condition, such as depressive disorder, can be considered a high risk population. One explanation for the divergence between current and remitted diagnoses is that the group with current psychopathology also includes people who are chronically affected by, or frequently relapse into, depressive or anxious episodes. As compared with a remitted diagnosis, a current diagnosis thus might indicate a more sustained exposure to psychological distress. Our study on arterial stiffness (Seldenrijk *et al.* 2011b) did provide more direct support for a cumulative effect: the higher the percentage of time affected by depressed or anxious symptoms, the stiffer one's arteries were. Although depression was not significantly associated with CVD independent of anxiety in (Vogelzangs *et al.* 2010), it was demonstrated that participants with both current anxiety and depression carried the highest risk of having coronary heart disease. The additive effect of different psychiatric conditions (e.g. panic disorder and depression) on vascular health previously had been described by (Gomez-Caminero *et al.* 2005). These individuals who suffer from both depression and anxiety at the same time might well define a chronically depressed population. This hypothesis is supported by prospective data from the NESDA cohort, which indicated that a chronic course of depressive disorder is predicated by having a co-morbid anxiety disorder (Penninx *et al.* 2011). In line with this, other studies (e.g. (Fava *et al.* 2008)) have found that depressed patients with high levels of anxiety are less likely to respond to treatment.

As mentioned before, the observations discussed are not without inconsistencies. Some studies did not find significant associations between depression and subclinical atherosclerosis. Likewise, our own studies provided no evidence for an association between depression and stroke or carotid arterial stiffness, nor did we find an effect of the duration of depressive symptoms on some vascular outcomes. These discrepancies across studies could be due to differences in populations and in vascular outcome measures. At a younger age, the prevalence of clinical CVD is not very high, and the range of aberrant subclinical values is not wide. 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 discrepant findings. It has been demonstrated that subclinical atherosclerosis probably does not affect all arterial beds in a uniform and contemporaneous manner (DeCara, 2011). This may be due to differential composition of the vascular wall (elastic versus muscular arteries) as well as the location of the arteries in the body.

The association between chronic depression and CVD has also received support from other lines of research. First, it has been suggested that specific subtypes of depression may be partly caused by CVD or cardiovascular risk factors. Some evidence exists that these subtypes are more chronic in course. One of the primary criteria of a 'vascular depression' (Alexopoulos *et al.* 1997) is clinical or subclinical evidence of cerebrovascular impairment. Another potential characteristic of this depression subtype is a late first onset of someone's first depressive episode. Patients with vascular depression seem to be less likely to respond to antidepressant treatment (Navarro *et al.* 2004; Patankar *et al.* 2007). Likewise, the metabolic syndrome has been investigated as a prognostic factor for the course of depressive disorder. Metabolic syndrome is a combination of cardiovascular risk factors (Mottillo *et al.*

2010), including abdominal obesity, lipid abnormalities, hypertension, and hyperglycaemia. Based on a community sample of older persons, (Vogelzangs *et al.* 2011) found that depressed subjects with metabolic syndrome ('metabolic depression') were almost 3-fold more likely to have persistent or recurrent depression. In addition, depression and more specifically treatment resistant depression has been associated with inflammation (Miller *et al.* 2009). Since inflammation is considered one of the important mechanisms that enhance the development of CVD (Willerson & Ridker, 2004), individuals who are nonresponsive to antidepressant treatment may have a higher likelihood of future cardiovascular events. Furthermore, specific types of antidepressant medications (e.g. TCAs and SNRIs) have been associated with unfavourable side-effects on metabolism, sympathetic activity and the immune system (Licht *et al.* 2012; van Reedt Dortland *et al.* 2010; Vogelzangs *et al.* 2012). Although the prospective nature of some evidence suggests that active ingredients of the antidepressants might be responsible (Licht *et al.* 2012), it also is likely that patients who use these antidepressants differ from non-users or SSRI users by having more severe and more chronic psychopathology.

4. Possible implications

The above reviewed epidemiological evidence seems to indicate that chronic depression can be considered a cardiovascular risk factor. The question now arises of how this knowledge may be useful in clinical practice. First, modification of the risk factor would be expected to have beneficial effects on vascular health. Apart from the challenge this by definition means in chronic depression, it is still unknown whether successful treatment of depression indeed leads to improvement in cardiovascular morbidity and mortality. As for now, randomized controlled trials in CVD-free populations have not yet been carried out. Some trials (SADHART, (Glassman *et al.* 2002); ENRICHD, (Berkman *et al.* 2003); MIND-IT, (van Melle *et al.* 2007)) did investigate the effects of antidepressant psychotherapy or pharmacotherapy on cardiovascular morbidity and mortality in coronary patient populations. Although these studies have shown that depression is treatable in coronary patients, no significant differences were found in medical end-points between intervention and control groups. However, (Carney & Freedland, 2007) have pointed out that future studies are still needed to reinvestigate this issue with more effective therapies and in larger, sufficiently powered samples.

Until we know how the associations between depression and (subclinical) CVD come about in terms of physiological pathways, the best advice appears to be to focus on general cardiovascular risk reduction in high-risk populations. With respect to pharmacologic treatment in chronically depressed patients, extra caution taken by psychiatrists potentially could prevent the occurrence of some cardiovascular events. Before and during the start of treatment with especially TCAs and SNRIs, it now is common practice to screen for CVD by measuring blood pressure and performing an ECG in patients with cardiovascular risk factors and in elderly patients. In view of the available evidence as discussed in the former paragraphs, there are reasons to belief that a broader range of people might benefit from more active cardiovascular screening. For some subgroups (such as older patients with

a chronic depression or with both depressive and anxiety disorders) regular measurements of blood pressure, cholesterol and glucose levels could be incorporated as a matter of standard practice. In addition, because of the increased prevalence of (subclinical) CVD in this population, extra attention to a healthy lifestyle appears an important aspect of the treatment of depressed patients. As to the primary target of cardiovascular risk intervention, the American Heart Associations has stated:

> "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." (Pearson *et al.* 2002)

Regarding exercise, some inspiring observations for the improvement of both mental and vascular health have recently been published: physical activity reduces the risk of CVD events (Hamer *et al.* 2011) and positively influences depressive complaints (Carek *et al.* 2011; Hoffman *et al.* 2011). The reinforcing and supporting role thus also fits professionals in the field of chronic depression, particularly since a tendency to ignore cardiovascular symptoms and taking action from it might be inherent in serious mental illnesses.

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