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Preliminary communication

Sensitivity to depression or anxiety and subclinical cardiovascular disease

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ABSTRACT

Background: Depressive and anxiety disorders are highly overlapping, heterogeneous conditions that both have been associated with an increased risk of cardiovascular disease (CVD). Cognitive vulnerability traits for these disorders could help to specify what exactly drives CVD risk in depressed and anxious subjects. Our aim is to examine sensitivity to depression or anxiety in association with indicators of subclinical CVD.

Methods: Data from 635 participants (aged 20–66 years) of the Netherlands Study of Depression and Anxiety were analyzed. Depression sensitivity was measured by the revised Leiden Index of Depression Sensitivity. Anxiety sensitivity was measured by the Anxiety Sensitivity Index. Subclinical CVD was measured as (1) carotid intima-media thickness and plaque presence using B-mode ultrasonography and (2) central arterial stiffness (augmentation index) using calibrated radial applanation tonometry.

Results: After adjustment for sociodemographics, blood pressure, and LDL cholesterol, higher scores of anxiety sensitivity were associated with both increased likelihood of carotid plaques (OR per SD increase=1.34, 95%CI=1.06–1.68) and increased arterial stiffness (β=.06, p=.01). No significant associations were found with carotid intima-media thickness nor for depression sensitivity.

Limitations: The cross-sectional design precludes causal inference. Current mood state could have influenced the self-reported sensitivity data.

Conclusions: The presence of carotid plaques and central arterial stiffness was especially increased in subjects who tend to be highly fearful of anxiety-related symptoms. These observations suggest that vulnerability to anxiety, rather than to depression, represents a correlate of subclinical CVD.

1. Introduction

Depression and anxiety have both been associated with an increased risk of subclinical (Lavoie et al., 2010; Seldenrijk et al., 2011a; Tiemeier et al., 2004) and overt (Nicholson et al., 2006; Roest et al., 2010) cardiovascular disease (CVD). Comparison of the effect sizes of two meta-analyses would suggest that depression (pooled RR=1.81 (Nicholson et al., 2006)) more than anxiety (pooled HR=1.26 (Roest et al., 2010)) is associated with increased CVD risk. However, since most studies focus on either depression or anxiety, it is impossible to properly compare their respective contribution to CVD risk. The heterogeneity of clinical diagnoses further complicates the disentangling of CVD risk in depression and anxiety, since symptoms (Hiller et al., 1989) and occurrence (Kessler et al., 2005) of these psychiatric syndromes are largely overlapping. Because emotional distress likely exerts its effects on the arteries in a cumulative manner, it may be worthwhile to study the clustering of mental and vascular disease at the level of cognitive vulnerability to depression or anxiety.

Dysfunctional cognitions are thought to contribute to the development and maintenance of depressive and anxiety disorders. The 'gold standard' psychotherapy therefore is based on the idea that information processing is disturbed in depression (negative view of self, world and future) and anxiety (overestimation of danger and risk). Several 'cognitive' characteristics have been closely linked to depression, such as hopelessness,

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rumination, and hostility (Stewart et al., 2010; Wiersma et al., 2011; Drost et al., 2011; Nolen-Hoeksema, 2000). Anxiety sensitivity refers to the perception that bodily symptoms are harmful in physical, psychological, or social sense. It is considered a characteristic preceding the development of anxiety disorders, and particularly (but not only) panic attacks (Olatunji and Wolitzky-Taylor, 2009). If the concept of depression is related to CVD, depression-specific characteristics would be associated with CVD. If anxiety, in turn, is a more important risk factor, anxiety-specific beliefs in particular would show associations with CVD.

Some studies already have examined these cognitive dispositions in association with cardiovascular outcomes. Both positive (Everson et al., 1997b; Matthews et al., 1998) and absent (Stewart et al., 2007) associations were found for hostility and atherosclerosis. Hopelessness has been associated with increased atherosclerosis (Everson et al., 1997a) and ischemic heart disease (Anda et al., 1993), but an inverse association was found between cardiac anxiety (partly covering anxiety sensitivity) and coronary calcification (Marker et al., 2008). Previous results thus are inconclusive of associations between cognitive vulnerability and CVD risk and a direct comparison between depression- and anxiety-related characteristics in one population is still lacking. This study examines cognitive vulnerability to depression and anxiety in association with carotid atherosclerosis and central arterial stiffness.

2. Methods

2.1. Sample

The present study was conducted as an extension of the 2-year assessment of the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study examining the course of depressive and anxiety disorders. Participants were recruited from community, primary care and outpatient psychiatric clinics. The NESDA baseline sample (2004–2007) included 2329 persons with a lifetime depressive and/or anxiety disorder, and 652 controls, aged 18 through 65 years. Details of the study rationale, recruitment strategy and methods have been described elsewhere (Penninx et al., 2008). The research protocol was approved by the Ethical Committee of participating universities and all respondents provided written informed consent.

Of the 2981 baseline participants invited, 2596 joined the 2-year assessment. Afterwards, 650 participants underwent additional cardiovascular measurements (for details of recruitment strategy, see (Seldenrijk et al., 2011b, 2011a) of whom 635 had valid cognitive vulnerability data.

2.2. Psychological characteristics

The revised Leiden Index of Depression Sensitivity (LEIDS-R; (Van der Does, 2002; Van der Does and Williams, 2003)) assessed the extent to which dysfunctional cognitions are triggered during normal mood variations. The LEIDS-R comprises six subscales, based on 34 items that are answered on a 5-point Likert scale (0='not at all' to 4='very strongly'). Since a previous study (Drost et al., 2011) has shown that Hopelessness and Rumination are unique factors in major depressive disorder and Aggression is unique for dysthymic disorder, only these subscales were included in the current analyses. Hopelessness consists of 5 items (e.g., 'When I feel down, I more often feel hopeless about everything'), with a maximum score of 20. Rumination and Aggression are each based on 6 items (e.g., 'When in a sad mood, I more often think about how my life could have been different' or 'When I feel bad, I more often feel like breaking things') with maximum scores of 24. The three subscales showed good internal consistency in the present sample (all α's $>$ .95).

The anxiety sensitivity index (ASI; (Reiss et al., 1986)) was used to assess the degree to which one is concerned about possible negative consequences of bodily, cognitive or publicly observable sensations. The questionnaire includes 16 items, which are answered on a 5-point Likert scale (0='hardly' to 4='very much'), e.g., 'It scares me when my heart beats rapidly' or 'It scares me when I am unable to keep my mind on a task'. The scale has a maximum score of 64 and showed good internal consistency in the present sample (α=.89).

As expected, strong correlations were found between NESDA baseline and 2-year assessment scores (LEIDS-R Hopelessness r=.74, Aggression r=.65, Rumination r=76, *p-values* $<$ .001; ASI r=.73, $p<.001$). We averaged scores over both assessments in order to maximize the reliability of these cognitive vulnerability measures.

2.3. Subclinical cardiovascular disease

Carotid intima-media thickness (CIMT) and plaque presence were assessed using an Acuson Aspen ultrasound instrument equipped with a near-field L7 linear array 5–10 MHz broadband transducer (Siemens, Erlangen, Germany). Details on the ultrasonography measurement can be found elsewhere (Seldenrijk et al., 2011b). We used *bifurcation CIMT* ($CIMT_{bif}$) as outcome measure, since bifurcations are particularly prone to progression of atherosclerosis (Stary et al., 1992). Previous observations in this relatively young sample indeed have favoured the bifurcation as predilection segment over total CIMT in terms of sensitivity to difference (Seldenrijk et al., 2011b).

As described before (Seldenrijk et al., 2011a), we used *central augmentation index* normalized for a heart rate of 75 beats per minute (AIx75) as a measure of arterial stiffness. Ascending aortic blood pressure waveform was generated, based on radial pressure waveforms including a generalized transfer function (2000 version 7, AtCor Medical, Sydney, Australia) and oscillometrically determined brachial pressures (Dinamap®PRO100, GE Medical Systems, Tampa, FL).

2.4. Covariates

Sociodemographics included age, sex and education (years). Additionally, several lifestyle and health factors were assessed at the time of 2-year assessment or cardiovascular assessment (average in-between time is 2 months). Blood pressure was measured at the right arm during supine rest (Seldenrijk et al., 2011a). Mean arterial pressure (MAP) was calculated as (2*diastolic pressure+systolic pressure)/3. Low density lipoprotein (LDL) cholesterol (mmol/l) was determined, based on fasting blood samples. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Smoking status was defined as non-smoker, former smoker or current smoker. Physical activity was measured with the International Physical Activity Questionnaire (Craig et al., 2003) in MET-minutes per week and categorized as low, medium or high.

Use of antihypertensive or lipid-modifying medication was based on drug-container inspection of all drugs used in the past month and classified according to Anatomical Therapeutic Chemical (ATC) coding: C02, C03, C07, C08 and C09 for antihypertensive and C10 for lipid-modifying agents. Type 2 Diabetes Mellitus was based on fasting glucose levels $\geq$7 mmol/l or use of blood-glucose lowering medication [ATC code A10]. CVD (including myocardial infarction, stroke, angina-pectoris, percutaneous transluminal coronary angioplasty and coronary artery bypass grafting) was adjudicated using standardized algorithms