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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

considering self-report and medication use (see (Vogelzangs et al., 2010). Since we previously found no straight-forward associations between the use of antidepressant medication and subclinical CVD (Seldenrijk et al., 2011b, 2011a), we did not include antidepressants among the covariates in the current analyses.

2.5. Statistical analyses

First, linear regression analyses (for continuous subclinical CVD outcomes) and logistic regression analyses (for dichotomous outcomes) adjusted for sociodemographics, blood pressure and LDL cholesterol (model 1) were conducted to assess associations with depression or anxiety sensitivity. Analyses were additionally adjusted for lifestyle factors (BMI, smoking and physical activity; model 2). In case of significant associations, and in order to rule out the possibility that any observed relationship was driven by subjects with known or suspected cardiovascular health (i.e., CVD, diabetes, use of antihypertensive/ lipid-modifying medication), model 1 analyses were repeated without those cases.

3. Results

3.1. Sample characteristics

Characteristics of the 635 participants are presented in Table 1. The mean age was 46.7 ± 12.0 years and 65.5% was female. A strong correlation between psychological factors was found for hopelessness and rumination ($r=.82$, $p<.001$), but less strong correlations existed for other factors (anxiety sensitivity and aggression, $r=.38$; anxiety sensitivity and hopelessness or rumination, $r=.51$; rumination and aggression, $r=.59$).

3.2. Cognitive vulnerability and subclinical CVD

Table 2 shows results of regression analyses for carotid atherosclerosis and central arterial stiffness. No significant associations were found for depression sensitivity, though a tendency was seen for aggression reactivity to be associated with carotid plaque. No significant associations were observed between any cognitive vulnerability factor and $CIMT_{bif}$. Subjects scoring higher on anxiety sensitivity, however, had a higher likelihood of plaque presence and showed increased arterial stiffness. Additional adjustment for BMI, smoking and physical activity hardly influenced the associations (plaque: $OR_{Agression}=1.22$, 95%CI=0.97–1.54; $OR_{ASI}=1.30$, 95%CI=1.03–1.65; AIx75: $\beta_{ASI}=.05$, $p=.04$); neither did correction for the use of antidepressant medication (not shown).

To check whether significant associations were driven by subjects with known or suspected cardiovascular health, analyses were repeated without those cases. Associations among healthy subjects were even stronger: higher anxiety sensitivity was associated to more carotid plaques ($n=46/488$; OR per SD increase=1.49, 95%CI=1.09–2.03, $p=.01$) and increased stiffness ($n=481$; $\beta=.08$, $p=.01$). Furthermore, the trend for increased plaque presence in subjects scoring high on aggression reactivity gained strength (OR=1.34, 95%CI=0.99–1.81; $p=.06$).

3.3. Post-hoc analyses

Additional 5000 estimates bootstrapping analyses (Preacher and Hayes, 2008) were conducted to evaluate whether associations for anxiety sensitivity were independent of psychopathology, since we previously found that current depression or anxiety (highly characterized by lifetime comorbidity) was associated with increased AIx (Seldenrijk et al., 2011a). Fig. 1 shows the results of mediation models in which the ASI and psychopathology (sum of lifetime diagnoses) were entered while controlling for model 1 covariates. These results indicate that psychopathology partly mediates the association between ASI and increased arterial stiffness.

4. Discussion

When studying increased cardiovascular risk associated with psychopathology, clinical diagnoses have the disadvantage of being broad concepts, that include much heterogeneity, high comorbidity and overlapping symptoms. We therefore investigated associations between subclinical CVD and cognitive vulnerability to depression or anxiety in a sample of subjects with lifetime depressive or anxiety disorders and controls. We found that carotid plaque presence and central arterial stiffness were especially increased in subjects who tend to be highly fearful of anxiety-related bodily sensations. No significant associations were found with CIMT as the outcome, nor for any of the depression sensitivity measures.

Our observation that anxiety sensitivity more than depression sensitivity represents a correlate of subclinical CVD is in close agreement with some previous observations that anxiety disorders rather than depressive disorders are associated with coronary heart disease (Janszky et al., 2010; Vogelzangs et al., 2010). The notion that anxiety-proneness increases the risk of carotid atherosclerosis has been supported previously (Paterniti et al., 2001). Anxiety sensitivity itself has hardly been studied in association with cardiovascular outcomes. We found only one study that examined cardiac anxiety (using the Cardiac Anxiety Questionnaire) in 658 subjects who received EBT screening for determining the presence of coronary calcification (Marker et al., 2008). In contrast with our observations, this study showed higher rates of heart focused attention and worry to be associated with the absence of coronary calcification. However, the population included both self-referred and physician-referred participants, which potentially has influenced this counterintuitive finding. The authors state that their observation is ‘‘consistent with what could be expected from individuals who are overly focused on health related concerns’’. Although overestimation of danger indeed is a cognitive error associated with anxiety, this does not mean that fear of anxiety-related bodily sensations should be ignored in the cardiovascular realm. For example, it recently has been shown that (high) anxiety sensitivity is a psychological factor that makes prognostic difference in atrium fibrillation and congestive heart failure and should be taken into account in the choice of treatment (Frasure-Smith et al., 2010).

Apart from a suggestive finding for aggression, none of the depression sensitivity measures were associated with subclinical CVD in our sample. The trend we observed for aggression – indicating that a higher aggression reactivity was associated with an increased odds for carotid plaque – is in line with a study that found hostile attitudes to be predictive of carotid atherosclerosis (Matthews et al., 1998). This cardiotoxic influence of hostility has also been confirmed by a meta-analysis (Chida and Steptoe, 2009).

A notable inconsistency is the difference seen for ultrasonographic phenotypes of carotid atherosclerosis: unlike plaque presence, $CIMT_{bif}$ shows no significant association with anxiety sensitivity. CIMT and plaque are both considered indicators of atherosclerosis (de Groot et al., 2004; Wyman et al., 2005) and, as such, would be expected to show a similar relationship with anxiety sensitivity. One explanation for the divergent findings could be that $CIMT_{bif}$ is not associated with CVD in a continuous way throughout its full range and that plaque is qualitatively

Table 1
Sample characteristics (N=635).

	Mean (SD) or %
Sociodemographics	
Age, years	46.7 (12.0)
Sex, female	65.5
Education, years	12.8 (3.2)
Lifestyle and health indicators	
Body mass index, (kg/m^2)	25.4 (4.6)
Smoking status	
Never	30.7
Former	43.1
Current	26.1
Physical activity level	
Low	17.6
Moderate	47.1
High	35.3
Systolic blood pressure, (mmHg)	114.2 (15.1)
Diastolic blood pressure, (mmHg)	67.9 (9.3)
Mean arterial blood pressure, (mmHg)	83.3 (10.5)
LDL cholesterol, (mmol/l)	2.99 (0.88)
Use of antihypertensive agents	18.6
Use of lipid-modifying agents	7.6
Diabetes mellitus (type 2)	4.3
Cardiovascular disease	7.9
Psychiatric characteristics	
Psychopathology status, lifetime	
Controls	27.9
Depressive disorder(s) only	14.6
Anxiety disorder(s) only	11.2
Depressive and anxiety disorders	46.3
Type of depressive or anxiety disorder, lifetime	
Major depressive disorder	58.9
Dysthymic disorder	24.7
Panic disorder	30.6
Agoraphobia	12.1
Social phobia	32.1
General anxiety disorder	29.6
Sum of lifetime depression and anxiety diagnoses, median (IQR)	2 (3)
Use of antidepressant medication	16.5
Cognitive vulnerability factors	
Depression sensitivity (LEIDS-R)	
Hopelessness reactivity	4.11 (4.00)
Aggression reactivity	4.07 (3.49)
Rumination on sadness	8.43 (4.92)
Anxiety sensitivity (ASI)	12.7 (8.4)
Markers of subclinical cardiovascular disease	
Carotid bifurcation intima-media thickness, (mm)	0.75 (0.21)
Carotid plaque	14.6
Central augmentation index corrected for heart rate, percentage	14.3 (14.7)

ASI=anxiety sensitivity index; IQR= inter-quartile range; LEIDS-R=Leiden inventory of depression sensitivity, revised; LDL=low density lipoprotein.

different from general increases in CIMT, as suggested elsewhere (Ebrahim et al., 1999). Arguing against this, however, is the fact that we have found similar associations for CIMT and plaque with respect to age of depression onset (Seldenrijk et al., 2011b).

Previous analyses in the current sample focused on associations between depressive or anxiety disorders and subclinical CVD. We had found depressive and anxiety disorders to be associated with increased arterial stiffness (Seldenrijk et al., 2011a). Mediation analyses were conducted in order to investigate whether this finding was interrelated to the currently observed association for anxiety sensitivity. Our results suggest that anxiety sensitivity indeed might uncover one of the underlying dimensions responsible for the increased stiffness previously found in subject with current depressive or anxiety disorders. With respect to carotid plaque, we earlier observed no significant association with diagnoses of depressive or anxiety disorders (Seldenrijk et al., 2011b). Based on observations in the current study, the continuous concept of cognitive vulnerability to anxiety appears to be a more sensitive correlate of carotid plaques than dichotomous and more heterogeneous diagnoses.

Which are potential mechanisms responsible for the increased carotid plaque presence and central arterial stiffness found in subjects who are highly fearful of anxiety-related sensations? Anxiety sensitivity and CVD are both strongly inheritable (Lloyd-Jones et al., 2004; Stein et al., 1999) and might share a genetic basis. Lifestyle factors could also provide an explanation for increased CVD risk since anxiety sensitivity has been linked with risk-promoting behaviours (Brown et al., 2001; Smits and Zvolensky, 2006). However, observed associations in this study were independent of BMI, smoking and physical activity. The arousal associated with high anxiety sensitivity could as well exert its effects through systemic pro-inflammatory state or released stress-hormones. Immune system abnormalities indeed have been found in subjects with panic disorder and post-traumatic stress disorder (Hoge et al., 2009). Previous observations in NESDA seem to object to the stress-hormone idea, since anxiety sensitivity was found to be unrelated to salivary cortisol levels (Van Santen et al., 2011). In case of reverse causality, subclinical CVD would elicit certain symptoms that enhance anxiety sensitivity. This explanation is possible though not very likely, because exclusion of subjects with a compromised cardiovascular status (CVD, diabetes, use of antihypertensive/lipid-modifying agents) did not weaken associations.

To our knowledge this is the first study to investigate associations between sensitivity to either depressive or anxiety disorders and subclinical CVD outcomes measured by using state-of-the-art techniques. The findings should be viewed in the context of the study's limitations. Because of the study's cross-sectional design, the causal nature of the associations between anxiety sensitivity and subclinical CVD remains unsolved. Prospective evidence is needed to examine whether anxiety sensitivity (e.g., through physiological arousal accompanying the fear of anxiety-related sensations) indeed is responsible for the deleterious arterial conditions. Since the sample size was not very large, it is possible that a low statistical power has led to small effects or even to ignoring an existing association (Type II error). Besides, the self-report sensitivity measures could have been influenced by the current mood status, so that report bias might have taken place. However, correlations between the NESDA baseline and 2-year scores were high despite changes in psychopathology status that have occurred. Furthermore, it would have been interesting to examine dimensions of anxiety sensitivity in association with subclinical CVD, but the questionnaire version used in NESDA ((ASI) (Reiss et al., 1986)) is held psychometrically unsuitable for these purposes (Olatunji and Wolitzky-Taylor, 2009).

Anxiety sensitivity now has been presented as a psychological characteristic capable of detecting subjects at increased cardiovascular risk. Because anxiety often overlaps depression in prevalence and symptoms, cardiovascular research needs to be paying attention to the two at one go. For general practice and other primary health care services, implications might include detection of subjects who are highly fearful of bodily sensations and referral for psychological interventions (e.g., cognitive behavioural therapy) or prescriptive exercise, both of which have shown to successfully reduce anxiety sensitivity (Smits et al., 2008b, 2008a). Although this deserves proper research, in doing so, the increased CVD risk associated with depressive and anxiety disorders could be potentially alleviated. Since our findings suggest that cognitive vulnerability to anxiety, rather than depression sensitivity, is associated with indicators of increased cardiovascular risk, it seems important to widen the habitual

Table 2
Associations between cognitive vulnerability factors and subclinical CVD.

	Carotid atherosclerosis					Arterial stiffness	
	$CIMT_{bif}$ N=629		Plaque N=634			AIx75 N=605	
	β	p	OR*	95%CI	p	β	p
Depression sensitivity							
Hopelessness reactivity	−.02	.52	0.97	0.76–1.24	.82	.03	.18
Aggression reactivity	.04	.15	1.24	0.98–1.56	.07	.01	.69
Rumination on sadness	−.01	.65	1.06	0.83–1.36	.64	.02	.34
Anxiety sensitivity	.02	.41	1.34	1.06–1.68	.01	.06	.01

Model 1 associations adjusted for age, sex, education, blood pressure (atherosclerosis: systolic; stiffness: mean arterial), LDL cholesterol.
$CIMT_{bif}$=carotid bifurcation intima-media thickness; AIx75= central augmentation index corrected for heart rate; LDL=low density lipoprotein.

* Odds ratio's are per SD increase in cognitive vulnerability score.

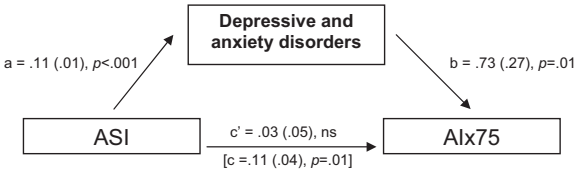

Fig. 1. Effect of anxiety sensitivity on arterial stiffness, mediated by psychopathology. Model 1 associations adjusted for age, sex, education, mean arterial pressure, LDL cholesterol. a=effect of ASI on psychopathology; b=effect of psychopathology on stiffness independent of ASI; c'=direct effect of ASI on stiffness; c=total effect of ASI on stiffness ($c'+ab$). ASI=anxiety sensitivity index; Aix75=central augmentation index corrected for heart rate; LDL=low density lipoprotein.

main focus of research and clinical practice on depression and CVD, and include anxiety as well.

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Conflict of interest

Dr. Diamant disclosed advisory board membership for Eli Lilly & Co, Merck Sharp & Dohme, Novo Nordisk; is consultant for Astra Zeneca/BMS, Eli Lilly & Co, Merck Sharp & Dohme, Novo Nordisk, Sanofi Aventis; is on the speaker's buro for Eli Lilly & Co, Merck Sharp & Dohme, Novo Nordisk; received research support from Amylin Pharmaceuticals Inc., Eli Lilly & Co, Merck Sharp & Dohme, Novartis, Novo Nordisk, Takeda. All other authors reported no conflicts of interest.

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