

Sensitivity to
depression or
anxiety &
subclinical
cardiovascular
disease

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ABSTRACT

Background | Depression and anxiety have both been associated with an increased risk of cardiovascular disease (CVD). Studies that simultaneously address the contribution of those highly overlapping and heterogeneous conditions to date are largely lacking. Characteristics that specify what exactly drives CVD risk in depressed or anxious subjects could be found on the level cognitive vulnerability. Our aim is therefore to examine sensitivity to depression or anxiety in association with indicators of subclinical CVD.

Methods | Data from 635 participants of the Netherlands Study of Depression and Anxiety (NESDA) 2-year assessment were analyzed. Depression sensitivity (hopelessness, acceptance, aggression, control, risk aversion, rumination) was measured by the revised Leiden Index of Depression Sensitivity, and anxiety sensitivity was measured by the Anxiety Sensitivity Index. Subclinical CVD was measured as 1) carotid intima-media thickness and the presence of plaques using B-mode ultrasonography and 2) central arterial stiffness (heart rate normalized augmentation index) using calibrated radial applanation tonometry.

Results | Mean age of the sample was 46.7 (range 20-66) years and 65.5% was female. 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 ($\beta=0.06$, $p=0.01$). No significant associations were found with intima-media thickness, nor for depression sensitivity.

Conclusion | 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, rather than depression sensitivity, appears to represent a correlate of subclinical CVD.

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INTRODUCTION

Depression and anxiety have both been associated with an increased risk of subclinical¹⁻⁵ and overt^{6,7} cardiovascular disease (CVD). Comparison of the effect sizes of two meta-analyses would suggest that depression (pooled RR=1.81⁶) more than anxiety (pooled HR=1.26⁷) is associated with increased cardiovascular risk. However, most studies focus on either depression or anxiety, so that it is impossible to properly compare their respective contribution to observed CVD risk. When depressive and anxiety disorders are examined in concert, some cross-sectional⁸ and longitudinal⁹ evidence points to anxiety as an important predictor of CVD. Other studies, however, have shown that both depression and anxiety were independent prognostic factors after a myocardial infarction¹⁰, and that depression but not anxiety was associated with 3-year progression of subclinical carotid atherosclerosis¹¹.

The heterogeneity of clinical diagnoses further complicates the sorting out of the excess CVD risk in depression and anxiety, since symptoms¹² as well as lifetime occurrence¹³⁻¹⁵ of these psychiatric syndromes are largely overlapping. Since 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 trait-like, cognitive vulnerability to depression or anxiety. Dysfunctional cognitions are thought to contribute to the development and maintenance of depressive and anxiety disorders¹⁶. The 'gold standard' psychotherapy treatment 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)¹⁷. Several 'cognitive' characteristics have been closely linked to depression, such as hopelessness¹⁸, rumination¹⁹ and hostility²⁰. Anxiety sensitivity refers to certain beliefs that anxiety-related bodily symptoms have harmful physical, psychological, or social consequences and is considered a trait-like characteristic that precedes the development of anxiety disorders, in particular (but not limited to) panic attacks^{21,22}. If the concept of depression is related to CVD, this would suggest that depression-specific characteristics are 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 but these studies are inconclusive. Both positive^{23,24} and absent¹¹ associations were found for hostility and atherosclerosis. Hopelessness has been associated with increased risk of carotid atherosclerosis²⁵ and ischemic heart disease²⁶, and an inverse association was found between cardiac anxiety (partly covering anxiety sensitivity) and coronary calcification²⁷. Taken together, these results are indicative, but far from conclusive, of associations between cognitive vulnerability and CVD risk. Besides, a direct comparison between depression- and anxiety-related characteristics and subclinical CVD in one population is still lacking.

Detailing associations between cognitive vulnerability factors and cardiovascular outcomes can yield knowledge on whether CVD risk depends on particular anxiety-related or depression-related dispositions. Here, we aimed to examine sensitivity to depression or

anxiety – the degree to which low mood or anxiety-related symptoms trigger dysfunctional cognitions – in association with indicators of subclinical CVD, i.e. carotid atherosclerosis and central arterial stiffness.

METHODS

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 to examine the course of depressive and anxiety disorders. In order to represent various health care settings and stages of psychopathology, 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 and of predominantly North European origin. Details of the study rationale, recruitment strategy and methods have been described elsewhere²⁸. 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 participated in the 2-year assessment. After the 2-year assessment, 650 participants who lived in the area close to the location of measurements underwent additional cardiovascular measurements. As compared with participants, non-participants (n=1946) were younger (mean: 43.2 versus 46.4 years, $p < .001$) and more often had lifetime depressive or anxiety disorders (81.3% versus 72.5%, $p < .001$). No significant differences between participants and non-participants were found with respect to indicators of suspected cardiovascular health (i.e. history of CVD, diabetes, use of statins or antihypertensive agents; all p -values $> .10$). Further details of the recruitment strategy and protocol, can be found in⁴ and²⁹. Because of missing data on the cognitive vulnerability questionnaires, 635 of 650 subjects were included in the current analyses.

Psychological characteristics

The revised Leiden Index of Depression Sensitivity (LEIDS-R questionnaire^{30,31}) assesses the extent to which dysfunctional cognitions are triggered during normal mood variations, that is cognitive reactivity to sadness. The measure consists of 34 items, e.g. ‘When I feel down, I more easily become cynical (blunt) or sarcastic’ or ‘When in a sad mood, I become more bothered by perfectionism’ that are answered on a 5-point Likert scale (0= ‘not at all’ to 4= ‘very strongly’). The LEIDS-R comprises six depression sensitivity subscales, which showed good internal consistency in the present sample (all α 's $> .95$): hopelessness, acceptance/coping, aggression, control/perfectionism, risk aversion, and rumination. Hopelessness reactivity and acceptance/coping reactivity both constitute of 5 items, with a maximum score of 20, whereas the other scales are based on 6 items with maximum scores of 24.

The Anxiety Sensitivity Index (ASI;³²) 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, such as ‘It scares me when my

heart beats rapidly’ or ‘It scares me when I am unable to keep my mind on a task’, which are answered on a 5-point Likert scale (0 = ‘hardly’ to 4 = ‘very much’). The total score of anxiety sensitivity ranges from 0 to 64 and the scale showed good internal consistency in the present sample ($\alpha = .89$).

As expected, strong correlations were found between the NESDA baseline and 2-year assessment scores for LEIDS-R (overall score $r = .79$, $p < .001$) and ASI ($r = .73$, $p < .001$). We averaged scores over both measurements in the current analyses, in order to obtain the most reliable indicators of these sensitivity measures.

Markers of 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 5-10MHz broadband transducer (Siemens, Erlangen, Germany) according to a previously described standardized and validated protocol³³. High resolution B-mode images of the bilateral carotid artery were scanned with the subject in supine position. Details on the measurement of CIMT can be found elsewhere²⁹. We used bifurcation CIMT (CIMT_{bif}) as outcome measure instead of total CIMT, since bifurcations are particularly prone to progression of atherosclerosis^{34,35}. Previous observations in this relatively young sample indeed have favoured the bifurcation as predilection segment over total CIMT in terms of sensitivity to difference²⁹. Additionally, near and far walls of the bilateral common carotid artery, carotid bifurcation and internal carotid artery were evaluated for the presence of plaques (yes/no), defined as widening of the intimal and medial layers relative to adjacent segments, with the area of focal increased thickness ≥ 1.10 mm.

We determined the central pulse waveform and calculated the central augmentation index (late systolic pressure augmentation / central pulse pressure) 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), as described elsewhere⁴. Because Alx is inversely related to acute changes in heart rate³⁶, we here report the central augmentation index normalized for a heart rate of 75 beats per minute (Alx75).

Covariates

Sociodemographic characteristics included age, sex and education (years). Additionally, several lifestyle and health factors were assessed. Blood pressure was measured at the right arm during supine rest⁴. Mean arterial pressure (MAP) was calculated as $(2 * \text{diastolic pressure} + \text{systolic pressure})/3$. 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 Questionnaire³⁷ in MET-minutes per week [ratio of energy expenditure during activity compared to rest times the number of minutes performing the activity] 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 ≥ 7 mmol/l or use of blood-glucose lowering medication [ATC code A10]. Cardiovascular disease (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 (for details, see ⁸).

We previously found that current depressive or anxiety disorders – also highly characterized by lifetime comorbidity – were associated with higher central arterial stiffness ⁴. In order to be able to examine whether associations for cognitive sensitivity are driving psychopathology findings or whether they are independent of psychopathology, depression and anxiety disorders were considered in additional mediation analyses. Lifetime diagnoses of depressive (major depression, dysthymia) or anxiety (generalized anxiety disorder, social phobia, panic disorder and/or agoraphobia) disorders were obtained by using the DSM-IV based Composite International Diagnostic Interview (CIDI; WHO version 2.1) ³⁸.

Although we previously found no straight-forward associations between the use of antidepressant medication and subclinical CVD ^{4, 29}, we assessed current medication use based on drug container inspection of all drugs used in the past month and subsequent ATC coding. Use of antidepressant medication (tricyclic antidepressants, N06AA; selective serotonin reuptake inhibitors, N06AB; other antidepressants, N06AF/N06AX) was considered present when taken at least 50% of days and for at least one year. Weight, blood pressure, and changes in medication use were assessed at the time of cardiovascular measurements, whereas other measures were taken at the NESDA 2-year assessment. Median time between 2-year assessment and subclinical CVD measurements was 2 months.

Statistical analyses

First, regression analyses adjusted for sociodemographics, blood pressure and LDL cholesterol (model 1) were conducted to assess associations between depression or anxiety sensitivity and subclinical CVD. Second, analyses were additionally adjusted for lifestyle factors (BMI, smoking and physical activity; model 2). Linear regression was used for continuous and logistic regression for dichotomous outcomes. In case of significant associations between depression or anxiety sensitivity and indicators of arterial disease, and in order to rule out the possibility that any observed relationship was driven by subjects with suspected cardiovascular health (i.e. subjects with known CVD or diabetes, or using antihypertensive or lipid-modifying medication), analyses were repeated without those cases. We also examined whether found associations for sensitivity variables are the driving factors for some of our prior findings for psychopathology itself. Mediation by psychopathology was tested using a 5000 estimates bootstrapping approach ³⁹. Since the mediating variable needs to be continuous, the sum of lifetime diagnoses for depressive and anxiety disorders was taken as psychopathology variable. Indirect effects were considered as significant when the bias corrected and accelerated confidence interval did not include zero.

RESULTS

Sample characteristics

Characteristics of the 635 participants are presented in **Table 1**. The mean age was 46.7 \pm 12.0 years and 65.5% was female. Strong correlations between psychological factors were found for hopelessness and rumination ($r=.71$, $p<.001$) and for risk aversion and rumination ($r=.82$, $p<.001$). Correlations between anxiety sensitivity and depression sensitivity measures were less strong (highest correlation for anxiety sensitivity and risk aversion or rumination, both of $r=.51$).

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 any of the depression sensitivity measures, though a tendency was seen for aggression reactivity to be associated with carotid plaque. Subjects scoring higher on anxiety sensitivity, however, both 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: $OR_{Aggression}=1.22$, $95\%CI=0.97-1.54$; $OR_{ASI}=1.30$, $95\%CI=1.03-1.65$; $\Delta Ix75: \beta_{ASI}=.05$, $p=.04$). Use of psychotropic medication did not weaken model 1 associations between anxiety sensitivity and subclinical CVD (results not shown).

Exclusion of subjects with compromised cardiovascular health

In order to find out whether significant associations were driven by subjects with known or suspected major cardiovascular health problems (CVD, diabetes, using antihypertensive or lipid-modifying medication), model 1 analyses were repeated without those cases. Associations among healthy subjects became even stronger: Healthy subjects who reported higher anxiety sensitivity more often had carotid plaques ($n=46/488$; OR per SD increase= 1.49 , $95\%CI=1.09-2.03$, $p=.01$). Likewise, anxiety sensitivity remained associated with increased stiffness ($n=481$; $\beta=.08$, $p=.01$). Furthermore, the trend for increased plaque presence in subjects scoring high on aggression reactivity gained strength, though not at significance level ($OR=1.34$, $95\%CI=0.99-1.81$; $p=.06$).

Mediating role of psychopathology?

We then conducted analyses to evaluate whether associations for anxiety sensitivity are independent of psychopathology. Using linear regression analyses, we first examined associations between lifetime diagnoses of depression or anxiety as independent factors and ASI as the outcome. Comparable to meta-analytic evidence ²², in our sample ASI was strongly related to panic disorder ($\beta=.31$, $p<.001$), but also to other anxiety disorders (β social phobia $=.20$; β general anxiety disorder $=.15$; β agoraphobia $=.15$; all p -values $\leq .001$), and less strongly to depression (β depressive disorders $=.10$, $p=.01$).

Figure 1 shows the results of bootstrapping mediation models in which the ASI as well as psychopathology (sum of lifetime diagnoses) were entered while controlling for model 1 covariates. After adjustment for depressive and anxiety disorders, the direct

	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
Dysthymia	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 traits	
Depression sensitivity (LEIDS-R), total score	30.69 (17.86)
Hopelessness	4.11 (4.00)
Acceptance	1.41 (1.75)
Aggression	4.07 (3.49)
Risk aversion	7.59 (4.42)
Control	5.08 (3.46)
Rumination	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)

TABLE 1. Sample characteristics (N=635)

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

	Carotid atherosclerosis				Arterial stiffness		
	CIMT _{bif} N=629		OR* 95%CI	p	Alx75 N=605		
	β	p			β	p	
Depression sensitivity							
Hopelessness	-.02	.52	0.97	0.76-1.24	.82	.03	.18
Acceptance	.002	.95	1.00	0.79-1.26	1.00	-.02	.47
Aggression	.04	.15	1.24	0.98-1.56	.07	.01	.69
Control	.02	.50	1.08	0.84-1.40	.54	-.02	.53
Risk aversion	-.01	.75	0.98	0.77-1.26	.88	-.002	.93
Rumination	-.01	.65	1.06	0.83-1.36	.64	.02	.34
Anxiety sensitivity	.02	.41	1.34	1.06-1.68	.01	.06	.01

TABLE 2. Associations between cognitive vulnerability traits and subclinical CVD

Model 1 associations adjusted for age, sex, education, blood pressure (atherosclerosis: systolic; stiffness: mean arterial), LDL cholesterol.

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

Alx75= central augmentation index corrected for heart rate; CIMT_{bif} = carotid bifurcation intima-media thickness; LDL = low density lipoprotein.

effect (c' path) of ASI turns insignificant and a significant indirect effect (ab path) = .07 (.02-.14) is seen, suggesting that psychopathology⁴ partly mediates the association of ASI and increased stiffness. Regarding the association between ASI and plaque presence, however, psychopathology cannot play a mediating role, since depressive or anxiety disorders are not significantly associated to plaque presence²⁹. Cognitive vulnerability to anxiety disorders thus appears to be a better correlate of carotid plaques than dichotomous, more heterogeneous clinical diagnoses.

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 and 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 previous observations that anxiety disorders rather than depressive disorders are associated with coronary heart disease^{8,9}. The notion that anxiety-proneness (i.e. trait anxiety, which shows some overlap with ASI⁴⁰) increases the risk of carotid atherosclerosis has been supported previously⁴¹. Anxiety

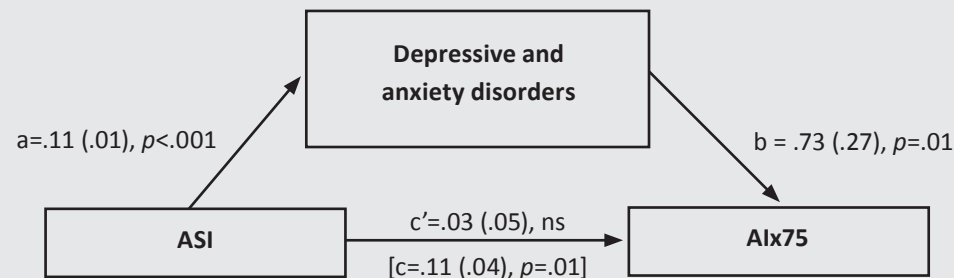


FIGURE 1. Effect of anxiety sensitivity on arterial stiffness, mediated by psychopathology Model 1 associations adjusted for age, sex, education, mean arterial pressure, LDL cholesterol.

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 ($c' + ab$).

Alx75 = central augmentation index corrected for heart rate; ASI = anxiety sensitivity index; LDL = low density lipoprotein.

sensitivity itself has hardly been studied in association with cardiovascular outcomes. We found only one study that examined cardiac related anxiety (using the Cardiac Anxiety Questionnaire) in 658 subjects who received EBT screening for determining the presence of coronary calcification²⁷. In contrast with the increased likelihood of subclinical CVD we found for high anxiety sensitivity, this study showed higher rates of heart focused attention and worry to be associated with the absence of coronary artery calcification. However, the population included both self-referred and physician-referred participants, which potentially has influenced this counterintuitive finding. The authors state that this 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 treatment⁴².

Apart from a suggestive finding for aggression, none of the depression sensitivity measures was 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 atherosclerosis²⁴. This cardiotoxic influence of hostility has also been confirmed by a meta-analysis⁴³.

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^{44,45} and prognosticators of major CVD events^{46,47}. As such, they would be expected to show a similar relationship with anxiety sensitivity, especially as $CIMT_{bif}$ was used which had the highest correlation with plaque ($r=.68$ versus $r=.40$ for common carotid artery and $r=.50$ for internal carotid artery). 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 different from general increases in CIMT, as suggested elsewhere⁴⁸. Arguing against this, however, is the fact that we have found similar associations for CIMT and plaque with respect to age of depression onset²⁹.

Previous analyses in the current sample had focused on associations between depressive or anxiety disorders and subclinical CVD. We had found depressive and anxiety disorders to be associated with increased arterial stiffness⁴. 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 subjects with current depressive or anxiety disorders. With respect to carotid plaque, we had found no significant association with depressive or anxiety disorders²⁹, and this was confirmed in the current analyses. Psychopathology was therefore disqualified as a mediator in the association between anxiety sensitivity and plaque presence. What can be concluded, though, is that the continuous concept of

cognitive vulnerability to psychopathology (particularly to anxiety disorders) appears to be a better correlate of carotid plaques than dichotomous, more heterogeneous clinical 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^{49,50} and might share a genetic basis. Lifestyle factors could also provide an explanation for increased CVD risk and high anxiety sensitivity has been linked with risk-promoting behaviours, such as smoking and having less exercise^{51,52}. However, observed associations in this study were independent of BMI, smoking and physical activity level. 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^{53,54}. Previous observations in the NESDA study seem to object to the stress-hormone idea, since anxiety sensitivity was found to be unrelated to salivary cortisol levels⁵⁵. 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 or lipid-modifying agents) did not weaken associations.

Strengths of the current study include the availability of cognitive vulnerability factors as well as DSM-IV based clinical diagnoses of both depressive and anxiety disorders and the measurement of subclinical CVD outcomes by using state-of-the-art techniques. However, some limitations have to be mentioned as well. 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 of atherosclerosis and stiffness. Also because of this cross-sectional design, the possibility to distinguish whether psychopathology is predictor or mediator has been obscured. 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 the changes in psychopathology status that have occurred. This supports the idea of the sensitivity measures reflecting quite stable characteristics. 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)³² is psychometrically unsuitable for these purposes²². Besides, a unifactorial ASI is shown to be the most reliable factor structure⁵⁶.

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 to detect subjects who are highly fearful of bodily sensations and consider to refer them for psychological interventions (e.g. cognitive behavioural

therapy) or prescriptive exercise, both of which have shown to successfully reduce anxiety sensitivity⁵⁷⁻⁵⁹. Although this deserves proper research, in doing so, the increased CVD risk associated with depressive and anxiety disorders could be potentially alleviated.

In conclusion, our findings suggest that cognitive vulnerability to anxiety, rather than depression sensitivity, is associated with indicators of increased cardiovascular risk. While a tendency of equalization already can be observed, the current study further stresses the importance of the habitual main focus of research and clinical practice on depression and CVD to be widened to include anxiety as well.

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