Depressive & anxiety disorders and risk of subclinical atherosclerosis

Findings from the Netherlands Study of Depression and Anxiety (NESDA)
ABSTRACT

Background | Current evidence regarding the association between psychopathology and subclinical atherosclerosis shows inconsistent results. The present study examined whether subclinical atherosclerosis was more prevalent in a large cohort of persons with depressive or anxiety disorders as compared to non-depressed and non-anxious controls.

Methods | Baseline data from the Netherlands Study of Depression and Anxiety (NESDA) were used, including 2717 persons, free of clinical cardiovascular disease. Participants had a DSM-IV based current or remitted depressive (major depressive disorder, dysthymia) or anxiety (social phobia, generalized anxiety disorder, panic disorder, agoraphobia) disorder (n=2115) or were healthy controls (n=602). Additional clinical characteristics (severity, duration, age of onset and medication) were assessed. Ankle-brachial index (ABI) was used as a measure of vascular risk and was categorized as low (≤0.90) and mildly low ABI (0.90 – 1.11) indicating subclinical atherosclerosis, and high ABI (>1.40), which was previously designated as a cardiovascular risk factor, reflecting arterial stiffness and wall calcification.

Results | As compared to normal controls, persons with current (i.e. past year) depressive, anxiety or comorbid depressive and anxiety disorders showed a 2- to 3-fold increased odds of low ABI (OR=2.78, 95%CI=1.05-7.35; OR=3.14, 95%CI=1.25-7.85; OR=2.67, 95%CI=1.09-6.51, respectively). No associations were found with mildly low or high ABI. Also, we did not further find a differential role for symptoms severity, duration, age of onset, and use of psychotropic medication in the link between psychopathology and subclinical atherosclerosis.

Conclusion | Persons with current depressive or anxiety disorders were more likely to have subclinical atherosclerosis compared to healthy controls.

INTRODUCTION

A large body of evidence relates depressive and anxiety disorders to cardiovascular disease (CVD). Depressive symptoms and disorders have been found to be independent risk factors for a wide range of cardiovascular abnormalities. Recent evidence also relates anxiety disorders to CVD endpoints. Inflammatory processes, dysfunction of the autonomous nervous system and hyperactivity of the hypothalamic-pituitary-adrenal axis have been suggested as pathophysiological pathways linking depressive and anxiety disorders to an enhanced process of atherosclerosis, ultimately resulting in CVD. Because even 80% of major cardiovascular events occur in persons without a history of CVD, early detection of atherosclerosis by means of subclinical markers is of great importance and can already provide us with information on underlying pathophysiological mechanisms.

The association of depression or anxiety and subclinical atherosclerosis has been studied previously in several populations, but those investigations have yielded conflicting results. Various studies measuring intima-media thickness (IMT) by using carotid ultrasonography showed atherosclerosis to be associated with depression or anxiety, whereas other studies found an association for depressive symptoms in men only but not in women, or found no association at all for depression or anxiety. An alternative non-invasive, quick and inexpensive way to obtain clinically relevant information regarding the severity of cardiovascular risk and subclinical atherosclerosis is through the ankle-brachial index (ABI). The ABI is calculated as the ratio of arm systolic pressure to ankle systolic pressure. ABI is used to screen for peripheral arterial disease (PAD), but low ABI (≤0.90) has also been recognized as an indicator of systemic atherosclerosis and of preclinical CVD. Recently, the Ankle Brachial Index Collaboration published a meta-analysis providing a new ABI risk categorization. They showed that not only low, but also mildly low (0.90–1.11) and high (≥1.40) ABI is associated with increased risk of subsequent mortality, coronary heart disease and stroke. Results so far, however, have been conflicting with one confirming the association with low ABI in the depressed but others finding no significant association between depression and low ABI or anxiety and ABI ratio.

Previous studies were mainly performed in older populations, raising the question if earlier findings apply to younger adults as well. In addition, few studies examined depression and anxiety together, despite the fact that these are highly co-morbid conditions. Consequently, whether the association with subclinical atherosclerosis is comparable for depressive and anxiety disorders remains unknown. Besides, only few studies have examined subclinical atherosclerosis in populations with confirmed psychiatric diagnoses of depression and anxiety, while the majority of studies used self-reported measures for depression or anxiety symptoms, which are more likely to overdiagnose psychopathology in presence of underlying somatic health problems. Finally, if depression and anxiety are truly associated with subclinical atherosclerosis, the question arises whether specific clinical characteristics, such as severity, duration, age of onset and psychotropic medication, have a role in this association or in the way this relationship can be described. The present study assessed whether subclinical atherosclerosis measured by ABI was more prevalent in a large cohort of persons with depressive and anxiety disorders (remitted or current) as compared to normal controls.
compared to healthy controls. In addition, we explored the role of clinical characteristics (severity, duration, age of onset and psychotropic medication) in the association between psychopathology and subclinical atherosclerosis.

**METHODS**

**Sample**

Participants of the present study were enrolled in the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study to examine the prevalence and course of depressive and anxiety disorders. Participants were 2981 men and women, aged 18 to 65 years at the baseline assessment in 2004-2007. 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 sample included 2329 persons with a current or remitted depressive and/or anxiety disorder, and 652 controls. Details of the study rationale, recruitment strategy and methods have been described elsewhere 23. The research protocol was approved by the Ethical Committee of participating universities and all respondents provided written informed consent.

We excluded 176 persons with any evidence of cardiovascular disease (self-reported myocardial infarction, angina pectoris or physical strain-related transient chest pain combined with heart medication, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting and stroke) and 88 persons with missing blood pressure data, leaving 2717 persons for the present analyses (19.4% from community, 52.7% from primary care and 27.9% from outpatient psychiatric clinics).

**Psychopathology & clinical characteristics**

Diagnoses of depressive disorders (major depressive disorder, dysthymia) and anxiety disorders (generalized anxiety disorder, social phobia, panic disorder and/or agoraphobia) were established according to the DSM-IV based Composite International Diagnostic Interview (CIDI; WHO version 2.1) 23. The CIDI is a highly reliable and valid instrument for assessing depressive and anxiety disorders 24 and was administered by specially trained research staff. Based on the CIDI, participants were categorized as having no (n=602), remitted (lifetime, but not current; n=496) or current (in past year; n=1619) depressive and/or anxiety disorder. To examine the relative importance of depressive and anxiety disorders in the association with subclinical atherosclerosis, a categorical variable was constructed, classifying persons as having current depressive disorder only, current anxiety disorder only, or current comorbid depressive and anxiety disorder.

Because more chronic and more severe depressive or anxiety disorders could possibly be more strongly associated with atherosclerosis 23, 26, severity and duration of symptoms were taken into account in additional exploratory analyses. Severity of depressive symptoms was measured with the 30-item Inventory of Depressive Symptomatology (IDS) self-report version 27. Severity of anxiety symptoms was measured using the 21-item Beck Anxiety Inventory (BAI) 28. Among persons with a depression or anxiety diagnosis, the presence of depressive and anxiety symptoms during the past four to five years was assessed using the Life Chart method 29, 30. From this, the percent of time with depressive or anxiety symptoms was computed as a measure of duration. Additionally, data concerning age of first onset of depressive or anxiety disorders were derived from the CIDI interview.

Since psychotropic medications have shown several effects on cardiovascular physiology 31, we also examined the role of psychotropic medication. Medication use was assessed based on drug container inspection of all drugs used in the past month and classified according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification 32. Use of psychotropic medication was considered present when taken at least 50% of days (of the month). Antidepressants included tricyclic antidepressants (TCAs; ATC code N06AA), selective serotonin reuptake inhibitors (SSRIs; ATC code N06AB), and other antidepressants (ATC codes N06AF/N06AX). Benzodiazepines included ATC codes N03AE, N05BA, N05CD and N05CF.

**Subclinical atherosclerosis**

Both ankle and arm systolic blood pressure was measured by an ultrasound Doppler device at 8-MHz (UltraTech PD1v, Ultrasound Technologies Ltd, Itton, Chepstow, UK) in combination with an ordinary blood pressure cuff, as previously described 23. Blood pressure was assessed with the respondent in supine position. Ankle-brachial index was calculated as the mean of two consecutive systolic right posterior tibial artery blood pressures divided by the mean of two consecutive systolic right humeral artery blood pressures.

Subclinical atherosclerosis was defined as the presence of an ABI score associated with increased cardiovascular risk. In line with recommendations from the recently published meta-analysis of the Ankle Brachial Index Collaboration 31 which showed a non-linear association between ABI and CVD risk, three groups of increased CVD risk were distinguished: low ABI (0.90 or less), mildly low ABI (ranging 0.90 to 1.11) and high ABI (greater than 1.40). While subclinical atherosclerosis is largely acknowledged to be associated with an increased risk of clinical CVD among those with low and mildly low ABI levels 31, 34, the mechanisms explaining the increased CVD risk among those with a high ABI have not been definitely established, but could likely reflect poor arterial compliance resulting from stiffness and calcification of the medial arterial wall 31, 32. An ABI of 1.11 to 1.40 was considered to be normal and is used as the reference value in the analyses.

**Covariates**

Sociodemographic characteristics included age, sex and years of education. In addition, various health indicators were considered as covariates since these have been linked with both depression/anxiety and atherosclerosis and might confound a possible association between them. 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. Alcohol intake was measured as the amount of alcoholic consumptions a week. The presence of diabetes mellitus was based on fasting glucose levels ≥7 mmol/l (blood drawn in the morning, analyzed using standard laboratory techniques) or the use of blood-glucose lowering medication (ATC code A10). Systolic and diastolic blood pressure was measured twice on the right arm during supine rest, using an OMRON M4 IntelliSense.
### Psychopathology

<table>
<thead>
<tr>
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<th>Healthy controls</th>
<th>Remitted psychopathology</th>
<th>Current psychopathology</th>
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<tbody>
<tr>
<td>Depressive disorder, %</td>
<td>0</td>
<td>81.9</td>
<td>91.9</td>
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<td>Anxiety disorder, %</td>
<td>0</td>
<td>54.6</td>
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### Sociodemographic variables

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<tr>
<td>Age, mean years ± SD</td>
<td>40.4 ± 14.5</td>
<td>44.0 ± 12.8</td>
<td>40.5 ± 12.2</td>
<td>&lt;0.001</td>
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<td>Education, mean years ± SD</td>
<td>12.9 ± 1.2</td>
<td>12.7 ± 3.1</td>
<td>11.9 ± 3.3</td>
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### Health indicators

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<td>Smoking status</td>
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<td>Never, % yes</td>
<td>38.5</td>
<td>27.0</td>
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<tr>
<td>Former, % yes</td>
<td>35.4</td>
<td>37.7</td>
<td>29.7</td>
<td></td>
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<tr>
<td>Current, % yes</td>
<td>26.1</td>
<td>35.3</td>
<td>44.5</td>
<td></td>
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<tr>
<td>Alcohol use, mean intake/week ± SD</td>
<td>7.4 ± 9.2</td>
<td>6.9 ± 8.7</td>
<td>6.9 ± 10.7</td>
<td>0.58</td>
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<tr>
<td>Body mass index, mean ± SD</td>
<td>24.9 ± 4.5</td>
<td>25.6 ± 4.4</td>
<td>25.4 ± 5.1</td>
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<tr>
<td>Diabetes Mellitus, %</td>
<td>3.7</td>
<td>4.0</td>
<td>3.8</td>
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<tr>
<td>Hypertension, %</td>
<td>39.2</td>
<td>39.3</td>
<td>37.7</td>
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### Clinical characteristics

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<th>Indicator</th>
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<th>Remitted psychopathology</th>
<th>Current psychopathology</th>
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<tr>
<td>IDS, mean score ± SD</td>
<td>8.4 ± 7.4</td>
<td>13.2 ± 8.7</td>
<td>28.5 ± 12.4</td>
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<td>BAI, mean score ± SD</td>
<td>4.0 ± 4.7</td>
<td>6.4 ± 6.0</td>
<td>16.5 ± 10.8</td>
<td>&lt;0.001</td>
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<td>Life Chart, mean % time affected ± SD</td>
<td>n.a.</td>
<td>15.9 ± 25.0</td>
<td>51.2 ± 35.9</td>
<td>&lt;0.001</td>
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<td>Age of first onset, mean ± SD</td>
<td>n.a.</td>
<td>25.9 ± 12.9</td>
<td>21.1 ± 12.1</td>
<td>&lt;0.001</td>
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### Ankle-Brachial Index (ABI)

<table>
<thead>
<tr>
<th>Category</th>
<th>Healthy controls</th>
<th>Remitted psychopathology</th>
<th>Current psychopathology</th>
<th>(p^*)</th>
</tr>
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<tbody>
<tr>
<td>Low (≤ 0.90), %</td>
<td>1.2</td>
<td>1.4</td>
<td>2.9</td>
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<tr>
<td>Mildly low (0.90 – 1.11), %</td>
<td>34.1</td>
<td>36.3</td>
<td>36.1</td>
<td></td>
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<tr>
<td>Normal (1.11 – 1.40), %</td>
<td>61.6</td>
<td>60.7</td>
<td>58.5</td>
<td></td>
</tr>
<tr>
<td>High (&gt; 1.40), %</td>
<td>3.2</td>
<td>1.6</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 1. Baseline characteristics according to psychopathology groups**

*p-values based on analyses of variance (continuous variables) and \(\chi^2\) (categorical and dichotomous variables).

BAI = Beck Anxiety Inventory; IDS = Inventory of Depressive Symptomatology; n.a. = not applicable.
Effect of clinical characteristics
To explore whether the associations observed could be specifically attributed to certain clinical characteristics, multinomial logistic regression analyses were conducted in the sub-sample of persons with current psychopathology. As significant associations between psychopathology and ABI were restricted to low ABI, only results for low versus normal ABI are presented. Table 3 shows that no statistically significant associations were found for severity, duration, age of onset and use of psychotropic medication on low ABI, indicating that these characteristics did not further differentiate the risk of low ABI among depressed or anxious persons.

**DISCUSSION**

This study examined the association between depressive and anxiety disorders and subclinical atherosclerosis measured by ABI. We found that persons with current depressive or anxiety disorders were almost three times more likely to have a low ABI. No significant associations were found for mildly low or high ABI, nor between additional clinical characteristics (severity, duration, age of onset or psychotropic treatment) and low ABI.

Our findings of a higher odds for low ABI among currently depressed persons are in line with findings from one earlier study by Wattanakit et al. that showed that high levels of depressive symptoms increased the risk of incident PAD in a middle-aged population-based cohort. However, our results contrast with those from two previous studies regarding depression and low ABI, which found no significant relationship. This discrepancy can be due to differences in population, sample size and psychopathology measures. Tiemeier et al. studied a community-based population with relatively low prevalence (3%) of depressive disorder, the OR is 3.14 (95%CI=1.25-7.85) for those with depressive disorder, the OR is 3.14 (95%CI=1.25-7.85) for those with anxiety disorder and the OR is 2.67 (95%CI=1.09-6.51) for those with comorbid conditions. No statistically significant associations of current psychopathology were found with mildly low or high ABI.

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In order to examine whether the association with low ABI was specific for a certain type of psychopathology, we repeated the analyses without remitted cases, this time entering separate indicators for current depressive disorder only, current anxiety disorder only and current comorbid conditions. As compared to healthy controls, the odds for low ABI was significantly increased for all three groups: the OR is 2.78 (95%CI=1.05-7.35) for those with depressive disorder, the OR is 3.14 (95%CI=1.25-7.85) for those with anxiety disorder and the OR is 2.67 (95%CI=1.09-6.51) for those with comorbid conditions. No statistically significant associations of current psychopathology were found with mildly low or high ABI.

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Our findings clearly illustrate that increased odds of subclinical atherosclerosis is not restricted to depressive disorders, but extends to anxiety disorders as well. There have not been many previous studies that examined anxiety disorders in relationship to low ABI status, but our findings are in line with earlier findings by Patroniti et al., who reported an association of sustained anxiety with subclinical atherosclerosis, however, measured as...
4-year plaque occurrence (men only) and intima-media thickness increase in the carotid artery in a community-based sample of older persons. Our findings, showing that not only depressive disorder but also anxiety disorder do have impact on cardiovascular disease risk, are also in line with earlier findings in our study, showing that a diagnosis of anxiety disorder increases the odds of having coronary heart disease.

To our knowledge, the mildly low and high ABI categories have never been examined in association with depressive or anxiety disorders in earlier studies. The finding that depressive and anxiety disorders were not associated with mildly low or high ABI was not entirely in line with our expectations, while the Ankle-Brachial Index Collaboration has found these categories to be associated with slightly higher cardiovascular risk. However, ABI less than 0.90 is clearly the most pronounced marker of atherosclerosis and associated with high cardiovascular risk, which is underlined by the fact that it has been used as ABI cut-off score in most studies on subclinical atherosclerosis. High ABI has also been used as surrogate marker of lower-extremity arterial calcification as well. Although lower-extremity arterial calcification is predicted by classical risk factors for atherothrombotic disease, it probably rather reflects medial wall calcification instead of atherosclerotic plaque, which is rather located in the intima. This may indicate that high ABI reflects some other processes than those underlying atherosclerotic plaque formation, which could be the reason why an association was found between depressive and anxiety disorders and low but not high ABI in our sample.

Unexpectedly, we found no evidence that particular clinical characteristics such as severity, duration, age of onset or psychoactive medication further contributed in the association with subclinical atherosclerosis. Consequently, we could not demonstrate a dose-response relationship between depression and anxiety severity and atherosclerosis, though it should be mentioned that power for these additional exploratory analyses was not extremely high. In addition, we did not find a higher prevalence of low ABI among those with a remitted depressive or anxiety disorder. Possible explanations are that remitted diagnoses are less reliable because of their retrospective character and that they indicate increasingly less severe exposure to depression or anxiety over time.

Which are the mechanisms relating depressive and anxiety disorders to subclinical atherosclerosis? Underlying pathophysiological mechanisms may be through activation of immune system pathways or hypothalamic-pituitary-adrenal axis dysfunction, which can enhance the process of atherosclerosis. Indeed, especially for depression, higher circulating inflammatory marker levels, and a higher cortisol awakening response has been found. Another underlying mechanism could be through proatherogenic metabolic abnormalities, such as abdominal obesity and dyslipidemia, that are related to psychiatric disorders. Both depressive and anxiety symptoms have shown to increase the odds of the metabolic syndrome. Also within the NESDA population, metabolic abnormalities predisposing to CVD were more prevalent among – only the most severe – depression and anxiety patients. Still another hypothesis suggests that sympathetic nervous overactivity in depressed and anxious persons can mediate the association with atherosclerosis, e.g. through elevated resting and 24-hour heart rate and reduced heart rate variability. Conversely, depression and anxiety may contribute to unhealthy lifestyle habits as smoking, low physical activity, unhealthy diet, which in turn enhance atherogenesis. However, lifestyle factors did not explain the associations found since unadjusted and adjusted results yielded very similar results. Finally, depressive and anxiety disorders possibly share a genetic basis with atherosclerosis.

This study has several important assets. First, its large sample size enabled to study ABI in a relatively young population, while abnormal ABI is generally, although not exclusively, found in persons aged 50 years and older. Second, we used clinical, DSM-IV-based diagnoses instead of mere self-reports of disease symptoms. Third, we examined

| low ABI (≤0.90) versus normal ABI |
|-------------------------------|---|---|---|
| **Severity of depressive symptoms** | N | OR | 95% CI | p |
| IDS* | 1594 | 0.91 | 0.66 – 1.25 | .55 |
| **Severity of anxious symptoms** | N | OR | 95% CI | p |
| BAI* | 1596 | 0.87 | 0.63 – 1.21 | .41 |
| **Duration of depressive or anxious symptoms** | N | OR | 95% CI | p |
| % of time affected on Life Chart* | 1609 | 1.01 | 0.75 – 1.37 | .93 |
| **Onset of depressive or anxiety disorder** | N | OR | 95% CI | p |
| Age of onset per 10 years increase | 1591 | 1.05 | 0.83 – 1.33 | .66 |
| **Medical treatment** | N | OR | 95% CI | p |
| TCA | 1619 | 0.49 | 0.13 – 1.82 | .29 |
| SSRI | 0.95 | 0.47 – 1.93 | .89 |
| Other antidepressant | 1.09 | 0.36 – 3.32 | .88 |
| Benzodiazepine | 0.88 | 0.34 – 2.28 | .79 |

* based on multinomial logistic regression analyses, adjusted for age, sex, education, smoking status, alcohol intake, body mass index, diabetes and hypertension (results for mildly low or high ABI not shown).
Current = last year; IDS = Inventory of Depressive Symptomatology; BAI = Beck Anxiety Inventory; TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor
* per SD increase; SD of IDS = 12.6 ; SD of BAI = 10.5; SD on Life Chart = 0.36

TABLE 3. Association of clinical characteristics with ankle-brachial index (ABI) status comparing low ABI with normal ABI (1.11 – 1.40) in current cases

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TABLE 3. Association of clinical characteristics with ankle-brachial index (ABI) status comparing low ABI with normal ABI (1.11 – 1.40) in current cases*
the associations of both depression and anxiety simultaneously. The current study also has some limitations. First, it should be noted that we used a cross-sectional design, which does not allow causal interference. Further research is needed to explore whether depressive and anxiety disorders contribute to subclinical atherosclerosis over time, or whether depressive and anxiety disorders are the consequence of subclinical atherosclerosis. It should be mentioned that the vast majority (78%) of the currently depressed and anxious cases had their first disease onset before the age of 30 years, i.e. long before our study assessment, making it less likely that depressive or anxiety disorders really reflect consequences of subclinical atherosclerosis. A second limitation is that ABI was measured for only one leg. This may have contributed to underestimating the prevalence of subclinical atherosclerosis, although a high correlation was found between ABI measured in both legs. Third, despite the large total sample size, we had few subjects in the low and high ABI outcome-groups. This may have been due to the relatively young age of our sample. As a consequence, our study lacked power to examine the possible effects of subtype of depressive and anxiety disorders, and to examine gender- and age-specific effects.

In conclusion, our findings suggest that subclinical atherosclerosis is more prevalent among persons with a depressive or anxiety disorder as compared to healthy controls. This puts depressed and anxious persons at an increased risk for the development of subsequent cardiovascular disease. It also illustrates that further studies are needed that elucidate the mechanisms that lead to the increased prevalence of subclinical atherosclerosis in depressed and anxious persons.

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