The weight of subclinical vascular disease & neuroticism in late-life depression
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Atherosclerosis decreases the impact of neuroticism in late-life depression: hypothesis of vascular apathy

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Atherosclerosis decreases the impact of neuroticism in late-life depression: hypothesis of vascular apathy

Radboud M. Marijnissen, Boudewijn A.A. Bus, Robert A. Schoevers, Lonneke Wouts, Suzanne Holewijn, Barbara Franke, Jacqueline de Graaf, Martin den Heijer and Richard C. Oude Voshaar

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Abstract

**Background** – Neuroticism and cardiovascular disease are vulnerability factors in late-life depression, but have hardly been examined in relation to each other. The objective of the study was to examine the interplay between subclinical atherosclerotic disease and neuroticism in explaining variance in late-life depressive symptoms.

**Methods** – This study was part of the Nijmegen Biomedical Study (NBS), a population based survey and included 1517 participants aged 50 through 70 years. Depressive symptoms were measured by the Beck Depression Inventory (BDI). Principal components analysis of the BDI-items yielded two factors, representing a cognitive-affective symptom cluster and a somatic-affective symptom cluster. Atherosclerotic disease was measured by the Intima Media Thickness of the carotid arteries (IMT) and neuroticism by the revised Eysenck Personality Questionnaire (EPQ-RSS).

**Results** – Multiple linear regression analyses using different measures of depressive symptoms as the dependent variable showed that neuroticism was strongly and significantly associated with the sum score of the BDI as well as with the two depressive symptom clusters. IMT, however, was only significantly associated with the somatic-affective symptom cluster, but not with the cognitive-affective symptom cluster. Interestingly, we found a significant negative interaction between neuroticism and IMT in explaining the severity of the cognitive-affective symptom cluster, but not with respect to the somatic-affective symptom cluster.

**Conclusions** – The negative interaction between neuroticism and atherosclerosis indicates that neuroticism is less strongly associated with cognitive-depressive symptoms in the presence of more severe atherosclerosis. This may be explained by apathy due to cerebrovascular disease and fits with a hypothesis of vascular apathy.

**Keywords**

Atherosclerosis, neuroticism, late-life depression, apathy, elderly
**Introduction**

Clinically relevant depressive symptoms are highly prevalent in late life, affecting 13.5% of elderly people in the community, with 1.8% meeting the criteria for major depressive disorder and 9.8% for minor depression. (Beekman et al, 1999). The stress-vulnerability model is a widely used model to explain depressive symptoms. This model states that stressors may lead to depression, especially in the presence of a long-standing vulnerability. Two major vulnerability factors in late-life depression are neuroticism and cardiovascular disease. Neuroticism yields a relative risk of 3.7 of becoming depressed in later life (Steunenberg et al, 2005). The prevalence of depression is significantly increased in patients with vascular disease, e.g. the cumulative 1-year incidence of depression was 39% in stroke patients and 25% in patients with myocardial infarction (Aben et al, 2002).

Both major risk factors have hardly been examined in relation to each other. Different hypotheses can be made as to how these factors act or interact. First, neuroticism and cardiovascular disease may act independently of each other. Second, such factors may interact with each other and increase the risk by more than the sum of both effects independently. A third, but more speculative hypothesis, is that of a negative interaction between high neuroticism and a higher prevalence of cardiovascular disease. A recent study of our group found that in elderly people aged 70 years and older, the effect of neuroticism on explaining depressive symptoms was attenuated by the presence of cerebrovascular disease (Wouts et al, 2011). Similarly, a small case-control study, also found a negative interaction between vascular risk and psychosocial vulnerability for depression (Oldehinkel et al, 2003). Although these findings may have been chance findings or ceiling effects of two important risk factors, one also may hypothesize that cerebrovascular disease causes apathy which in turn decreases the effect of neuroticism on depression (Wouts et al, 2011). This is in line with a previous finding of the Leiden 85+ study, showing that vascular risk factors were prospectively related to apathy, but not depression (Van der Mast et al, 2008). The effect of apathy however, might only be present in the very old population as studied by Wouts et al (2011) and Van der Mast et al (2008). Furthermore, cardiovascular disease was assessed by self-report of vascular events, whereas it is known that older people do have significant subclinical cerebrovascular damage indicated by white matter disease without ever experiencing a vascular event. It has been shown that subclinical vascular disease can be measured by the Intima Media Thickness (IMT) of the carotid artery and provide a good indicator of generalized atherosclerosis (Cheng et al 2002). Interestingly, IMT is correlated with both depressive disorder and symptoms (Tiemeier et al, 2004; Bus et al, 2010). Where
Van der Mast et al (2008) divided depression from apathy, Tiemeier et al (2004) did not. This could be an explanation why Tiemeier et al (2004) found the correlation between depression and atherosclerosis. Therefore, research is needed in which both the more sensitive IMT of the carotid artery is used as indicator of atherosclerosis whereas depression operationalized in more homogeneous symptom clusters. Previously, we showed that the somatic-affective symptoms of depression are specifically associated with a higher level of atherosclerotic disease (Bus et al, 2010) and with cardiovascular risk factors like visceral obesity (Marijnissen et al, 2011). On the other hand, cognitive-affective symptoms, like worrying or suicidal thoughts, may be more specifically associated with neuroticism. After all, cognitive reactivity, i.e. the ease with which particular patterns of negative thinking are reactivated in response to low mood, mediates the predisposing effects of neuroticism to depression (Barnhofer & Chittka, 2010; Boyle et al, 2010; Chapman et al, 2012; Merema et al, 2013; Hayward et al, 2013).

The present study was conducted to examine our hypothesis that neuroticism and sub-clinical atherosclerotic disease, as measured by IMT, negatively interact with regard to the presence of depressive symptoms in a population aged 50 through 70 years. We examined this hypothesis with respect to both, overall depressive symptoms as well as more homogeneous measures of depressive symptoms, including cognitive-affective and somatic-affective symptoms.

**Methods**

**Sample**

The present sample was drawn from the Nijmegen Biomedical Study (NBS), a population-based survey conducted in Nijmegen of people aged 20 through 90 years (Hoogendoorn et al, 2006). In 2004 and 2005 a questionnaire was sent to all participants (n=2807) in the age group 50 through 70 years. Of these persons 1517 (54%) gave additional informed consent to participate in a study on atherosclerosis. These participants visited the hospital for a detailed assessment of atherosclerotic disease, its risk factors and consequences (Holewijn et al, 2010). Exclusion criteria were a diagnosis of dementia or a history of stroke, because these conditions might directly affect the neurobiological brain circuits involved in depression (Alexopoulos, 2005). The Medical Ethics Committee of the Radboud University Nijmegen Medical Centre approved the study protocol.

**Variables of interest**

**Carotid intima media thickness (IMT)** - Carotid IMT was determined using semi-
automatic edge-detection software (M'ATHSTD version 2.0, Metris, Argenteuil, France). IMT was defined as the mean IMT of four measured segments of the distal common carotid artery: far wall left, near wall left, far wall right and near wall right. Longitudinal images of the most distal 10 mm of both the far wall and the near wall of both common carotid arteries were obtained in the optimal projection (anterolateral, lateral or posterolateral). IMT was measured in an area free of plaque, which was defined as an area with an IMT ≥ 1.5 times the surrounding IMT. All measurements were carried out in end-diastole using the R-wave of a simultaneously recorded ECG as a reference frame. From each frame the mean IMT was calculated over at least 7.5 mm of the above mentioned 10 mm segment (yielding a quality index of at least 75%). The outcome variable was defined as the mean IMT of the near and far wall of both common carotid arteries. IMT measurements were performed after an overnight fast or in the afternoon 6 hours after a standardized breakfast. Participants were asked to abstain from caffineinated products for at least 12 hours and they were asked not to smoke for 12 hours before the visit. After standardizing the measurement conditions, there were no significant differences between the measurements performed in the morning and those performed in the afternoon (described elsewhere: Ter Avest et al, 2005). Participants were measured in supine position in a room with controlled temperature (23º - 24º C). The equipment used was a 7.5 MHz transducer of an AU5 ultrasound system (Esaote Biomedical, Genova Italy), connected to a computer with a data acquisition board. All measurements were highly standardized and performed by well-trained and certified sonographers. Reproducibility of our IMT-measurements was investigated and reported before as good (Ter Avest et al, 2005).

**Depressive symptoms** - Depressive symptoms were measured with the Beck Depression Inventory (BDI-I). The BDI-I is a 21-item self-report questionnaire with excellent psychometric characteristics (Beck et al, 1987). Each item is rated on a 0 to 3 scale, with 0 representing ‘absence’ and 1-3 representing increasing levels of severity of the symptom. The BDI-I yields a total score ranging from 0 to 63. Based on previous research in this field, a sum score ≥ 10 is indicative of clinically significant depressive symptoms (Marijnissen et al, 2011).

**Neuroticism** - Neuroticism was measured using the Dutch version of the revised Eysenck Personality Questionnaire (EPQ-RSS)(Eysenck et al, 1985). The EPQ-RSS yields a total score ranging from 0 to 12. Results of the Dutch version of this questionnaire strongly resemble those of the English version (Sanderman et al, 1991). The EPQ-RSS is based on a three-factor model of personality: neuroticism, extraversion and psychoticism. Neuroticism is a stable personality trait that also can be measured reliably in later life.
because it is not significantly affected by physical health variables (Steunenberg et al, 2005). Nonetheless, an acute depression amplifies the personality profile of people prone to depression (Ormel et al, 2004). After recovery neuroticism decreases, but the overall shape of the profile does not change (Costa, Jr et al, 2005; Santor et al, 1997). The relationship between change in personality and change in depressive symptoms is at most moderate and does not differ between men and women (Santor et al, 1997).

**Covariates**

Sociodemographic variables, a history of depression and health variables predict a large portion of elderly major and subsyndromal depression in the general population (Schoevers et al, 2000; Marijnissen et al, 2011). Therefore the following variables were examined as potential confounders: age, sex, living circumstances (together versus alone), higher education level, metabolic syndrome (MS), smoking status, physical activity, alcohol use, antidepressant use, cardiovascular medication, history of treated depression, coronary artery disease (CAD), and other chronic somatic diseases. MS was defined according to the International Diabetes Federation (IDF) (www.idf.org/webdata/docs/IDF-Meta_def_final.pdf, 2009). Individual components of the MS were measured; mean arterial pressure was measured using an oscillometric sphygmanometer (Criticon model no. 1846, Criticon Inc., FL). Waist circumference was measured at the level of the umbilicus. Triglycerides and glucose concentrations were determined using commercially available enzymatic reagents (AEROSET1 System, Abbott, Chicago IL). Smoking status, alcohol use, physical activity and cardio-vascular disease status were assessed during a short interview. Smoking behavior was categorized as current, former or never. Physical activity was based on the number of exercise sessions of more than 30 min moderate to vigorous activity per week (Stampfer et al, 2000). Because of a skewed distribution (that could not be normalized by transformation), a median split was used (0 or 1 v. 2 or more exercise moments/week). Alcohol intake was dichotomized into severe use (>21 units for men and >14 units for woman) and non-severe use. CAD was assessed by a trained interviewer and defined as a history of treated angina pectoris, myocardial infarction, a history of percutaneous transluminal coronary angioplasty or coronary artery bypass grafting (Kriegsman et al, 1996). The chronic comorbid status was defined as the presence of one or more chronic co-morbid somatic diseases (yes/no). The self-reported presence of somatic disease was scored in case of current treatment for rheumatic disorder (or arthrosis), current treatment for COPD, current treatment for liver disease, current treatment for kidney disease, history or current treatment of morbus Crohn or colitis ulcerosis in history or history or current treatment of cancer. The history of treated lifetime depression was based on self-report data (yes/no). Medication use was defined by the use of at least half of the defined daily dose and based on medication
containers brought to the interview. Eight different classes of medication were selected based on their potential influence on atherosclerotic disease and/or its association with depression and entered as dichotomies (yes/no). These classes were antidepressants (ATC N06AXXX), statins (ATC C10AXXX), angiotensin-converting enzyme (ACE) inhibitors (ATC C09AXXX), angiotensin II antagonists (C09CATC), Ca++-channel blockers (C08CXXX, C08DXXX, C08EXXX), beta-blockers (ATC C07AXXX), diuretics (C03XXXX), and analgesics (N02BAXX).

**Statistical Methods**
Because the BDI sum score had a skewed distribution in our sample, we applied a log-transformation in order to more closely approximate a normal distribution. All further analyses were conducted using the log-transformed sum score. IMT scores and neuroticism scores appeared to be normally distributed.

As described in a previous paper, principal components analysis (PCA) with oblimin rotation was conducted on the 21 individual BDI items to obtain fewer factors/components while retaining the original item information (Bus et al., 2010). In short, a two-factor solution appeared to be most optimal compared with the traditional two-factor structure of the BDI, i.e. a factor representing a cognitive-affective symptom cluster and factor representing a somatic-affective symptom cluster (Kaiser–Meyer–Olkin (KMO) measure of sampling adequacy: 0.898; Bartlett’s test of sphericity: $\chi^2=5074$, df=210, p<0.001, explained variance factor 1: 24.3%; factor 2: 7.6%). The association between all primary dependent variables (BDI-I, cognitive-affective symptoms, somatic-affective symptoms) and independent (neuroticism, carotid IMT) were examined by Pearson correlation test.

Subsequently, separate linear regression analyses were conducted with the different measures of depressive symptoms as the dependent variable, i.e. the log-transformed BDI sum score, the cognitive-affective symptom cluster and the somatic-affective symptom cluster. First, we examined the correlation between neuroticism and depression (Model 1). Second, we examined the correlation between the IMT and depression (Model 2). Third, we examined whether neuroticism and the IMT interacted in explaining the variance of depression (Model 3). All models were fully adjusted for the potential confounders described above.

All analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 17.0 (Inc. Chicago, IL).
Results

Of the 1517 subjects who consented to participation in the study of non-invasive measurements of atherosclerosis, 29 subjects were excluded because of a history of stroke. None of the participants was diagnosed with dementia. In addition, 238 (15.3%) subjects were excluded because of missing data caused by the following: not responding to the postal questionnaire containing the BDI (n=181); having three or more missing items on the BDI (n=36); missing data on the EPQ-RSS (n=11); or violating the rules for a reliable measurement of atherosclerotic disease (IMT) or its risk factors (i.e. having smoked before coming to the hospital, n=3; no adherence to non-fasting or light breakfast instructions n=2; and not stopping their lipid lowering medication (n=5).

Table 1 presents the characteristics of the final study population (n=1250). Subjects with missing data (238/1488, 16.0%) differed from subjects included with respect to mean (SD) age (62.3 (5.9) v. 61.0 (5.9) years, t=3.24, df=1492, p=.001), IMT (0.86 (0.13) v 0.84 (0.12) mm, t=2.31, df=1492, p=.021), but not with respect to sex (χ²=0.1, df=1, p=.75), neuroticism (t=-0.2, df=1294, p=.86) and depressive symptoms (t=1.1, df=1259, p=.27).

The Pearson correlation (r) coefficient of the BDI sum score (after log-transformation) was 0.56 (df= 1247, p<.001) with the cognitive–affective symptom cluster and 0.87 (df=1247, p<.001) with the somatic-affective symptom cluster. Neuroticism was associated with both, the sum score of the BDI (r= 0.60, df=1248, p< .001), and the two depressive symptom clusters (cognitive-affective cluster, r= 0.58, df= 1247, p<.001; somatic-affective symptom cluster, r= 0.52, df=1247, p<.001). Finally, we found a significant but modest association between the BDI sum score and the IMT (r= 0.06, df=1248, p= .039). However, the IMT was only associated with the somatic-affective symptom cluster (r= 0.11, df=1247, p<.001), and not with the cognitive-affective symptom cluster (r= -0.05, df=1247, p=.06). Neuroticism and IMT were not significantly associated (r= 0.04, df=1248, p=.19).

As shown in Table 2, the above-described univariate associations between neuroticism and IMT values with the different measures of depression remained statistically significant in a multivariate regression model.

The association between cognitive-affective symptoms and IMT, which approached significance in the univariate analyses, completely lost significance after correction for confounders. Interestingly, we found a significant negative interaction term between the IMT and neuroticism in explaining the variance in the cognitive-affective symptoms (β= -.40, t= -2.66, df=1155, p=.008) but not with either the somatic-affective symptom cluster (β= -.06, t= -0.42, df=1155, p=.678) or the BDI total score (β= -24, t= -1.62, df=1155, p=.106).
Table 1  Baseline characteristics (n=1250).

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Descriptives</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age (years)</td>
<td>mean (SD)</td>
<td>61.0 (5.9)</td>
</tr>
<tr>
<td>• Male sex</td>
<td>n (%)</td>
<td>616 (49)</td>
</tr>
<tr>
<td>• Married or living together</td>
<td>n (%)</td>
<td>975 (78)</td>
</tr>
<tr>
<td>• Higher education</td>
<td>n (%)</td>
<td>510 (41)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychopathology</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• BDI sum score</td>
<td>median (IQR)</td>
<td>4.0 (2.0 – 8.0)</td>
</tr>
<tr>
<td>• BDI sum score ≥10</td>
<td>n (%)</td>
<td>206 (17)</td>
</tr>
<tr>
<td>• History of treated depression</td>
<td>n (%)</td>
<td>242 (19)</td>
</tr>
<tr>
<td>• Use of antidepressants</td>
<td>n (%)</td>
<td>47 (4)</td>
</tr>
<tr>
<td>• Neuroticism score</td>
<td>mean (SD)</td>
<td>3.4 (2.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lifestyle factors</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Smoking:</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>o Never</td>
<td>626 (50)</td>
<td></td>
</tr>
<tr>
<td>o Ever</td>
<td>410 (33)</td>
<td></td>
</tr>
<tr>
<td>o Current</td>
<td>212 (17)</td>
<td></td>
</tr>
<tr>
<td>• Severe alcohol usage</td>
<td>n (%)</td>
<td>146 (12)</td>
</tr>
<tr>
<td>• Physical activity</td>
<td>n (%)</td>
<td>462 (37)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Somatic co-morbidity</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Intima media thickness (mm)</td>
<td>mean (SD)</td>
<td>0.84 (0.12)</td>
</tr>
<tr>
<td>• Metabolic syndrome (IDF)</td>
<td>n (%)</td>
<td>409 (33)</td>
</tr>
<tr>
<td>o Triglycerides (mmol/L)</td>
<td>mean (SD)</td>
<td>1.44 (0.82)</td>
</tr>
<tr>
<td>o HDL-cholesterol (mmol/L)</td>
<td>mean (SD)</td>
<td>1.41 (0.37)</td>
</tr>
<tr>
<td>o Waist circumference (cm)</td>
<td>mean (SD)</td>
<td>94.2 (12.3)</td>
</tr>
<tr>
<td>o Diastolic blood pressure (mmHg)</td>
<td>mean (SD)</td>
<td>78 (11)</td>
</tr>
<tr>
<td>o Systolic blood pressure (mmHg)</td>
<td>mean (SD)</td>
<td>128 (15)</td>
</tr>
<tr>
<td>o Fasting glucose (mmol/L)</td>
<td>mean (SD)</td>
<td>5.2 (0.9)</td>
</tr>
<tr>
<td>o Diabetes mellitus type 2</td>
<td>n (%)</td>
<td>74 (6)</td>
</tr>
<tr>
<td>• Coronary artery disease (yes/no)</td>
<td>n (%)</td>
<td>82 (7)</td>
</tr>
<tr>
<td>• Somatic co-morbidity (0 or 1 versus ≥2)</td>
<td>n (%)</td>
<td>172 (14)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Cardiovascular medication</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>• Diurectics</td>
<td>n (%)</td>
<td>139 (11)</td>
</tr>
<tr>
<td>• Beta blocker</td>
<td>n (%)</td>
<td>199 (16)</td>
</tr>
<tr>
<td>• Calcium antagonist</td>
<td>n (%)</td>
<td>44 (4)</td>
</tr>
<tr>
<td>• ACE inhibitor</td>
<td>n (%)</td>
<td>93 (7)</td>
</tr>
<tr>
<td>• Angiotensin II antagonist</td>
<td>n (%)</td>
<td>45 (4)</td>
</tr>
<tr>
<td>• Nitrate</td>
<td>n (%)</td>
<td>14 (1)</td>
</tr>
<tr>
<td>• Other</td>
<td>n (%)</td>
<td>24 (2)</td>
</tr>
</tbody>
</table>

**Abbreviations:** SD, standard deviation; n, number of participants; BDI, Beck Depression Inventory; IQR, Interquartile Range. IDF, International Diabetes Foundation; HDL, high-density lipoprotein
Table 2  Regression of neuroticism, intima-media thickness and their interaction on different measures of depressive symptoms assessed with the Beck Depression Inventory (BDI).

<table>
<thead>
<tr>
<th>BDI Log (sum score BDI)</th>
<th>Factor scores BDI</th>
<th>Cognitive-affective</th>
<th>Somatic-affective</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>β</td>
<td>P value</td>
</tr>
<tr>
<td>Model 1 *</td>
<td></td>
<td>.54</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neuroticism</td>
<td></td>
<td>.54</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Model 2 *</td>
<td></td>
<td>.06</td>
<td>.040</td>
</tr>
<tr>
<td>Intima-media thickness (IMT)</td>
<td></td>
<td>.06</td>
<td>.040</td>
</tr>
<tr>
<td>Model 3 * #</td>
<td></td>
<td>.54</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neuroticism</td>
<td></td>
<td>.54</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IMT</td>
<td></td>
<td>.02</td>
<td>.49</td>
</tr>
<tr>
<td>Interaction neuroticism – IMT</td>
<td></td>
<td>not significant</td>
<td>-.40</td>
</tr>
</tbody>
</table>

* All linear regression analyses are based on a final sample of 1179 participants; significance of beta's are based on t-statistics, with 1157 degrees of freedom in model 1 and 2 and, 1155 in model 3 in case of a significant interaction term and 1156 in case the interaction term was not significant.

All models are adjusted for age, sex, married or living together, higher education, history of treated depression, use of antidepressants, smoking (dummy: never, ever, current), severe alcohol usage, sport moments, metabolic syndrome according to the IDF, presence of coronary artery disease, presence of chronic co-morbid somatic diseases, cardiovascular medication (antihypertensives, ACE inhibitors, calcium channel blockers, betablockers, nitrates, diuretics and analgesics.)

# In case of non-significant interaction terms, the interaction term was removed from the model and runned again

In Figure 1, we have visualized the interaction effects between neuroticism and IMT by presenting the estimated marginal mean values of the different depressive symptoms scores adjusted for covariates and stratified by neuroticism score (highest quartile versus others) and IMT values (highest quartile versus others). Please note that the estimated marginal mean for the BDI sum score was calculated on the Log-transformed, whereas in the figure we present the inverse log (enabling interpretation of the absolute values).
Figure 1  Depressive symptom scores by IMT and neuroticism status (i.e. highest quartile vs others; bars represent estimated marginal mean values with error bars representing the 95% confidence interval based on the standard error of the mean).

Abbreviations: IMT, Intima Media Thickness; BDI, Beck Depression Inventory.

Statistics:
- All overall ANCOVAs are significant: for BDI sum score (F=75.7; df=3,1156; p<.001), for cognitive-affective BDI factor score (F=102.5; df=3,1156; p<.001), and for somatic-affective BDI factor score (F=67.2; df=3,1156; p<.001).
- Post-hoc t-tests restricted to subjects with high neuroticism scores, showed that subjects with high IMT values differed significantly from those with low IMT values with respect to the BDI sum score (t=3.05, df=239, p=.003) and the cognitive-affective BDI factor score (t=11.10, df=239, p<.001), but not with respect to the somatic-affective BDI factor score (t=-0.75, df=239, p=.46).
Discussion

Main findings
Neuroticism is strongly associated with the total number of depressive symptoms, and with both cognitive-affective and somatic-affective symptoms, whereas the somatic affective symptom cluster specially drives the association between depression and subclinical atherosclerosis. Nevertheless, we found a negative interaction between neuroticism and atherosclerosis in explaining the cognitive-affective symptoms of depression. In line with our hypothesis, the effect of neuroticism in explaining depressive symptoms diminishes in the presence of more severe atherosclerosis. A possible explanation for these results is the hypothesis that cerebrovascular disease may cause apathy, which in turn decreases the association between neuroticism and depression. Below we will discuss this hypothesis in context of previous findings in the literature.

Comparison with the literature
The vascular depression hypothesis has stimulated research into the biological predictors of late-life depression, thereby often paying less attention to other theories of depression (Sneed et al, 2011). Neuroticism is strongly related to depression (Kendler et al, 2006), although limited data are available with respect to middle aged and older people (Steunenberg et al, 2005). Interestingly, our results show that the association between neuroticism and the somatic-affective symptom cluster is of similar strength as the association between neuroticism and the cognitive-affective symptom cluster. Because previous studies show that neuroticism is not significantly affected by physical health (Steunenberg et al, 2005), we may conclude, having corrected for somatic comorbidity, that neuroticism is associated with those somatic symptoms that are intrinsically part of the depressive syndrome. Nevertheless, neuroticism only interacted with atherosclerosis in the association with cognitive-affective symptom cluster. We hypothesize this to be caused by apathy due to cerebrovascular atherosclerosis. Neuroticism is a trait-characteristic that closely resembles the cognitive domain of depression. This contributes to the strong correlation between neuroticism and depressive symptoms. Nevertheless, in case of a higher level of atherosclerosis, the association between neuroticism and cognitive-affective symptoms becomes less pronounced (Wouts et al, 2011). We hypothesize this to be due to apathy as a result of vascular damage to the frontostriatal pathways (Kim et al, 2011; Murakami et al, 2013). Support for this second possibility is provided by comparable results found by our group in another sample (Wouts et al, 2011) and by the fact that levels of neuroticism were less pronounced in late-onset compared to early-onset late-life depression (Sneed et al, 2011).
The relationship between atherosclerosis, depression and apathy is complicated and has relatively rarely been studied. In 1997, two research groups independently proposed the vascular depression hypothesis (Alexopoulos et al, 1997; Krishnan et al, 1997). This hypothesis postulates that cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes. Until now, the evidence for a real distinctive disorder remains limited with many inconsistent results (Baldwin et al, 2005). Most likely, cerebrovascular disease, especially deep white matter hyperintensities are associated with neuropsychological deficits, which not only predispose elderly people to depression, but also shape the depressive phenotype. Decreased processing speed and executive dysfunction have been identified as the two underlying neuropsychological core deficits (Sheline et al, 2008). Subsequently, the depression executive dysfunction (DED) syndrome has been introduced (Alexopoulos, 2005), validated by both treatment resistance of the DED syndrome (Alexopoulos et al, 2004) and by persisting cognitive deficits in case of remitted depression (Kohler et al, 2010). Executive dysfunction, however, has been consistently linked with atherosclerosis and vascular disease (Lamar et al, 2009/2010). Interestingly, directly after launching the vascular depression hypothesis in the literature, it has been suggested that vascular brain disease would be more specific for apathy than for depression (Fones et al, 1998). Although the association between executive functioning and apathy has hardly been examined, both constructs appear to be associated with each other in Alzheimer’s disease (Esposito et al, 2010). Interestingly, in line with our findings, Archer et al (2007) found that the presence of Alzheimer’s disease attenuated the association between neuroticism and depression.

Studies examining both depression and apathy in relation to vascular disease show a relationship with both syndromes (Withall et al, 2011) or with apathy only (Van der Mast, 2008; Sugawara et al, 2010). Atherosclerosis at baseline did not predict incident depression in older adults in a large prospective, population-based study (Newson et al, 2010). We propose that cerebrovascular disease will lead to neuropsychological deficits that are more specifically linked with apathy than with depressed mood per se.

Methodological considerations

The strengths of the present study are the large sample size and reliable measures of depressive symptom clusters and subclinical atherosclerotic disease in middle-aged and older people at risk of cerebrovascular disease but prior to clinical stroke.

As explanation for our findings we postulate a hypothesis of vascular apathy. Unfortunately, apathy was not directly measured and to our knowledge, the relationship between cognitive-affective symptoms of depression and apathy has not been studied yet. From a clinical perspective, it is conceivable that apathy is associated with indif-
ference and lower cognitive activity like rumination, worrying or suicidal thoughts. On the other hand, we also need to acknowledge that the absence of cognitive-affective symptoms in apathy is only part of the apathy-syndrome as recently defined by consensus (Robert et al, 2009). Some minor limitations should be addressed. First, we assessed the IMT as measure for generalised atherosclerosis. Although it is assumed that the IMT in the common carotid arteries is highly associated with cerebrovascular disease (Cao et al, 2003) we did not directly assess (subclinical) cerebrovascular disease by neuroimaging. Nonetheless, IMT is widely used as a surrogate marker of subclinical atherosclerosis nowadays. Several studies reported about the predictive value of IMT in cardiovascular risk stratification and IMT has been depicted as a strong predictor of future vascular events (see Holewijn et al, 2009). Second the cross-sectional design of this study does not allow our results to be interpreted causally. To date, no prospective studies are available relating neuroticism and vascular disease to depressive symptoms or symptoms clusters in concert. Third, we used a population sample, so bias towards the most healthy people may have occurred, resulting in less (advanced) atherosclerosis and depressive symptoms. This may have resulted in less overall variance of the atherosclerosis and depression measures and also lowered the variance explained by the factors found.

**Final conclusion and clinical implications**
The present study illustrates the complexities of late-life depression on different levels. Within the clinical setting depression and apathy can be hard to distinguish and may frequently overlap. Research paradigms on late-life depression, shift from the importance of vascular disease to more complex neuropsychological deficits (especially executive dysfunctions) (Alexopoulos, 2005). Nevertheless, within an randomized controlled trial on late-life depression, both vascular disease and executive dysfunction were correlated as well as independently associated with a worse prognosis and slower time to response (Alexopoulos et al, 2004). As shown by our study, personality traits like neuroticism should be included in examining late-life depression as the strong relationship between neuroticism and depression changes dependent on the presence of vascular disease, probably due to the emergence of apathy.
References
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Atherosclerosis and neuroticism in late-life depression


