Late-life depression in context of low neuroticism is risk factor for stroke: a 9-year cohort study

In press

Depression in context of low neuroticism is risk factor for stroke: a 9-year cohort study


Neurology
Abstract

Objectives – Depression predicts stroke, however meta-analyses show significant heterogeneity. We hypothesise that the risk of depression on incident stroke is conditional upon the relative contribution of vascular disease and of neuroticism in the underlying pathways to depression in a specific patient. We examined whether depression increases stroke in persons with low neuroticism and without pre-existing cardiac disease.

Methods – Population-based cohort study with 9-year follow-up (n=2050; ≥ 55 years, 52% female). The incidence of stroke was determined by self-report data as well as data from general practitioners and death-certificates. Neuroticism was measured using the Dutch Personality Questionnaire (DPQ) and depression using the Center for Epidemiological Studies-Depression Scale (CESD). All data were analysed by Cox proportional hazards regression.

Results – 117 incident cases of stroke occurred during follow-up. Among persons with a history of cardiac disease (n=401), depression predicted incident stroke independent of neuroticism-level with a hazard rate (HR) of 1.05 [95% CI: 1.01 – 1.10] (p=.02). In persons without cardiac disease (n=1649), depression and neuroticism interacted significantly in predicting incident stroke (p=.028). Stratified analyses showed that depression predicted incident stroke in those with low neuroticism: HR =1.05 [95% CI: 1.00 – 1.09] (p=.033), but not in those with high neuroticism: HR =1.01 [95%: 0.96 – 1.05] (p=.82).

Conclusions - In persons without pre-existent cardiac disease, depression is only predictive for future stroke in absence of high neuroticism. This might be explained by the hypothesis that late-life depression in context of low neuroticism is a marker of subclinical vascular disease.

Keywords

Stroke; Subclinical vascular disease; Cardiac disease; Depression; Neuroticism.
Introduction

Late-life depression is not only a common and disabling condition in later life, it also predicts the onset of major medical illnesses, such as stroke (van der Kooy et al, 2007; Wouts et al, 2008; Taylor et al, 2013; Valkanova et al, 2013). Depression is driven by multiple etiological factors, including personality (such as neuroticism) (Steunenberg et al, 2006) and vascular factors (Sneed et al, 2008; Ormel et al, 2011; Taylor et al, 2013). Especially among older people, both of these pathways may act to a certain degree in individual patients. Therefore, the degree to which depression is a predictor of incident stroke might be conditional on the relative weight of vascular disease (so called ‘vascular depression’) and of neuroticism (so called ‘neurotic-depression’) as the underlying pathways to depression.

Meta-analyses indeed show that late-life depression is prospectively associated with stroke (Pan et al, 2011; Valkanova et al, 2013). Nonetheless, the same meta-analyses point to significant heterogeneity across studies (Pan et al, 2011), which has not been explained properly yet (Pan et al, 2011). Recently, it was found that depression in the oldest-old does not increase stroke risk, but still is a risk factor for all-cause mortality (Kohler et al, 2013). The effects of depression on stroke risk may be due to residual confounding by the severity of subclinical vascular disease (de Jonge et al, 2012). Many older persons without a history of ischaemic heart disease or stroke do have a significant level of vascular pathology in the presence of generalised atherosclerosis. Recently, we have shown that the intima media thickness of the carotid artery, a marker for generalised atherosclerosis, is associated with depressive symptoms, even in the absence of a history of vascular events (Bus et al, 2011). This association, however, was confined to the somatic-affective symptoms domain of depression, which may indeed point to overlap or confounding between subclinical vascular disease and depression (Bus et al, 2011). Interestingly, incident depression after a myocardial infarction also predicted a poorer prognosis of heart disease, whereas recurrent depression as well as depression associated with a high level of neuroticism did not (Spijkerman et al, 2005; de Jonge et al 2006; Dickens et al, 2008). These findings fit with the hypothesis that the risk of depression on future vascular events is conditional upon depressive symptoms related to underlying vascular disease and not upon ‘neuroticism-associated’ depression.

In the Longitudinal Aging Study Amsterdam (LASA), we have shown that depression only predicted incident stroke in older persons with pre-existing cardiac disease (Wouts et al, 2008). A logical explanation would be that in non-cardiac patients the contribution of vascular disease burden to depression is minimal and other pathways like high levels
of neuroticism may be more important. Nonetheless, this explanation does not fully fit with the abovementioned findings that depression is also associated with subclinical vascular disease (Bus et al, 2011). The present study, therefore, is an extension of our previous findings in LASA (Wouts et al, 2008).

We assume that the association between depression and vascular events is confounded by underlying vascular disease in later life and that this may differ for different subtypes of depression (vascular versus neurotic-associated depression). The aim of this study was to examine whether a lower level of neuroticism in depressed older persons without pre-existing cardiac disease indeed would be associated with an increased risk of stroke in LASA. We a priori hypothesise that vascular depression, defined theoretically by a high aetiological contribution of vascular disease, increases the risk on future strokes, whereas ‘neuroticism-associated’ depression does not.

**Methods**

*Study design and population*

This study was performed as part of the Longitudinal Aging Study Amsterdam (LASA). LASA is a prospective cohort study focusing on physical functioning and wellbeing of an older (≥ 55 years) population (N=3107). LASA started in 1992/93, with follow-up measurements every three years and its methods have been described in more detail elsewhere (see Beekman et al, 1995; Beekman et al, 2002). For this particular study 9 years of follow-up data were available. Eligible were those participants without a history of stroke (n=3018, 97.1%) allowing us to study incident stroke and availability of baseline data on depressive symptoms (missing for 51 participants) and stroke (missing for 2 participants). Of these 2965 eligible LASA participants, 915 participants had no data on neuroticism, leaving a final sample of 2050 participants. The number of missing measurements on neuroticism was high because of the method of measurement: participants were asked to return a self-report questionnaire on neuroticism after being interviewed. Table 1 presents the baseline characteristics for those participants with and without data on neuroticism.

*Standard protocol approvals, registrations, and patient consents*

All participants of LASA completed an informed consent after oral and written information. The Medical Ethics committee of the VU University Medical Center approved the study design and procedures.
**Variables of interest**

**Stroke morbidity and mortality** - Non-fatal stroke was assessed using an algorithm based on the 3-yearly prospective interviews and GP-information (as in the Netherlands all patients are linked to only one GP who receives all medical information from specialists). Previously, a LASA-study showed that self-report information on stroke was reasonably moderately accurate when compared with GP-information (concordance: \( \kappa = 0.56; \ CI \ 0.48-0.64 \)) and that concordance did not covary with level of depressive symptoms of patients (Kriegsman et al, 1996). We considered a stroke to have occurred if self-reported and GP information was consistent or if a medical specialist had confirmed the GP diagnosis of stroke.

Fatal stroke was defined as an ICD-9 codes 431, 433, 434 and 436 and ICD-10 codes I-61,I-63 and I-64 on the death certificates registered by the Netherlands Central Bureau of Statistics. These were 100% complete.

The primary outcome, time to stroke, is calculated for non-fatal stroke as the time between baseline and halfway the year for which the stroke has been reported, for fatal stroke the exact time between baseline and death.

**Depression** - Depressive symptoms were measured using the self-report Center for Epidemiologic Studies Depression scale (CESD). All 20-items refer to the past-week and are scored on a 4-point scale (range sum score 0-60). The psychometric properties of the scale were found to be good in older populations and overlap with symptoms of physical illness is minimal (Beekman et al, 1997). A score of \( \geq 16 \) indicates clinically relevant depressive symptoms (Beekman et al, 1997). In LASA, the cut-off of 16 or higher had a sensitivity of 100% and a specificity of 88% for major depressive disorder according to DSM-IV-criteria (Berkman et al, 1986).

**Neuroticism** - Neuroticism is a personality trait that is stable across the life span and not affected by physical health status (Steunenberg et al, 2007). People with a high level of neuroticism are sensitive to negative stimuli (Tellegen et al, 1985), causing emotional instability and negative moods like anxiety, sadness, guilt, hostility and self-dissatisfaction(Watson et al, 1984; Steunenberg et al, 2007). Neuroticism was measured using the Dutch Personality Questionnaire (DPQ) (Luteijn et al, 2000). Pilot-studies before LASA started showed that the original scale of 36 items could be abbreviated without loss of validity or reliability (Smits et al, 1995; Steunenberg et al, 2003). These DPQ items have strong negative relations with the Emotional Stability-Scale of the NEO-PI-R (Luteijn et al, 2000). The DPQ asks respondents if statements apply to them; possible answers are yes/do not know/ no. Scores range between 0 and 50.
Cardiac disease - As previously described (Wouts et al, 2008); ‘Cardiac disease was defined as myocardial infarction, congestive heart failure, angina pectoris, or cardiac arrhythmia and established at baseline using an algorithm used earlier in LASA (Bremmer et al, 2006). This algorithm uses 3 sources of information: self-reported, medication, and GP information. We considered only 1 confirmative source necessary for diagnosis because self-reported cardiac disease is sufficiently accurate in LASA (concordance with GP: κ=0.69; 95% CI, 0.65-0.73) (Beekman et al, 1997).‘

Covariates
Age, sex, general health-related variables (functional limitations and cognitive impairments) and established stroke risk factors (smoking, obesity, diabetes mellitus, hypertension) were considered potential confounders and as such included in the analyses (Berkman et al, 1986).
Functional limitations were scored as none, 1 or ≥2, using a 3-item questionnaire (van Sonsbeek et al 1988). Cognition was measured with the Mini Mental State Examination (MMSE) (Folstein et al, 1975). The variable smoking included current smoking. Obesity was defined as a body mass index of 30 kg/m² or greater (Ogden et al, 2007). Diabetes mellitus (yes/no) was based on self-report data, the use of antidiabetic agents or a GP diagnosis (Kriegsman et al, 1996). Blood pressure (mmHG) with an oscillometric blood pressure monitor (model HEM-706; Omron Corporation, Tokyo, Japan) after 5 minutes of rest. Out of the three measurements, a mean systolic blood pressure of 140-159 mm Hg or a mean diastolic blood pressure of 90-99 mm Hg was categorized as stage 1 hypertension. A mean systolic blood pressure of ≥ 160 mm Hg or a mean diastolic blood pressure of ≥ 100 mm Hg was categorized as stage 2 hypertension (Chobanian et al, 2003). Antidepressant use was established by visually checking all of the participants’ medications during interview at their homes.

Statistical methods
Differences between groups were explored by calculating descriptive statistics (e.g. means, standard deviations, frequencies) and performing t-tests for continuous measures with normal distributions, Mann-Whitney U-tests for continuous measures with skewed distributions and Chi-Square tests for categorical variables.
We checked the primary variables for normality, collinearity and proportionality of hazards. Neuroticism was not normally distributed, therefore we classified respondents as low or high on neuroticism based on the median split (< ≥5) in order to prevent that influential outliers cause results. We also performed sensitivity analyses by repeating all analyses on the log-transformed continuous neuroticism score.
The predictive effect of depression on incidence of stroke was tested with multiple
Late-life depression, neuroticism and the risk for stroke

Cox-regression analyses with time to a fatal or non-fatal stroke as the dependent variable and corrected for age, sex, global cognitive functioning (MMSE-score), one or more functional limitations, smoking, hypertension (stage 1 or 2), diabetes mellitus, and obesity. Depression was examined both as a continuous measure based on the CESD total sum score as well as dichotomised (≥16), indicative of clinically relevant depressive symptoms.

We first checked for an interaction between depression and the presence of cardiac disease using Cox-proportional hazards regression models with stroke as the dependent variable. In the fully adjusted models, the hazard rate (HR) for clinically relevant depressive symptoms by cardiac disease status was 4.03 [95% confidence interval (CI): 1.22 – 13.28] (p=.022) and HR for severity of depressive symptoms by cardiac disease status was 1.06 [95% CI: 1.01 – 1.11] (p=.032). Therefore, all analyses will be stratified for baseline cardiac disease status.

For the objective of the present chapter we examined interaction terms between depression and neuroticism on incidence of stroke when stratified for pre-existing cardiac disease using multiple Cox-regression analyses. In case of significant interactions with neuroticism, results will be presented separately for participants with low and high neuroticism scores. All analyses were conducted in SPSS for Mac, 2011. We considered p-values <.05 as significant.

Results

Baseline characteristics
The mean (SD) age of the 2050 study participants was 69.3 (8.5) years and 1046 (51.0%) were women (see Table 1). At baseline 261 (12.7%) participants suffered from clinically relevant depressive symptoms, whereas the median neuroticism score was 4.0 (interquartile range 7.0). A total of 117 incident strokes occurred during follow-up, resulting in an overall stroke rate of 7.0 per 1000 person years. Table 2 presents the baseline characteristics by cardiac disease status.

Results by level of neuroticism
Table 3 shows the effect of depression and neuroticism on the onset of stroke in patients with and without cardiac disease separately. Adjusted for covariates, the interaction term of neuroticism (median split) by depression was only significant in patients without cardiac disease.

Removing the interaction term from analyses within those participants with cardiac disease (n=401) showed that depression predicted incident stroke (HR depressive
Table 1  Characteristics of included patients versus those with missing data on neuroticism.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Included (n=2050)</th>
<th>Excluded (n=915)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>69.3 (8.5)</td>
<td>73.2 (8.6)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>1046 (51.0)</td>
<td>500 (54.6)</td>
</tr>
<tr>
<td>Female sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1046 (51.0)</td>
<td>500 (54.6)</td>
</tr>
<tr>
<td>Cognitive functioning (MMSE score)</td>
<td>Mean (SD)</td>
<td>27.5 (2.3)</td>
<td>25.9 (3.6)</td>
</tr>
<tr>
<td>Depressive symptoms (CESD score)</td>
<td>Mean (SD)</td>
<td>7.4 (7.4)</td>
<td>8.9 (8.4)</td>
</tr>
<tr>
<td>One or more functional limitations</td>
<td>n (%)</td>
<td>728 (35.7)</td>
<td>445 (49.3)</td>
</tr>
<tr>
<td>Smoking (yes)</td>
<td>n (%)</td>
<td>477 (24.4)</td>
<td>171 (27.7)</td>
</tr>
<tr>
<td>Stage 1 or 2 hypertension</td>
<td>n (%)</td>
<td>479 (24.9)</td>
<td>144 (23.6)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>n (%)</td>
<td>401 (19.6)</td>
<td>210 (23.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>n (%)</td>
<td>224 (10.9)</td>
<td>134 (14.7)</td>
</tr>
<tr>
<td>Obesity</td>
<td>n (%)</td>
<td>323 (17.6)</td>
<td>134 (21.6)</td>
</tr>
<tr>
<td>Use of antidepressants</td>
<td>n (%)</td>
<td>37 (1.9)</td>
<td>12 (1.9)</td>
</tr>
<tr>
<td>Incident stroke</td>
<td>n (%)</td>
<td>117 (5.7)</td>
<td>59 (6.4)</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; n, number of participants; MMSE, Mini Mental State Examination; CESD, Center for Epidemiologic Studies Depression scale.
Table 2  Characteristics of included patients by cardiac disease status.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No cardiac disease (n=1649)</th>
<th>Cardiac disease (n=410)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Mean (SD)</td>
<td>68.6 (8.4)</td>
<td>72.4 (8.3)</td>
<td>t=-8.1, df=2048, p&lt;.001</td>
</tr>
<tr>
<td>Female sex n (%)</td>
<td>889 (53.9)</td>
<td>157 (39.2)</td>
<td>χ²=28.1, df=1, p&lt;.001</td>
</tr>
<tr>
<td>Cognitive functioning (MMSE score) Mean (SD)</td>
<td>27.5 (2.3)</td>
<td>27.2 (2.4)</td>
<td>t=2.7, df=2048, p=.007</td>
</tr>
<tr>
<td>Depressive symptoms (CESD score) Mean (SD)</td>
<td>7.1 (7.2)</td>
<td>8.9 (8.3)</td>
<td>t=-4.4, df=2048, p&lt;.001</td>
</tr>
<tr>
<td>Neuroticism (DPQ score) median (IQR)</td>
<td>4.0 (7.0)</td>
<td>5.0 (9.0)</td>
<td>Z=-2.4, p=.018</td>
</tr>
<tr>
<td>One or more functional limitations n (%)</td>
<td>520 (31.7)</td>
<td>208 (52.4)</td>
<td>χ²=59.6, df=1, p&lt;.001</td>
</tr>
<tr>
<td>Smoking (yes) n (%)</td>
<td>384 (24.6)</td>
<td>93 (23.8)</td>
<td>χ²=0.1, df=1, p=.752</td>
</tr>
<tr>
<td>Stage 1 or 2 hypertension n (%)</td>
<td>398 (25.8)</td>
<td>81 (21.0)</td>
<td>χ²=3.8, df=1, p=.052</td>
</tr>
<tr>
<td>Diabetes mellitus n (%)</td>
<td>159 (9.6)</td>
<td>65 (16.2)</td>
<td>χ²=14.3, df=1, p&lt;.001</td>
</tr>
<tr>
<td>Obesity n (%)</td>
<td>251 (17.0)</td>
<td>72 (20.1)</td>
<td>χ²=2.0, df=1, p=.160</td>
</tr>
<tr>
<td>Use of antidepressants n (%)</td>
<td>32 (2.0)</td>
<td>5 (1.3)</td>
<td>χ²=1.0, df=1, p=.319</td>
</tr>
<tr>
<td>Incident stroke n (%)</td>
<td>85 (5.2)</td>
<td>32 (8.0)</td>
<td>χ²=4.8, df=1, p=.029</td>
</tr>
</tbody>
</table>

Abbreviations: Mean, standard deviation; n, number of participants; SD, standard deviation; MMSE, Mini Mental State Examination; CESD, Center for Epidemiologic Studies Depression scale; DPQ, Dutch Personality Questionnaire; IQR, Interquartile Range.
CHAPTER 7

symptoms = 1.05 [95% CI: 1.01 – 1.10], p=.020; HR clinically relevant depressive symptoms = 2.08 [95% CI: 0.93 – 4.63], p=.075, respectively), whereas neuroticism did not (HR = 1.06 [95% CI: 0.47 – 2.38], p=.88 and HR = 1.23 [95% CI: 0.57 – 2.68], p=.60, respectively). Neuroticism was not identified as an independent predictor of stroke risk in any of the models (all p-values >.05).

Stratified analyses by neuroticism status in participants without cardiac disease (n=1649), showed that when adjusted for covariates depression predicted incident stroke in those with low neuroticism (n=838): HR depressive symptoms = 1.05 [95% CI: 1.00 – 1.09] (p=.033) and HR clinically relevant depressive symptoms = 4.53 [95% CI: 1.72 – 11.9] (p=.002), respectively, but not in those with high neuroticism (n=811): HR depressive symptoms = 1.01 [95% CI: 0.96 – 1.05] (p=.82) and HR clinically relevant depressive symptoms = 0.78 [95% CI: 0.30 – 2.06] (p=.62), respectively. See Figure 1. Figure 1 presents the absolute stroke rates per 1000 person years by depression and neuroticism status in patients with no cardiac history (n=1649).

Stratifying on dichotomised CESD-scores and neuroticism scores (as done for figure 1) results in low numbers per group. In the non-depressed group (n=1463), 5.2% (42/805) of persons with low neuroticism had an incident stroke and 5.0% (33/658) of persons with high neuroticism. In the depressed group (n=186), 15.2% (5/33) of persons with low neuroticism had an incident stroke and 3.3% (5/153) of persons with high neuroticism.

As dichotomised data are more prone for chance findings, we also re-analysed the data using 10Log transformation of neuroticism and the sum score of the CESD. These analyses fully supported the results (data not shown).
Table 3  Models for Stroke which include interaction neuroticism (median split) by depression*.

<table>
<thead>
<tr>
<th></th>
<th>No cardiac disease</th>
<th></th>
<th>Cardiac disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>[95% CI]</td>
<td>P value</td>
<td>HR</td>
</tr>
<tr>
<td>Model 1:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CESD score</td>
<td>1.12</td>
<td>[1.03 – 1.22]</td>
<td>.008</td>
<td>0.97</td>
</tr>
<tr>
<td>• Neuroticism</td>
<td>1.06</td>
<td>[0.57 – 1.98]</td>
<td>.854</td>
<td>0.74</td>
</tr>
<tr>
<td>• CESD by Neuroticism</td>
<td>0.94</td>
<td>[0.89 – 0.99]</td>
<td>.028</td>
<td>1.05</td>
</tr>
<tr>
<td>Model 2:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CESD score ≥16</td>
<td>42.6</td>
<td>[5.23 – 347]</td>
<td>&lt;.001</td>
<td>0.37</td>
</tr>
<tr>
<td>• Neuroticism</td>
<td>0.85</td>
<td>[0.54 – 1.35]</td>
<td>.484</td>
<td>1.04</td>
</tr>
<tr>
<td>• CESD by Neuroticism</td>
<td>0.12</td>
<td>[0.03 – 0.45]</td>
<td>.002</td>
<td>2.60</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, cognitive functioning, smoking, obesity, diabetes mellitus, functional limitations and hypertension. 
Abbrevations: CESD, Center for Epidemiologic Studies Depression scale.

Figure 1  Absolute stroke rates per 1000 person years by depression and neuroticism status in patients with no cardiac history (n=1649).
Discussion

Main findings
In older persons without pre-existent cardiac disease, depression only predicts the onset of stroke over a 9-year follow-up in case of low neuroticism scores. Although we did not directly measure the level of subclinical vascular disease with imaging techniques, this finding may be explained by the presence of subclinical cardio- as well as cerebrovascular disease for the following reasons. Atherosclerosis generally develops over years, with the ultimate outcome of a cardiac or cerebrovascular event (Ross et al, 1993). Nonetheless, subclinical vascular disease is also associated with (specific) depressive symptoms (Bus et al, 2011). In case atherosclerosis first gives rise to an increased depressive symptom score, depression will emerge as a predictor for stroke in observational cohort studies. How does this theory fit with our results? First, our finding that depression increases the risk for stroke in patients with cardiac disease is in line with the theory that depressive symptoms in this population partly reflect the severity of underlying subclinical vascular disease (Ormel et al, 2011; de Jonge et al, 2012). In people without pre-existing cardiac disease, neuroticism may be assumed to be the most important pathway to depression (so called neurotic-depression) (Marijnissen et al, 2014). Nonetheless, in this group, several persons do have low neuroticism scores that by definition cannot have contributed to their depression. In this group, depressive symptoms may be a sign (or epiphenomenon) of subclinical vascular disease. Indeed, this hypothesis fits with our finding that depression in the presence of low neuroticism scores predicts the onset of stroke in these persons without manifest cardiac disease.

The interplay between neuroticism, vascular disease and depression is complex. Cross-sectional studies show that the association between depression and neuroticism is weaker in patients with vascular disease (Wouts et al, 2011; Marijnissen et al, 2014). Prospective studies studying the effect of neuroticism and depression on the incidence of stroke in concert are lacking. Nonetheless, some studies suggest that high levels of neuroticism may increase risk on vascular events. In the Swedish Twin Register, neuroticism predicted the development of coronary heart disease over 25 years of follow-up, but significance was lost after controlling for familial influences (Charles et al, 2008). In the UK Health and Lifestyle Survey, neuroticism predicted cardiac mortality, but not death from stroke (Shipley et al, 2007). In the Chicago Health and Aging Project, a psychosocial composite score including items of neuroticism was associated with an increased risk on stroke over and above the classical vascular risk factors for stroke.
(Henderson et al, 2013). As this composite score also included items of depression, perceived stress and life dissatisfaction, the net effect of neuroticism remains unknown. In summary, it is most likely that neuroticism by itself is not related to vascular health, as was found in our study.

**Methodological considerations**

Three limitations should be taken into account. First, there was a selective dropout at baseline, as persons with missing neuroticism scores were more depressed and more vascular comprised. This might have reduced the power of the results in the cardiac subgroup in which no differential impact of depression by neuroticism status could be demonstrated. Effects for the non-cardiac subgroup are difficult to estimate, but most likely, results are conservative.

Secondly, biological markers of physical diseases have not been measured extensively. Previous papers on LASA, however, have confirmed good validity and high accuracy of our interview and algorithms used to classify the presence or absence of disease states (Kriegsman et al, 1996; Bremmer et al, 2006). Nonetheless, many patients have asymptomatic atrial fibrillation in later life, which may have underestimated our prevalence of cardiac arrhythmias (Prystowsky et al, 2010).

Thirdly, the number of participants with a stroke within subgroups was rather low, especially in the subgroup of non-depressed, non-cardiac patients. Therefore, confirmation in other samples seems relevant in order to rule out chance findings. Nonetheless, our findings within subgroups categorised by depression (yes/no) and neuroticism (high/low) status, were confirmed by analyses using depressive symptoms and neuroticism dimensionally.

**Clinical implications**

Neuroticism and vascular disease are two major vulnerability factors in late-life depression (Steunenberg et al, 2007; Wouts et al, 2011; Taylor et al, 2013). Depressed patients with high levels of neuroticism are more likely to benefit from classical antidepressant treatment strategies, compared to depressed patients with higher level of vascular disease (Alexopoulos et al, 2004; Kohler et al, 2010). These latter patients are also at increased risk of future health events like stroke (Wouts et al, 2008) and might benefit from optimising vascular disease-management including lifestyle intervention like walking or running. Therefore, replication studies as well as randomised controlled studies on the surplus of vascular screening in non-neurotic depressed older patients without known vascular disease are warranted.
Final conclusion

In summary, the results of our study suggest that in depressed older persons without a history of clinically overt vascular disease, persons with a low level of neuroticism have a higher risk of developing stroke, compared to those with a high level of neuroticism. These results support the idea that neurotic depression is a different type of depression than depression associated with vascular disease. Moreover, late-life depression in the context of low neuroticism might be a marker of vascular depression. This can be explained by subclinical vascular disease, in line with previous findings of an association between measures of generalised atherosclerosis and depressive symptoms in the population (Bus et al, 2011).
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