Depression in context of low neuroticism is a risk factor for stroke

A 9-year cohort study

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ABSTRACT

Objective: Depression predicts stroke; however, meta-analyses show significant heterogeneity. We hypothesize 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 preexisting cardiac disease.

Methods: This was a population-based cohort study with 9-year follow-up ($n = 2,050$; ≥ 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 and depression using the Center for Epidemiologic Studies–Depression scale. All data were analysed by Cox proportional hazards regression.

Results: A total of 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 ratio (HR) of 1.05 (95% confidence interval [CI] 1.01–1.10) ($p = 0.02$). In persons without cardiac disease ($n = 1,649$), depression and neuroticism interacted significantly in predicting incident stroke ($p = 0.028$). Stratified analyses showed that depression predicted incident stroke in those with low neuroticism, HR 1.05 (95% CI 1.00–1.09) ($p = 0.033$), but not in those with high neuroticism, HR 1.01 (95% CI 0.96–1.05) ($p = 0.82$).

Conclusions: In persons without preexistent 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.

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GLOSSARY

CES-D = Center for Epidemiologic Studies–Depression scale; **CI** = confidence interval; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **GP** = general practitioner; **HR** = hazard ratio; **ICD** = International Classification of Diseases; **LASA** = Longitudinal Aging Study Amsterdam; **MMSE** = Mini-Mental State Examination.

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.^{1–4} Depression is driven by multiple etiologic factors, including personality (such as neuroticism)⁵ and vascular factors.^{2,6,7} 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 (vascular depression) and of neuroticism (neurotic depression) as the underlying pathways to depression.

Meta-analyses show that late-life depression is prospectively associated with stroke.^{3,8} Nonetheless, same meta-analyses point to significant heterogeneity across studies,⁸ which have not been explained properly.⁸ Recently, it was found that depression in the oldest-old does not increase stroke risk, but is a risk factor for all-cause mortality.⁹ The effects of depression on stroke risk may be due to residual confounding by severity of subclinical vascular disease.¹⁰

Editorial, page 1688

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Many older persons without a history of ischemic heart disease or stroke have a significant level of vascular pathology in presence of generalized atherosclerosis. Recently, we have shown that the intima-media thickness of the carotid artery, a marker for generalized atherosclerosis, is associated with depressive symptoms, even in the absence of a history of vascular events.¹¹ This association, however, was confined to the somatic-affective symptoms domain of depression, which may indeed point to overlap between subclinical vascular disease and depression.¹¹ 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.^{12–14} 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 preexisting cardiac disease.⁴ A logical explanation would be that in noncardiac 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 abovementioned findings that depression is also associated with subclinical vascular disease.¹¹ The present study, therefore, is an extension of our previous findings in LASA.⁴

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 vs neurotic-associated depression). The aim of this study was to examine whether a lower level of neuroticism in older persons with depression without preexisting cardiac disease would be associated with increased risk of stroke in LASA. We a priori hypothesize that vascular depression, defined theoretically by a high etiologic 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 LASA. LASA is a prospective cohort study focusing on physical functioning and well-being of an older (≥ 55 years) population ($n = 3,107$). LASA started in 1992/1993, with follow-up measurements every 3 years (see references 15 and 16). For this particular study, 9 years of follow-up data were available. Eligible were those participants without a history of stroke ($n = 3,018$, 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 2,965 eligible LASA participants, 915 participants had no data on neuroticism, leaving a final sample of 2,050 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 general practitioner (GP) information (as in the Netherlands all patients are linked to only 1 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: $\kappa = 0.56$; 95% confidence interval [CI] 0.48–0.64) and that concordance did not covary with level of depressive symptoms of patients.¹⁷ 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 *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 nonfatal 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 Center for Epidemiologic Studies–Depression (CES-D) scale. All 20 items refer to the past week and are scored on a 4-point scale (sumscore range 0–60). The psychometric properties of the scale are good in an older population and overlap with symptoms of physical illness is minimal.¹⁸ A score of ≥ 16 indicates clinically relevant depressive symptoms.¹⁹ In LASA, the cutoff of 16 or higher had a sensitivity of 100% and a specificity of 88% for major depressive disorder according to *DSM-IV* criteria.¹⁹

Neuroticism. Neuroticism is a personality trait that is stable across the lifespan and not affected by physical health status.²⁰ People with a high level of neuroticism are sensitive to negative stimuli,²¹ causing emotional instability and negative moods like anxiety, sadness, guilt, hostility, and self-dissatisfaction.^{20,22} Neuroticism was measured using the Dutch Personality Questionnaire (DPQ).²³ Pilot studies before LASA started showed that the original scale of 36 items could be abbreviated without loss of validity or reliability.^{24,25} These DPQ items have strong negative relations with the Emotional Stability Scale of the NEO

Table 1 Characteristics of included patients vs those with missing data on neuroticism

Characteristic	Included (n = 2,050)	Excluded (n = 915)	p Value
Age, y, mean (SD)	69.3 (8.5)	73.2 (8.6)	<0.001
Female sex, n (%)	1,046 (51.0)	500 (54.6)	0.068
Cognitive functioning (MMSE score), mean (SD)	27.5 (2.3)	25.9 (3.6)	<0.001
Depressive symptoms (CES-D score), mean (SD)	7.4 (7.4)	8.9 (8.4)	<0.001
One or more functional limitations, n (%)	728 (35.7)	445 (49.3)	<0.001
Smoking (yes), n (%)	477 (24.4)	171 (27.7)	0.098
Stage 1 or 2 hypertension, n (%)	479 (24.9)	144 (23.6)	0.528
Cardiac disease, n (%)	401 (19.6)	210 (23.0)	0.035
Diabetes mellitus, n (%)	224 (10.9)	134 (14.7)	0.004
Obesity, n (%)	323 (17.6)	134 (21.6)	0.024
Use of antidepressants, n (%)	37 (1.9)	12 (1.9)	0.946
Incident stroke, n (%)	117 (5.7)	59 (6.4)	0.430

Abbreviations: CES-D = Center for Epidemiologic Studies–Depression scale; MMSE = Mini-Mental State Examination.

Personality Inventory–Revised.²³ 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 described⁴: “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.²⁶ 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: $\kappa = 0.69$; 95% CI 0.65–0.73).”¹⁷

Potential confounders (covariates). Age, sex, general health-related variables (functional limitations and cognitive impairments), and established stroke risk factors (smoking, obesity, diabetes mellitus, and hypertension) were considered potential confounders and as such were included in the analyses.¹⁸

Functional limitations were scored as none, 1, or ≥ 2 , using a 3-item questionnaire.²⁷ Cognition was measured with the Mini-Mental State Examination (MMSE).²⁸ The variable smoking included current smoking. Obesity was defined as a body mass index of 30 kg/m² or greater.²⁹ Diabetes mellitus (yes/no) was based on self-report data, the use of antidiabetic agents, or a GP diagnosis.¹⁷ Blood pressure (mm Hg) was measured with an oscillometric blood pressure monitor (HEM-706; Omron Corporation, Tokyo, Japan) after 5 minutes of rest. Out of the 3 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.³⁰ 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, SDs, and frequencies) and performing *t* tests for continuous measures with normal distributions, Mann-Whitney *U* tests for continuous measures with skewed distributions, and χ^2 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 ($</\geq 5$) in order to prevent influential outliers from affecting 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 Cox regression analyses with time to a fatal or nonfatal 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 CES-D total sumscore as well as dichotomized (≥ 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 ratio (HR) for clinically relevant depressive symptoms by cardiac disease status was 4.03 (95% CI 1.22–13.28) ($p = 0.022$) and HR for severity of depressive symptoms by cardiac disease status was 1.06 (95% CI 1.01–1.11) ($p = 0.032$). Therefore, all analyses will be stratified for baseline cardiac disease status.

For the present article, we examined interaction terms between depression and neuroticism on incidence of stroke when stratified for preexisting cardiac disease using multiple Cox regression analyses. In case of significant interactions with neuroticism, results are presented separately for participants with low and high neuroticism scores.

All analyses were conducted in SPSS (Chicago, IL) for Macintosh 2011. We considered *p* values <0.05 as significant.

RESULTS Baseline characteristics. The mean (SD) age of the 2,050 study participants was 69.3 (8.5) years and 1,046 (51.0%) were women (table 1). At baseline, 261 (12.7%) participants had 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 1,000

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 symptoms = 1.05 [95% CI 1.01–1.10], $p = 0.020$; HR clinically relevant depressive symptoms = 2.08 [95% CI 0.93–4.63, $p = 0.075$, respectively]), whereas neuroticism did not (HR 1.06 [95% CI 0.47–2.38], $p = 0.88$; and HR 1.23 [95% CI 0.57–2.68], $p = 0.60$, respectively). Neuroticism was not identified as an independent predictor of stroke risk in any of the models (all p values > 0.05).

Stratified analyses by neuroticism status in participants without cardiac disease ($n = 1,649$) 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) ($p = 0.033$) and HR clinically relevant depressive symptoms = 4.53 (95% CI 1.72–11.9) ($p = 0.002$), respectively, but not in those with high neuroticism ($n = 811$): HR depressive symptoms = 1.01 (95% CI 0.96–1.05) ($p = 0.82$) and HR clinically relevant depressive symptoms = 0.78 (95% CI 0.30–2.06) ($p = 0.62$), respectively. The figure presents the absolute stroke rates per 1,000 person-years by depression and neuroticism status in patients with no cardiac history ($n = 1,649$).

Stratifying on dichotomized CES-D scores and neuroticism scores (as done in the figure) results in low numbers per group. In the nondepressed group ($n = 1,463$), 5.2% (42/805) of persons with low neuroticism had an incident stroke, vs 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, vs 3.3% (5/153) of persons with high neuroticism.

As dichotomized data are more prone to chance findings, we also reanalyzed the data using 10Log transformation of neuroticism and the sumscore of the CES-D. These analyses fully supported the results (data not shown).

DISCUSSION In older persons without preexistent 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 cardiovascular as well as cerebrovascular disease for the following reasons. Atherosclerosis generally develops over years, with the ultimate outcome of a cardiac or cerebrovascular event.³¹ Nonetheless, subclinical vascular disease is also associated with (specific) depressive symptoms.¹¹ 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

Table 2 Characteristics of included patients by cardiac disease status

Characteristic	No cardiac disease (n = 1,649)	Cardiac disease (n = 410)	p Value
Age, y, mean (SD)	68.6 (8.4)	72.4 (8.3)	<0.001
Female sex, n (%)	889 (53.9)	157 (39.2)	<0.001
Cognitive functioning (MMSE score), mean (SD)	27.5 (2.3)	27.2 (2.4)	0.007
Depressive symptoms (CES-D score), mean (SD)	7.1 (7.2)	8.9 (8.3)	<0.001
Neuroticism (DPQ score), median (IQR)	4.0 (7.0)	5.0 (9.0)	0.018
One or more functional limitations, n (%)	520 (31.7)	208 (52.4)	<0.001
Smoking (yes), n (%)	384 (24.6)	93 (23.8)	0.752
Stage 1 or 2 hypertension, n (%)	398 (25.8)	81 (21.0)	0.052
Diabetes mellitus, n (%)	159 (9.6)	65 (16.2)	<0.001
Obesity, n (%)	251 (17.0)	72 (20.1)	0.160
Use of antidepressants, n (%)	32 (2.0)	5 (1.3)	0.319
Incident stroke, n (%)	85 (5.2)	32 (8.0)	0.029

Abbreviations: CES-D = Center for Epidemiologic Studies-Depression scale; DPQ = Dutch Personality Questionnaire; IQR = interquartile range; MMSE = Mini-Mental State Examination.

Table 3 Models for stroke that include interaction neuroticism (median split) by depression

	No cardiac disease		Cardiac disease	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Model 1				
CES-D score	1.12 (1.03-1.22)	0.008	0.97 (0.79-1.20)	0.776
Neuroticism	1.06 (0.57-1.98)	0.854	0.74 (0.23-2.44)	0.625
CES-D by neuroticism	0.94 (0.89-0.99)	0.028	1.05 (0.94-1.17)	0.440
Model 2				
CES-D score ≥ 16	42.6 (5.23-347)	<0.001	0.37 (0.01-26.3)	0.649
Neuroticism	0.85 (0.54-1.35)	0.484	1.04 (0.43-2.48)	0.936
CES-D by neuroticism	0.12 (0.03-0.45)	0.002	2.60 (0.27-25.2)	0.408

Abbreviations: CES-D = Center for Epidemiologic Studies-Depression scale; CI = confidence interval; HR = hazard ratio. Adjusted for age, sex, cognitive functioning, smoking, obesity, diabetes mellitus, functional limitations, and hypertension.

disease.^{5,8} In people without preexisting cardiac disease, neuroticism may be assumed to be the most important pathway to depression (neurotic depression).³² Nonetheless, in this group, several persons 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 persons without manifest cardiac disease.

The interplay among 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.^{32,33} 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 of 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.³⁴ In the UK Health and Lifestyle Survey, neuroticism predicted cardiac mortality, but not death from stroke.³⁵ 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.³⁶ As this composite score also included depression, perceived stress, and life dissatisfaction, the net effect of neuroticism remains unknown. It is most likely that neuroticism by itself is not related to vascular health, as was found in our study.

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 noncardiac subgroup are difficult to estimate, but most likely, results are conservative.

Second, biological markers of physical diseases have not been measured extensively. Previous articles 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.^{17,26} Nonetheless, many patients have asymptomatic atrial fibrillation in later life, which may have underestimated our prevalence of cardiac arrhythmias.³⁷

Third, the number of participants with a stroke within subgroups was rather low, especially in the subgroup of nondepressed, noncardiac patients.

Figure Absolute stroke rates per 1,000 person-years by depression and neuroticism status in patients with no cardiac history (n = 1,649)

Therefore, confirmation in other samples seems relevant in order to rule out chance findings. Nonetheless, our findings within subgroups categorized by depression (yes/no) and neuroticism (high/low) status were confirmed by analyses using depressive symptoms and neuroticism dimensionally.

Neuroticism and vascular disease are 2 major vulnerability factors in late-life depression.^{1,22,32} Patients with depression with high levels of neuroticism are more likely to benefit from classical antidepressant treatment strategies, compared to patients with depression with higher level of vascular disease.^{38,39} These latter patients are also at increased risk of future health events like stroke⁴ and might benefit from optimizing vascular disease management, including lifestyle intervention like walking or running. Therefore, replication studies as well as randomized controlled studies on the surplus of vascular screening in non-neurotic older patients with depression without known vascular disease are warranted.

The results of our study suggest that in older persons with depression 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 generalized atherosclerosis and depressive symptoms in the population.¹¹

AUTHOR CONTRIBUTIONS

R.M. Marijnissen and R.C. Oude Voshaar completed the statistical analysis. All authors had substantial contributions to conception and design or analysis and interpretation of the data. All authors had substantial contributions to drafting the article and revising it critically for important intellectual content. All authors approved the final version.

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DISCLOSURE

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