



Depressive symptoms and risk of stroke: the Rotterdam Study

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ABSTRACT

Background: Previous studies that have assessed whether the presence of depressive symptoms predisposes to stroke in the general elderly population have been contradictory. Moreover, they did not distinguish between men and women and did not perform psychiatric workups in those with depressive symptoms. This study examines the association between depressive symptoms, depressive disorder and the risk of stroke in the general population.

Methods: This prospective population based cohort study included 4424 participants from the third Rotterdam Study Survey (1997–1999) who, at that time, were ≥ 61 years of age and free from stroke. Depressive symptoms were assessed using the Centre for Epidemiological Studies Depression Scale (CESD) and considered present if the CESD score was ≥ 16 . Participants with depressive symptoms had a diagnostic interview for depressive disorder. Follow-up was complete until 1 January 2005. Data were analysed using Cox proportional hazards models with adjustment for relevant confounders.

Results: Men with depressive symptoms ($n = 73$) were at increased risk of stroke (adjusted hazard ratio (HR) 2.17; 95% CI 1.11 to 4.23) and ischaemic stroke (adjusted HR 3.21; 95% CI 1.62 to 6.38). These associations were at least partly attributable to men who reported depressive symptoms but who did not fulfil Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV diagnostic criteria for depressive disorder ($n = 32$): they had a very high risk of stroke (adjusted HR 2.70; 95% CI 1.15 to 6.33) and ischaemic stroke (adjusted HR 4.01; 95% CI 1.68 to 9.57). In women there was no association between presence of depressive symptoms and risk of stroke.

Conclusions: Presence of depressive symptoms is a strong risk factor for stroke in men but not in women.

It was noted in the early 1970s that elderly patients with depressive disorder had a higher vascular disease burden than those without depressive disorder.¹ This observation evolved into the vascular depression hypothesis, which assumes that depressive disorder can be caused by otherwise subclinical cerebrovascular disease.² The vascular depression hypothesis is supported by the observation that those with depressive disorder have more white matter lesions on MRI.^{3,4} However, the directionality of the association between vascular disease and depressive disorder may also be the reverse, with depressive disorder not being a consequence but a cause of vascular disease. Depressive disorder may induce or enhance vascular disease by several mechanisms: for example, depressive disorder has been found to be associated

with increased cortisol levels,⁵ increased platelet reactivity⁶ and reduced heart rate variability.⁷ In addition, depressive disorder is associated with unhealthy lifestyle choices, including choices regarding smoking⁸ and medication adherence.⁹ However, it seems that the prevalence of classic vascular risk factors is similar among those with and without depressive disorder¹⁰ and does not predict incident depression.¹¹

It has been reported that patients with depressive symptoms are at increased risk of vascular disease.¹⁰ Salaycik *et al* recently found that the presence of depressive symptoms was a risk factor for stroke in persons younger than 65 years of age, but not in the elderly.¹² This contradicts earlier studies that reported an increased risk of stroke in elderly persons with depressive symptoms.^{13–14} More controversies remain regarding the association between depressive disorder and stroke. Firstly, most previous studies assessed the presence of depressive symptoms with a short questionnaire^{3,15–18} whereas the positive predictive value (the proportion of persons with depressive disorder among all those who score positive) has been reported to be low in selected populations¹⁹ but in particular in the general elderly population (13.2%).²⁰ By using these short questionnaires, there is a risk of ignoring the nature of depressive symptoms, which are often not part of a depressive disorder.²⁰ Although most researchers acknowledge this, they still opt for the view that depressive symptoms in general represent depressive disorders.²¹ Secondly, depressive symptoms have a much higher prevalence in women than in men,²² and it would be helpful to know whether gender differences in the association between depressive disorder and risk of stroke exist.

This study assessed the association between depressive symptoms, depressive disorder and risk of subsequent stroke in men and women in a population based cohort study.

METHODS

Source population

The present study forms part of the Rotterdam Study, a population based cohort study on chronic and disabling diseases.²³ Invitations to participate in the first study survey (1990–1993) were sent to all inhabitants of Ommoord (a district in the city of Rotterdam, The Netherlands) aged 55 years and over. The participation rate of those invited was 78%; in total, 7983 subjects agreed to take part in the study. Participants have been followed since, and screening for depressive symptoms was added to the core protocol of the Rotterdam Study at the

third survey (1997–1999), which constitutes the baseline survey for the present study. At this time, participants were 61 years of age and over. The Rotterdam Study was approved by the Medical Ethics Committee of Erasmus University Rotterdam. Written informed consent was obtained from all subjects following a thorough description of the study. Follow-up for incident stroke was complete until 1 January 2005.

Assessment of depressive symptoms and depressive disorder

Depressive disorders were assessed using a two step procedure. Firstly, participants completed the Dutch version of the original Centre for Epidemiological Studies Depression Scale (CESD) during a home interview. The CESD is a 20 item self-reported measure of symptoms, scored on a scale from 0 to 3.²⁴ We used a score of 16 as a cutoff to indicate depressive symptoms. This cutoff had a very high sensitivity for major depressive disorder in a random sample of older subjects in The Netherlands.²⁰ Previous studies have verified that a score of 16 and above on the CESD indicates clinically significant depressive symptoms.¹⁵ In a second step, screen positive subjects had a psychiatric workup. They were studied using the Dutch version of the Present State Examination, a semistructured psychiatric interview included in the schedules for Clinical Assessment in Neuropsychiatry.²⁵ All interviews were conducted by one of two experienced clinicians, a psychiatrist and a clinical psychologist. Psychiatric disorders were classified according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria with an algorithm based on the Present State Examination scores. The diagnostic criteria included major depression, dysthymia and minor depressive disorder, as defined in the DSM-IV and its appendix.

Other measurements

Blood pressure was measured twice in the right arm using a random zero sphygmomanometer, with the participant in the sitting position. We used the average of these two measurements. The carotid intima-media thickness was measured by longitudinal two-dimensional ultrasound of the carotid artery. We calculated the mean common carotid artery intima-media thickness as the mean of four locations: the near and far walls of both the right and left common carotid artery. Cognitive

performance was assessed using the Mini-Mental State Examination (MMSE).²⁶ We considered diabetes mellitus to be present if a fasting glucose level was 7.0 mmol/l or higher, or if a patient used antidiabetic medication. History of transient ischaemic attack (TIA) was positive if an attack of presumed vascular origin with focal symptoms that completely resolved within 24 h in the absence of signs of non-focal (global) brain dysfunction was reported during the interview or in general practitioners' files. TIAs that occurred more than 3 years before the first study survey were not considered. A history of myocardial infarction, percutaneous transluminal angioplasty (PTCA) and coronary artery bypass graft (CABG) was assessed during the first survey home interview and considered positive if confirmed by the medical records or by ECG; after enrolment into the study, medical records were monitored continuously. Smoking and medication use were assessed during the home interview.

Assessment of stroke

A history of stroke at the first Rotterdam Study Survey (1990–1993) was positive if a stroke was reported during the baseline interview and confirmed by the medical records. After enrolment into the Rotterdam Study, participants were continuously monitored for stroke and TIA through automated linkage of the study database with files from general practitioners and the municipality. Also, nursery home physicians' files and files from general practitioners of participants who moved out of the district were scrutinised. For reported events, additional information (including brain imaging) was obtained from the hospital records. Research physicians discussed information on all reported events with an experienced stroke neurologist (PJK) to verify all diagnoses. Strokes were coded according to the International Classification of Diseases, 10th edition (ICD-10). Strokes were ischaemic strokes (I63), primary intracerebral haemorrhages (I61) and unspecified strokes (I64). A stroke was subclassified as ischaemic (I63) if a CT or MRI scan made within 4 weeks after the onset of symptoms ruled out other diagnoses or if indirect evidence (deficit limited to one limb or complete recovery within 72 h, or atrial fibrillation in the absence of anticoagulant therapy) indicated the ischaemic nature of the stroke. Follow-up was complete until 1 January 2005 for 99.0% of potential person years.²⁷

Table 1 Baseline characteristics of the study population at the third Rotterdam Study Survey

Characteristic	Men (n = 1759)*	Women (n = 2665)*
Age (y)	71.2 (66.6–76.4)	72.5 (67.1–78.7)
Systolic blood pressure (mm Hg)	142 (129–157)	142 (128–156)
Intima-media thickness (mm)	0.89 (0.80–0.99)	0.83 (0.75–0.93)
MMSE score	28 (27–29)	28 (27–29)
Diabetes mellitus	266 (15%)	346 (13%)
Cigarette smoking (ever)	1546 (88%)	1314 (49%)
Cigarette smoking (current)	314 (18%)	414 (16%)
History of myocardial infarction	304 (17%)	189 (7%)
History of PTCA or CABG	167 (9%)	83 (3%)
History of TIA	107 (6%)	156 (6%)
Antithrombotic drug use	476 (27%)	535 (20%)
Antihypertensive drug use	654 (37%)	1051 (39%)
Cholesterol lowering drug use	224 (13%)	294 (11%)
Psycholeptic drug use	143 (8%)	526 (20%)
Psychoanaleptic drug use	35 (2%)	102 (4%)

*Values are presented as median (interquartile range) or number (%). CABG, coronary artery bypass graft; MMSE, Mini-Mental State Examination; PTCA, percutaneous transluminal angioplasty; TIA, transient ischaemic attack.

Population for analysis

A total of 5685 participants from the Rotterdam Study were free from stroke and eligible to participate in the third study survey. Of these, 1045 refused the interview and 140 were physically unable to participate. Consequently, 4500 participants were given the CESD interview. Incomplete information on CESD led to the exclusion of 76 participants, leaving a study population of 4424 for analyses of the association between depressive symptoms and risk of stroke. Thirty participants with depressive symptoms did not undergo psychiatric workup, leaving 4394 participants eligible for analyses of the association between depressive disorder and risk of stroke.

Statistical analysis

We compared the risk of stroke and ischaemic stroke in participants with depressive symptoms (CESD score ≥ 16) with the risk of stroke and ischaemic stroke in participants without depressive symptoms (CESD score < 16) using Cox proportional hazards models. Subsequently, we repeated these analyses distinguishing between participants who had depressive

Table 2 Depressive symptoms at third Rotterdam Study Survey and risk of subsequent first ever stroke

Participants	CESD score (n)	HR (95% CI)			
		All strokes*		Ischaemic strokes*	
		Model 1†	Model 2‡	Model 1†	Model 2‡
All participants (n = 4424)	CESD <16 (4100)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	CESD ≥16 (324)	1.20 (0.81–1.80)	1.21 (0.80–1.83)	1.43 (0.89–2.31)	1.43 (0.87–2.35)
Men (n = 1759)	CESD <16 (1686)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	CESD ≥16 (73)	2.11 (1.11–4.04)	2.17 (1.11–4.23)	3.09 (1.60–5.98)	3.21 (1.62–6.38)
Women (n = 2665)	CESD <16 (2414)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	CESD ≥16 (251)	0.94 (0.57–1.56)	0.91 (0.55–1.53)	0.86 (0.43–1.71)	0.78 (0.39–1.59)

*We observed 124 first ever strokes of any type in men and 167 in women. Of these, 91 were ischaemic in men and 99 in women.

†Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, systolic blood pressure, diabetes mellitus, cigarette smoking (ever), cigarette smoking (current), intima-media thickness, history of myocardial infarction, history of PTCA or CABG, history of TIA, antithrombotic drug use, antihypertensive drug use, cholesterol lowering drug use, psycholeptic drug use and psychoanaesthetic drug use.

CABG, coronary artery bypass graft; CESD, Centre for Epidemiological Studies Depression Scale; PTCA, percutaneous transluminal angioplasty; TIA, transient ischaemic attack.

symptoms with and without depressive disorder according to the DSM-IV. Participants were censored at the time of first ever stroke, death, study end or loss to follow-up, whichever occurred first. We performed the analyses for men and women combined and separately. We adjusted for confounding by age and sex (model 1), and additionally for confounding by other putative confounders (systolic blood pressure, diabetes mellitus, cigarette smoking (ever), cigarette smoking (current), intima-media thickness, history of myocardial infarction, history of PTCA or CABG, history of TIA, antithrombotic drug use, antihypertensive drug use, cholesterol lowering drug use, psycholeptic drug use and psychoanaesthetic drug use; model 2). We replaced missing values in putative confounders by the geometric mean. We had missing values for intima-media thickness (20%), systolic blood pressure (12%), MMSE score (12%) and medication use (8%). Analyses were performed with SPSS 11.0 for Windows and results expressed as hazard ratios (HR) with 95% confidence interval (CI).

RESULTS

During 24 657 person years of follow-up, 291 strokes (190 ischaemic, 31 haemorrhagic and 70 unspecified) occurred. At baseline, median age was 71.9 years and 60% of participants were women (see baseline characteristics in table 1). At baseline, the prevalence (95% CI) of major depression was 0.7% (0.3% to 1.1%) among men and 1.7% (1.2% to 2.2%) among women; the prevalence (95% CI) of dysthymia was 0.3% (0.04% to 0.5%)

among men and 0.6% (0.3% to 0.9%) among women; and the prevalence (95% CI) of minor depression was 0.8% (0.4% to 1.2%) among men and 1.6% (1.1% to 2.0%) among women.

Participants with depressive symptoms at baseline had a non-significantly higher risk of stroke (age and sex adjusted HR 1.20, 95% CI 0.81 to 1.80) and of ischaemic stroke (age and sex adjusted HR 1.43, 95% CI 0.89 to 2.31) than participants without depressive symptoms (table 2). Associations between depressive symptoms and risk of stroke were stronger in men than in women (p for interaction 0.05 for stroke and 0.008 for ischaemic stroke): men with depressive symptoms had a strongly increased risk of stroke and ischaemic stroke compared with men without depressive symptoms: the age and sex adjusted HR was 2.11 (95% CI 1.11 to 4.04) for stroke and 3.09 (95% CI 1.60 to 5.98) for ischaemic stroke. In women, there was no association between presence of depressive symptoms and risk of (ischaemic) stroke. HR values were not attenuated by further adjustment for confounding.

Of all participants with depressive symptoms on CESD, the subsequent clinical examination showed that only 46% had a DSM-IV depressive disorder (50% of men and 45% of women); the remainder had anxiety disorder (n = 21), other axis 1 psychiatric diagnosis (n = 14) or no axis 1 psychiatric diagnosis (n = 123).

Men who met DSM-IV criteria for depressive disorder were at increased risk of stroke (age and sex adjusted HR 1.75, 95% CI 0.56 to 5.51; table 3), although this was not statistically

Table 3 Depressive disorder at third Rotterdam Study Survey and risk of subsequent first ever stroke

Participants	Diagnostic classification (n)	Hazard ratio (95% CI)			
		All strokes†		Ischaemic strokes†	
		Model 1‡	Model 2‡	Model 1‡	Model 2‡
Men (n = 1759)	CESD <16 (1686)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	CESD ≥16 without depressive disorder (32)*	2.45 (1.07–5.58)	2.70 (1.15–6.33)	3.61 (1.57–8.30)	4.01 (1.68–9.57)
	CESD ≥16 with depressive disorder (32)*	1.75 (0.56–5.51)	1.63 (0.51–5.26)	2.52 (0.80–7.97)	2.43 (0.74–7.92)
Women (n = 2665)	CESD <16 (2414)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	CESD ≥16 without depressive disorder (126)*	1.27 (0.70–2.28)	1.30 (0.72–2.35)	1.44 (0.70–2.98)	1.41 (0.68–2.92)
	CESD ≥16 with depressive disorder (104)*	0.69 (0.28–1.68)	0.62 (0.25–1.54)	0.24 (0.03–1.72)	0.19 (0.03–1.41)

*Diagnostic workup missing in nine CESD positive men and 21 CESD positive women. Depressive disorders were major depression (13 men, 46 women), dysthymia (5 men, 16 women) and minor depression (14 men, 42 women). Participants with CESD ≥16 without depressive disorder had the following diagnoses: subclinical depressive symptoms and no underlying psychiatric diagnosis (20 men, 103 women), anxiety disorder (6 men, 15 women), other axis 1 psychiatric diagnosis (6 men, 8 women).

†We observed 123 first ever strokes of any type in men and 167 in women. Of these, 90 were ischaemic in men and 99 in women.

‡Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, systolic blood pressure, diabetes mellitus, cigarette smoking (ever), cigarette smoking (current), intima-media thickness, history of myocardial infarction, history of PTCA or CABG, history of TIA, antithrombotic drug use, antihypertensive drug use, cholesterol lowering drug use, psycholeptic drug use and psychoanaesthetic drug use.

CABG, coronary artery bypass graft; CESD, Centre for Epidemiological Studies Depression Scale; PTCA, percutaneous transluminal angioplasty; TIA, transient ischaemic attack.

significant at $\alpha = 0.05$. Men with depressive symptoms who did not meet DSM-IV criteria were at significantly increased risk of stroke (age and sex adjusted HR 2.45, 95% CI 1.07 to 5.58). When only ischaemic strokes were included, both associations became stronger. Like men, women with depressive symptoms in the absence of depressive disorder were at higher risk of stroke than women without depressive symptoms or women with depressive disorder. However, this was far from statistically significant. Adjustment for duration of symptoms did not materially change our findings.

DISCUSSION

In this population based study, persons with depressive symptoms had a slightly but not significantly increased risk of stroke compared with those without depressive symptoms. Although there was no association between presence of depressive symptoms and risk of stroke in women, men with depressive symptoms were at increased risk of subsequent stroke and ischaemic stroke compared with men without depressive symptoms. If anything, the associations between depressive symptoms in the absence of depressive disorder and risk of stroke were stronger than the associations between depressive disorder and risk of stroke.

Some methodological issues need to be discussed before these results can be interpreted. The strengths of our study were the large study population ($n = 4424$), the thorough stroke case finding, the diagnostic workup for depressive disorder and the nearly complete follow-up (loss of potential person years was 1%). Stringent stroke monitoring procedures made it possible to also include stroke patients who were not referred to a neurologist (31% of all stroke cases). As neuroimaging had not been performed in these non-referred cases, we subclassified only 16% of them into ischaemic or haemorrhagic. In contrast, 92% of strokes that had been diagnosed by a neurologist could be subclassified. For some putative confounding variables we had incomplete information. This is because participants were visited at home for the assessment of depressive symptoms and depressive disorder whereas for most other measurements they had to attend the research centre. Control of risk factors was assessed adequately at our research centre. We controlled for medication that was actually collected from the pharmacies. It is likely that patients used the medication that they collected, but we could not verify this. We therefore cannot completely rule out residual confounding by medication intake. It is possible that episodes of psychosomatic syndrome may have been mistaken for stroke. However, all strokes that were included in the ischaemic stroke analyses underwent extensive clinical workup, which for almost all of them (93%) included neuroimaging, and hence we believe it unlikely that in any of these cases was the true diagnosis psychosomatic syndrome.

Several previous studies reported on the association between depressive symptoms and stroke: a positive association has been reported between the presence of depressive symptoms and risk of fatal stroke,^{16, 28} and between the presence of depressive symptoms and stroke in patients with hypertension¹⁸ and in young persons.^{17, 29} Three studies were performed in the general elderly population; one of these found that the risk of stroke increased with increasing CESD score (adjusted HR 1.23, 95% CI 1.05 to 1.44 per unit increase in logged CESD score),¹³ another found an adjusted HR of 1.41 (95% CI 1.01 to 1.96) for stroke risk for highest versus lowest tertile of CESD score¹⁴ and the most recent one found no association between CESD score ≥ 16 and risk of stroke in subjects 65 years of age and over (adjusted HR 0.78, 95% CI 0.46 to 1.32). However, in the last

mentioned study there was an association between the presence of depressive symptoms and stroke in participants younger than 65 years of age. We found an association between the presence of depressive symptoms and the risk of stroke in elderly persons, but only in men and not in women.

Nearly all of the previous studies used self-reported depressive symptom scales to assess the presence of depressive symptoms at baseline and did not study clinical diagnosis of depressive disorder. In our study, more than half of participants who scored positive for depressive symptoms on CESD did not have depressive disorder, confirming earlier reports that the CESD has an extremely poor positive predictive value for diagnosing DSM-IV depressive disorders in the general elderly population.²⁰ One previous study described the association between depressive disorder and stroke,²⁹ but this was a small study with younger participants which only studied fatal or self-reported stroke.

Many mechanisms have been proposed that could explain the association between depressive disorder and vascular disease: for example, depressive disorder has been found to be associated with smoking,⁸ medication non-adherence,⁹ more cerebral white matter lesions,^{3, 4} increased platelet reactivity,⁶ raised cortisol levels,⁵ reduced heart rate variability,⁷ hypertension and glucose intolerance,³⁰ which can be either causes or consequences of depressive disorder. According to our analyses, classical vascular risk factors could not explain the associations we found. As mentioned, we found a strong association between depressive symptoms in the absence of depressive disorder and stroke. Similar mechanisms may play a role here.

Our finding that the association between depressive symptoms in the absence of depressive disorder and risk of stroke seemed stronger than the association between depressive disorder and risk of stroke could be a chance finding. There is no intuitive reason why milder symptoms would have more impact on health than severe symptoms, in particular since these depressive symptoms generally did not reflect other comorbid psychiatric disorders. However, hypoxic brain damage caused by irreversibly damaged cerebral arteries could cause depressive symptoms whereas the development of depressive disorder could be driven more by genetic factors than by vascular damage. This hypothesis is supported firstly by the observation that the prevalence of depressive disorder decreases with age³¹ whereas the prevalence of depressive symptoms increases with age,³² and secondly, by the observation in our study population that cerebral perfusion is more impaired in persons with depressive symptoms than in those with depressive disorder.³³ However, the subdivision of men and women, and the subdivision of the screen positives into those who fulfil DSM-IV criteria for depressive disorder and those who do not, requires substantial power, and therefore our results need to be interpreted carefully.

The absence of an association between depressive symptoms and stroke in women might be attributable to the different, and probably more heterogeneous, aetiology of depressive symptoms among women compared with men,²² which is illustrated by the 2.5-fold excess in prevalence of depressive symptoms in women (9.4%) compared with men (4.2%): non-biological or hormonal factors without somatic consequences may play a larger role in women than in men. These prevalence values are similar to those reported by others.³⁴

In conclusion, the presence of depressive symptoms is an important risk factor for stroke in men, perhaps more so if depressive symptoms cannot be attributed to depressive

disorder. The presence of depressive symptoms is not a risk factor for stroke in women.

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