Psychological distress, major depressive disorder, and risk of stroke

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ABSTRACT

Background: Studies have suggested that mood status is associated with an increased risk of stroke, though mostly based on measures of depression defined by symptoms alone rather than diagnostic criteria representative of clinically important distress and impairment. We investigated this association based upon a large population-based prospective cohort study.

Methods: Baseline assessment of major depressive disorder (MDD) and of mental health well-being (defined by the Mental Health Inventory, MHI-5) was completed by 20,627 stroke-free participants, aged 41 to 80 years, in the United Kingdom European Prospective Investigation into Cancer–Norfolk study.

Results: During 8.5 years of follow-up, 595 incident (fatal and nonfatal) stroke endpoints were recorded. Neither past year nor lifetime MDD was associated with stroke. A one SD decrease in MHI-5 scale score (representing greater emotional distress) was associated with an 11% increased risk of stroke after adjustment for age, sex, cigarette smoking, systolic blood pressure, cholesterol, obesity, preexisting myocardial infarction, diabetes, social class, education, hypertension treatment, family history of stroke, and antidepressant medication use (hazard ratio 1.11, 95% CI 1.00 to 1.22). This association was consistent for men and for women, for fatal and nonfatal stroke, and conformed to a dose-response relationship.

Conclusions: Findings from this large prospective cohort study suggest that increased psychological distress is associated with elevated stroke risk. Episodic major depressive disorder was not associated with incident stroke in this study. ***Neurology*® 2008;70:788–794**

GLOSSARY

BMI = body mass index; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; **EPIC** = European Prospective Investigation into Cancer; **GAD** = generalized anxiety disorder; **HLEQ** = Health and Life Experiences Questionnaire; **ICD** = International Classification of Diseases; **MDD** = major depressive disorder; **MHI-5** = Mental Health Inventory; **MI** = myocardial infarction; **SBP** = systolic blood pressure; **SF-36** = Short Form 36.

During the past decade, research has focused on increasing understanding of the bidirectional association between depression and stroke. Results from stroke survivor,[1,2] register,[3] and population-based[4] studies have suggested that depression commonly occurs following stroke, necessitates increased need for poststroke healthcare, is associated with an increased risk of suicide, particularly in women and in younger age groups, and following control for vascular and other risk factors, is associated with increased stroke incidence.

However, the evidence that depression may confer increased risk of incident stroke is controversial.[5,6] This follows from study limitations imposed by cohort size and endpoint rarity,[7,8] by restriction to special study groups,[9] by limited capacity to adjust for stroke

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risk factors,[7,10] and in particular, by a near-universal reliance on general measures of mental health status defined by symptom count alone rather than by depressive disorder diagnostic criteria that require recognition (for example) of evidence of a sustained period of clinically important distress and impairment.[4,9,11,12]

To advance understanding of the origin of the suggested association between depression and stroke, and to consider the clinical implications of such an association, evidence is needed, based upon large population-based prospective healthy (stroke-free) cohort studies, that include assessment of depressive disorder defined by diagnostic criteria. Based on data collected within the United Kingdom European Prospective Investigation into Cancer (EPIC)–Norfolk population-based prospective cohort study,[13] we evaluated the association between measures of general mental health well-being and of depressive disorder and incident fatal and nonfatal stroke, independent of cerebrovascular risk factors, for both men and women.

METHODS

Participants and measures. Residents of Norfolk (UK) were recruited during 1993–1997 into the United Kingdom European Prospective Investigation into Cancer (EPIC)–Norfolk study using general practice age-sex registers.[13] Baseline assessment included details of pre-existing physician diagnosed diabetes, myocardial infarction (MI), and stroke, cigarette smoking behavior, hypertension treatment, family history of stroke, education, and social class. Social class was classified according to the Registrar General's occupation-based social classification scheme, namely social class I (professionals), social class II (includes managerial and technical occupations), social class III (subdivided into nonmanual and manual skilled workers), social class IV (partly skilled workers), and social class V (unskilled workers). A subsequent health check attendance included assessment of systolic blood pressure (SBP in mm Hg), based on the mean of two readings taken by trained nurses (after each study participant had been seated for 5 minutes), and body mass index (BMI), determined according to the Quetelet Index (weight in kilograms divided by height in meters squared). Non-fasting blood samples taken by venipuncture enabled estimation of serum total cholesterol using an RA 1000 Technicon analyzer (Bayer Diagnostics, Basingstoke, UK). The study was approved by the Norwich District Health Authority Ethics Committee, and all participants gave signed informed consent. See references[13,14] for further details of study design and participant assessments.

During 1996–2000 a total of 20,921 (of 28,582 eligible EPIC-Norfolk) participants, aged 41 to 80 years, completed the Health and Life Experiences Questionnaire (HLEQ), an assessment of psychosocial circumstances, that included a representation of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)[15] criteria for major depressive disorder (MDD) and generalized anxiety disorder (GAD). The assessment was designed to identify those participants thought likely to have met a putative diagnosis of MDD at any time in their lives. Where any episode was reported, participants were asked also to estimate onset and (if appropriate) offset timings. Twelve-month MDD and 12-month GAD were defined as any episode that was either current at HLEQ completion or ended within 1 year of questionnaire assessment.[16,17] The HLEQ also included a five-item version of the Mental Health Inventory (MHI-5), with one or more items representing anxiety, depression, loss of behavioral/emotional control, and psychological well-being during the past 4 weeks, as part of a validated generic measure of subjective health status, the anglicized version of the Short Form 36 (SF-36).[18] The MHI-5, originally developed as a measure of well-being and psychological distress,[19] has been shown to be an effective measure of depression severity,[20-22] and to be a valid measure of MDD (among functionally impaired, community-dwelling elderly).[23] Recent antidepressant medication use was assessed through a questionnaire completed approximately 6 months prior to the HLEQ.

Participants with a history of stroke at EPIC baseline and those who were admitted to hospital with a stroke between EPIC baseline and HLEQ completion were excluded, leaving a sample 20,627 (of 20,921) HLEQ participants for analysis. Stroke morbidity and mortality among EPIC-Norfolk participants to July 31, 2006, was classified according to International Classification of Diseases, Ninth Revision (ICD-9) codes 430–438 or according to International Classification of Diseases, Tenth Revision (ICD-10) as codes I60–I69. Attending physicians assigned diagnostic codes for stroke events resulting in hospital admission. Nonfatal stroke was defined as hospital admission due to stroke that did not result in death (due to stroke in the same month), and any stroke was taken as the first occurrence of either hospital admission or death due to stroke.

Statistical analysis. Analyses were implemented in Stata version 8.2.[24] The associations among 12-month MDD, MHI-5, and any stroke, fatal stroke, and nonfatal stroke were investigated using Cox proportional hazards regression. Results are presented by sex and for men and women combined as hazard ratios for 12-month MDD, and as hazard ratios for a 1 SD decrease in MHI-5 score (representing greater psychological distress), with adjustment for age (in 5 year bands) and sex, and subsequently for cigarette smoking (current, former, never), SBP (included as a continuous measure), total cholesterol, obesity (BMI $\geq$ 30), preexisting MI, diabetes, social class (I, II, III nonmanual, III manual, IV, V), education (no qualifications, to age 16, to age 18, degree level), hypertension treatment (yes, no), family history of stroke (yes, no), and recent antidepressant medication use (yes, no). Sex differences were tested through inclusion of interaction terms. In addition, the presence of a dose-response relation between MHI-5 score and stroke was investigated through inclusion of MHI-5 as a categorical variable recoded into quintiles (score ranges 0 to 63, 64 to 75, 76 to 83, 84 to 91, 92 to 100).

Figure 1 Mental Health Inventory (MHI-5) scores

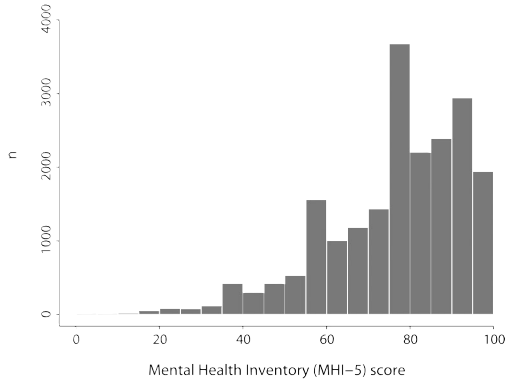


Table 1 Number (%) of participants with 12-month major depressive disorder according to stroke endpoints (any, fatal, and nonfatal, where some participants had both a nonfatal and a subsequent fatal endpoint)

	Men	Women	All
Any (fatal and nonfatal) stroke			
No	326 (3.9)	729 (6.7)	1,055 (5.4)
Yes	10 (3.8)	18 (6.0)	28 (5.0)
Fatal stroke			
No	334 (3.9)	745 (6.7)	1,079 (5.5)
Yes	2 (3.1)	2 (2.1)	4 (2.5)
Nonfatal stroke			
No	327 (3.9)	731 (6.7)	1,058 (5.4)
Yes	9 (4.0)	16 (6.7)	25 (5.4)

RESULTS Of 20,627 study participants aged between 41 and 80 years, 8,939 were men and 11,688 were women. Of these 1,083 (5.3%) reported episodes of MDD within 12 months of HLEQ assessment (336 [3.8%] for men and 747 [6.4%] for women, $p < 0.001$ for test of difference by sex), and 3,184 (15.4%) reported episodes of MDD at any time in their lives (1,012 [11.3%] for men and 2,172 [18.6%] for women, $p < 0.001$). Mean MHI-5 score was 76.9 (SD = 16.4), 78.9 (15.8) for men and 75.4 (16.6) for women ($p < 0.001$ for test of difference by sex), and was 55.2 (20.3) for participants who reported an episode of MDD in the past 12 months, 76.5 (14.4) for those who reported episodes of MDD in their lifetime (that was not in the past 12 months), and 78.5 (15.2) for participants who reported no episodes of MDD at any time in their lives. During a total of 170,593 (median 8.5) person-years of follow-up, 595 incident stroke endpoints were recorded (277 among men and 318 among women). Of these, 167 were fatal and 491 were hospital admissions (with 63 participants admitted to hospital and subsequently dying from stroke). Figure 1 shows the distribution of MHI-5 scores, and table 1 shows the number and percentage of participants reporting 12-month MDD according to stroke endpoints.

Table 2 shows prevalence rates of 12-month MDD and mean MHI-5 scores according to cerebrovascular risk factors and antidepressant medication use. Twelve-month prevalence rates of MDD were higher and MHI-5 scores were lower (representing greater psychological distress) for younger than for older participants (both $p < 0.0001$). After adjusting for age and sex, rates of 12-month MDD were higher and MHI-5 scores were lower (representing greater psychological distress) for participants who were current cigarette smokers, were obese, had previously had an MI, were of lower social class, reported hypertension treatment, and reported recent antidepressant medication use. Additionally, participants reported greater psychological distress (lower MHI-5 scores) if they had previously been diagnosed with diabetes, had higher total blood cholesterol, or had a lower level of educational attainment.

Table 3 shows that no association was observed between 12-month MDD and incident (fatal and nonfatal) stroke (hazard ratio 1.08 [95% CI 0.67, 1.75] after adjusting for age, sex, cigarette smoking, SBP, total cholesterol, obesity [BMI $\geq$ 30], preexisting MI, diabetes, social class, education, hypertension treatment, family history of stroke, and antidepressant medication use). In addition, no association was observed between lifetime MDD and (any fatal or nonfatal) stroke (hazard ratio 1.13 [95% CI 0.85, 1.50]), and no association was observed between either 12-month (0.81 [0.33, 1.98]) or lifetime GAD (0.58 [0.27, 1.24]) and (any fatal or nonfatal) stroke, with all adjustments as above.

Table 4 shows that a 1 SD decrease in MHI-5 scale score (representing greater psychological distress) was associated with an 11% increased risk of incident stroke after adjusting for all risk factors (as above). This association was consistent for men and for women ($p = 0.46$ for sex interaction), and was more pronounced for fatal than for nonfatal stroke endpoints. Figure 2 shows that this association conformed to a dose-response relationship with the risk of stroke progressively greater for participants reporting increased psychological distress. Table 5 shows that while the association between MHI-5 and stroke was strongest in the first 2 years of follow-

Table 2 Percentage of participants with 12-month major depressive disorder (MDD) and mean Mental Health Inventory (MHI-5) score (where a lower score represents greater psychological distress) according to cerebrovascular risk factors and antidepressant medication use

	12-month MDD			MHI-5		
	%*	%†	*p*	Mean*	Mean†	*p*
Age, y						
41–49 (n = 2,557)	8.6			73.3		
50–59 (n = 6,893)	7.1			75.4		
60–69 (n = 6,579)	3.9			78.7		
70–80 (n = 4,597)	3.4			78.8		
Cigarette smoking			<0.0001			<0.0001
Current (n = 2,222)	9.8	8.5		72.8	73.1	
Former (n = 8,467)	4.9	5.0		77.6	76.8	
Never (n = 9,771)	4.9	4.1		77.3	77.9	
Systolic blood pressure (mm Hg)			0.34			0.13
<140 (n = 11,425)	6.0	5.0		76.5	77.1	
≥140 (n = 6,540)	4.3	4.7		78.4	77.5	
Total cholesterol (mmol/L)				0.75		0.02
<6 (n = 7,605)	5.6	4.7		77.3	77.7	
≥6 (n = 9,217)	5.0	4.8		77.3	77.0	
Obesity (kg/m^2)			0.001			<0.0001
No (BMI <30) (n = 15,351)	5.2	4.7		77.4	77.4	
Yes (≥30) (n = 2,617)	6.7	6.2		76.0	76.0	
Preexisting myocardial infarction			0.04			<0.0001
No (n = 20,030)	5.4	4.9		77.0	77.0	
Yes (n = 587)	5.1	7.1		76.3	73.9	
Preexisting diabetes			0.85			0.003
No (n = 20,176)	5.5	4.9		77.0	77.0	
Yes (n = 441)	3.8	4.7		76.3	74.7	
Social class			0.02			<0.0001
I (n = 1,433)	4.5	4.0		78.3	78.3	
II (n = 7,373)	5.2	4.6		77.9	78.0	
IIIn (n = 3,437)	6.0	5.5		76.8	76.8	
IIIm (n = 4,531)	4.9	4.5		76.6	76.6	
IV (n = 2,679)	6.3	5.8		75.3	75.3	
V (n = 732)	6.0	5.5		73.3	73.3	
Education			0.56			<0.0001
No qualifications (n = 8,191)	5.3	5.1		76.1	75.9	
To age 16 (n = 2,666)	6.9	5.3		76.4	77.5	
To age 18 (n = 7,076)	5.1	4.8		77.7	77.4	
Degree level (n = 2,685)	5.4	4.6		78.0	78.4	
Hypertension treatment			<0.0001			<0.0001
No (n = 14,943)	5.3	4.6		77.3	77.6	
Yes (n = 3,216)	5.6	6.2		76.5	75.4	
Family history of stroke			0.74			0.34
No (n = 15,580)	5.5	5.0		76.9	77.0	
Yes (n = 5,036)	5.1	4.8		77.0	76.8	
Antidepressant medication			<0.0001			<0.0001
No (n = 19,759)	4.6	4.2		77.6	77.6	
Yes (n = 868)	24.8	22.5		62.7	63.2	

*Unadjusted.
†Adjusted for age and sex (and evaluated at mean values).

up, it remained after excluding the first 6 years, and there was no evidence of nonproportional hazards ($p = 0.39$).

DISCUSSION Based on data from 20,627 initially stroke-free participants in the EPIC-Norfolk study, we found no evidence that episodic mood state as defined by diagnostic criteria was associated with incident stroke. In contrast, we found evidence that a more general measure of current mental health well-being was associated with increased risk of incident stroke in men and in women and independently of known cerebrovascular risk factors. This association conformed to a dose-response relation and did not attenuate with increasing length of follow-up.

This large community-based population study has a number of strengths including prospective determination of endpoints through death certification and hospital record linkage for all study participants (with 167 fatal and 491 nonfatal strokes in 170,000 person-years of follow-up), availability of data for both men and for women, a measure of MDD defined according to core DSM-IV diagnostic criteria and a more general measure of mental health well-being, together with baseline assessments that allowed adjustment for a wide range of cerebrovascular risk factors.

However, the study has a number of important limitations. First, the restricted age range and characteristics of the cohort may reduce the generalizability of findings. Participation in the study involved commitment to future collection of detailed biologic and dietary data. While this resulted in a cohort that included fewer current cigarette smokers than the general resident population of England, the sample was representative in terms of anthropometric variables, blood pressure and serum lipids,[13] and in terms of physical and mental functional health.[25] Secondly, given that health care systems vary in their use of inpatient services for the assessment and treatment of patients with stroke, and perhaps because these might vary most for less severe stroke,[26] less severe stroke endpoints may have been underascertained through use only of data from death certificates and from hospital admissions.

Limitations of measurement and of power should be taken into account when interpreting the finding of no association between episodic mood state and incident stroke in these data. The HLEQ structured self-assessment of MDD represents a pragmatic solution to enabling such measures to be included in a large-scale chronic

Table 3 Associations between 12-month major depressive disorder [hazard ratios (95% CI)] and incident (fatal and nonfatal) stroke

	Men (n = 8,939)		Women (n = 11,688)		All (n = 20,627)	
	Endpoints	HR (95% CI)	Endpoints	HR (95% CI)	Endpoints	HR (95% CI)
Any (fatal and nonfatal) stroke	277		318		595	
A		1.53 (0.81–2.89)		1.31 (0.81–2.11)		1.38 (0.94–2.02)
B		1.12 (0.52–2.42)		1.03 (0.55–1.93)		1.08 (0.67–1.75)
Fatal stroke	68		99		167	
A		1.36 (0.33–5.57)		0.46 (0.11–1.87)		0.69 (0.25–1.85)
B		—		0.51 (0.12–2.15)		0.45 (0.11–1.84)
Nonfatal stroke	235		256		491	
A		1.63 (0.83–3.17)		1.45 (0.87–2.41)		1.51 (1.00–2.26)
B		1.32 (0.61–2.88)		1.06 (0.53–2.12)		1.18 (0.70–1.97)

A = adjusted for age and sex; B = adjusted for age, sex, cigarette smoking, systolic blood pressure, total cholesterol, obesity, preexisting myocardial infarction, diabetes, social class, education, hypertension treatment, family history of stroke, and antidepressant medication use.

disease epidemiology setting. Previous work (based upon a subsample of these data) has shown DSM-IV MDD prevalence estimates and associated demographic risk profiles to be broadly similar to those derived from dedicated large-scale psychiatric epidemiology research studies.[16] This study had 80% power (at the 5% level of significance) to detect a relative risk of magnitude 1.33 for lifetime and 1.53 for 12-month MDD. While this sample was large, with nearly 600 stroke endpoints observed in over 8 years of (median) follow-up, the relatively low prevalence of the exposure variables limits the capacity of the current study to have detected associations of more modest magnitude. In addition, the potential for differential recall bias arising from the requirement of a 4-week retrospective recall period for the MHI-5 vs 1-year and lifetime periods of recall for the MDD and GAD diagnostic modules may provide an alternative explanation to the negative findings observed in relation to these measures here.

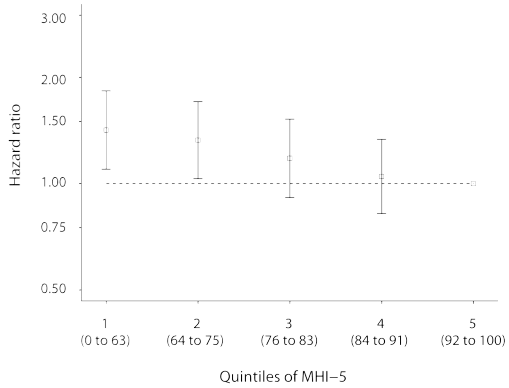
This community-based cohort study has been able to report associations between mental health status measures defined by a measure of psychological distress (previously identified as an effective screening instrument for mood disorders[21]), and by diagnostic criteria and incident (fatal and nonfatal) stroke. Our results are consistent with previous evidence, based upon a range of self-

Table 4 Associations between Mental Health Inventory score [hazard ratios (95% CIs)] per standard deviation decrease in scale scores, representing greater psychological distress, and incident (fatal and nonfatal) stroke

	Men (n = 8,939)		Women (n = 11,688)		All (n = 20,627)	
	Endpoints	HR (95% CI)	Endpoints	HR (95% CI)	Endpoints	HR (95% CI)
Any (fatal and nonfatal) stroke	277		318		595	
A		1.18 (1.05–1.33)		1.13 (1.02–1.26)		1.16 (1.07–1.26)
B		1.15 (1.00–1.32)		1.08 (0.94–1.23)		1.11 (1.00–1.22)
Fatal stroke	68		99		167	
A		1.37 (1.09–1.72)		1.13 (0.94–1.36)		1.22 (1.06–1.41)
B		1.42 (1.08–1.87)		1.12 (0.88–1.41)		1.22 (1.02–1.46)
Nonfatal stroke	235		256		491	
A		1.17 (1.02–1.33)		1.14 (1.01–1.28)		1.15 (1.06–1.26)
B		1.14 (0.98–1.33)		1.07 (0.92–1.25)		1.10 (0.99–1.22)

A = adjusted for age and sex; B = adjusted for age, sex, cigarette smoking, systolic blood pressure, total cholesterol, obesity, preexisting myocardial infarction, diabetes, social class, education, hypertension treatment, family history of stroke, and antidepressant medication use.

Figure 2 Hazard ratios (95% CIs) for incident (fatal and nonfatal) stroke, according to quintiles of Mental Health Inventory (MHI-5) score (where a lower score represents greater psychological distress), adjusted for age and sex



report depression symptom scales, that greater emotional symptomatic distress is associated with increased stroke risk.[4,8,9,11,12] A previous attempt to evaluate the association between a lifetime history of depressive disorder, defined through use of restricted diagnostic criteria, and stroke (involving a 13-year follow-up of 1,703 study participants) reported evidence of a two- to threefold increased risk of stroke but was limited by endpoint rarity (66 self-reported strokes and 29 stroke-related deaths during the follow-up), and by incomplete adjustment for cerebrovascular risk factors.[7] A further registry study also reported evidence of association between patients admitted to hospital for depression and subsequent stroke but was unable to adjust for relevant risk factors.[10] While previous evidence has shown anxiety, including GAD, to be common in patients for up to 3 years following stroke,[27,28] the authors are unaware of any previous examination of the association between GAD and stroke incidence. Given that depression is commonly comorbid with anxiety,[29] and that the MHI-5 includes a question concerned with current anxiety, our results suggesting no association between GAD and incident stroke, though limited by power considerations, are of interest in aiding collective interpretation of these findings.

Stroke is among the leading causes of long-term disability and death worldwide.[30] While evidence, based upon the Framingham Study original and offspring cohorts, has reported decreases in the incidence of stroke and atherothrombotic brain infarction over the past 50 years, achieved in part through improved risk factor control, continued efforts are needed to identify new risk factors that may aid primary prevention and reduce post-stroke disability and mortality.[31] Our results respond to calls for work to aid insight into understanding the origin of the relationship between mood status and stroke risk.[6] They focus attention on the conceptually more general nature of psychological distress and well-being, represented by the MHI-5, rather than the specific represented by MDD and GAD. However, limitations of statistical power in relation to both the measures of MDD and GAD diagnostic status warrant caution in discounting their respective association with incident stroke. In addition, difficulty in being able to demonstrate discontinuities or points of rarity between related psychiatric syndromes[32] has remained a challenge in the specification of diagnostic criteria.[33,34] It is possible that psychological distress, within a broader spectrum of mental health variation, is part of a prolonged prodrome to stroke or that the association may be due to residual confounding. Further work is needed to replicate these findings, to consider emotional health associations according to stroke subtypes, and to evaluate potential mechanisms such as for example the debated association between homocysteine concentration and depression and stroke.[35-37]

Table 5 Association between Mental Health Inventory score [hazard ratios (95% CIs)] per SD decrease in scale score, representing greater psychological distress, and incident (fatal and nonfatal) stroke for men and women combined, according to length of follow-up (adjusted for age and sex)

Length of follow-up	No. of endpoints	HR (95% CI)
0–23 months	69	1.30 (1.05–1.61)
24–47 months	98	1.17 (0.96–1.42)
48–71 months	149	1.09 (0.92–1.28)
≥72 months	279	1.16 (1.04–1.31)

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