

# Does Psychological Distress Predict the Risk of Ischemic Stroke and Transient Ischemic Attack?

## The Caerphilly Study

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**Background and Purpose**—Psychological distress is common after stroke, but little is known about its etiologic importance, although the general public often ascribes stroke to the experience of stress. Therefore, we examined whether psychological distress leads to an increased risk of ischemic stroke and transient ischemic attack (TIA).

**Methods**—The association between the 30-item General Health Questionnaire (GHQ), a measure of psychological distress, and the incidence of nonfatal and fatal ischemic stroke and TIA was measured by Cox regression modeling in a prospective observational study of 2201 men aged 45 to 59 years in phase II of the Caerphilly cohort. Hazard ratios comparing those with high ( $\geq 5$ ) and normal GHQ scores were calculated with adjustment for age and other covariates.

**Results**—Twenty-two percent of men suffered from psychological distress, indicated by a score of  $\geq 5$  on the GHQ. There were 130 incident strokes recorded, of which 17 were fatal and 113 nonfatal. The relative risk of incident ischemic stroke was 1.45 (95% CI, 0.98 to 2.14) for those who showed symptoms of psychological distress compared with those who did not. For fatal stroke the relative risk was 3.36 (95% CI, 1.29 to 8.71) and for nonfatal stroke 1.25 (95% CI, 0.82 to 1.92). The relative risk of TIA for the distressed group was 0.63 (95% CI, 0.26 to 1.53). The results were unchanged after adjustment for body mass index, systolic blood pressure, smoking, heavy drinking, social class, and marital status. However, additionally controlling for previously diagnosed ischemic heart disease, diabetes, respiratory disease, and retirement due to ill health attenuated the relative risks, but not markedly. For fatal strokes the relative risk decreased to 2.56 (95% CI, 0.97 to 6.75) when all confounding variables were included in the model. There was a graded association between degree of psychological distress and risk of fatal ischemic stroke.

**Conclusions**—Psychological distress is a predictor of fatal ischemic stroke but not of nonfatal ischemic stroke or TIA. Further work examining the mechanisms of this association is required. (*Stroke*. 2002;33:7-12.)

**Key Words:** depression ■ disease (etiology) ■ stress, psychological ■ stroke, ischemic

It is recognized that up to 30% of stroke victims suffer subsequent depression, and their speed of recovery is affected by the degree of mood disorder.<sup>1</sup> Of more recent interest is the issue of whether mood disorder can lead to stroke. While several recent epidemiological studies have reported positive associations between symptoms of psychological distress and coronary heart disease (CHD) risk,<sup>2-6</sup> fewer studies have examined the association with stroke, and the results of these were inconsistent or the studies had methodological limitations.

A prospective US study in an elderly population found no association between depressive symptoms and stroke mortality after adjustment for known risk factors.<sup>7</sup> However, in the Alameda County study, stroke mortality was increased in

individuals with depressive symptoms after controlling for possible confounders,<sup>8</sup> although data were not available to examine incident stroke. Findings using data from 3 study sites in the United States showed that the risk of stroke in elderly hypertensive men and women who reported high levels of depressive symptoms was more than twice that of nondepressed hypertensives.<sup>9</sup> In another study among elderly individuals, depressive symptoms measured at baseline were not prognostic, although subsequent increases in depression were predictive of stroke risk.<sup>10</sup> In neither of these 2 studies could the possibility of reverse causality—depressive symptoms occurring because of stroke—be discounted. Increased risk of fatal and nonfatal stroke was found in both black and white individuals reporting depressive symptoms studied in

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the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-Up Study, which persisted after adjustment for important stroke risk factors and which was also seen after exclusion of those with prevalent diabetes and CHD and those who died within 3 years of baseline measurements.<sup>11</sup> A positive relationship between depressive symptoms and incident ischemic stroke has been found in a small Japanese study<sup>12</sup> and in a larger Australian cohort study.<sup>13</sup>

Depression is a common illness and is responsible for much morbidity in its own right, and depressive symptoms are associated with increased mortality.<sup>14</sup> In this study we investigate whether psychological distress measured at baseline in healthy middle-aged men is associated with increased risk of incident fatal and nonfatal first ischemic stroke and also with transient ischemic attack (TIA) occurring over the following 14 years.

## Subjects and Methods

### Design

The Caerphilly Study is a community-based, prospective study of cardiovascular disease and related outcomes in men aged 45 to 59 years who were recruited during 1979–1983 from the town of Caerphilly, South Wales, and the adjacent villages. All men in the eligible age group were identified from the electoral register (2818) and invited to participate, with an 89% recruitment rate. During 1984–1988, 2398 men aged 49 to 64 years participated in phase II of the study, thus including all the original cohort recruited in phase I and men who had moved into the area during the interim. Full details of the Caerphilly Study are available elsewhere.<sup>15,16</sup>

### Measurement of Exposures

The phase II follow-up collected the following measurements: medical history, smoking history, London School of Hygiene and Tropical Medicine chest pain questionnaire, psychosocial questionnaires, height, weight, blood pressure measured with a random-zero sphygmomanometer, and a 12-lead ECG. Detailed methods for these and the wide range of other measures that were performed are described elsewhere.<sup>15,17</sup>

Psychological distress was measured by the 30-item General Health Questionnaire (GHQ).<sup>18</sup> The use of this questionnaire was validated with the use of a subsample of 97 men using the Clinical Interview Schedule (CIS).<sup>19</sup> Briefly, a psychiatrist (S.S.) trained in the use of the CIS conducted interviews at home with a subsample of 97 participants consecutively presenting for examination and stratified by GHQ score. The psychiatrist was blinded to the GHQ score. Sensitivity and specificity of a GHQ threshold of 4 of 5 were both 71%, with the CIS total weight score used as the reference. As a result of receiver-operating characteristic analysis, respondents scoring 0 to 4 on the GHQ were considered non-cases, and those scoring  $\geq 5$  were considered possible cases of minor psychiatric disorder. GHQ data were available on 2201 men. The analyses were repeated with the use of tertile groups of GHQ score rather than the dichotomized variable with the threshold of 5.

### Measurement of Outcome

The men were followed up for 14 years, during which ischemic stroke events were ascertained. Deaths from stroke comprised all those classified as *International Classification of Diseases, Ninth Revision* codes 430 to 438. Nonfatal strokes were defined clinically according to World Health Organization criteria as all those cerebrovascular events that produced a focal or global neurological deficit of acute onset that was present for  $>24$  hours. Stroke type was then classified by scrutiny of all medical records, including neuroradiology, and when records were poor, the participant or a relative was visited to obtain more information. Summaries of

symptoms, signs, past medical history, and clinical course were reviewed independently by 2 clinicians (a stroke specialist and a clinical epidemiologist), and in cases of diagnostic disagreement a third stroke epidemiologist arbitrated. Definite strokes were classified as those that met World Health Organization criteria, and these were further subdivided on the basis of neuroradiology or autopsy findings into infarction or hemorrhage. Probable ischemic strokes were those that met World Health Organization criteria but in which confirmatory neuroradiology or autopsy information was not available or noncontributory and without symptoms or signs suggestive of hemorrhage. Possible ischemic strokes were those in which clinical findings were limited and confirmatory information was lacking but in which it was most likely that the underlying pathology was ischemic. No attempt was made to distinguish lacunar or other subtypes of stroke from other ischemic strokes. Definite hemorrhagic strokes were excluded from the analyses, but all other cases were included. Those men who had symptoms or signs suggestive of a stroke or amaurosis fugax but who recovered within 24 hours were classified as suffering a TIA, together with those reporting a diagnosis of TIA. Detailed methods for ascertainment of strokes in the Caerphilly cohort are described elsewhere.<sup>16</sup>

### Statistical Methods

Cox regression was used to obtain the hazard ratios of all ischemic strokes, fatal and nonfatal, adjusted for age and other covariates. The hazard ratios of stroke in those with mood disorder compared with those without were calculated (1) with adjustment for age alone; (2) with adjustment for age, body mass index, systolic blood pressure, smoking, heavy drinking, social class, and marital status; (3) with adjustment for age and prevalent chronic disease; and (4) with adjustment for all of these variables. Age, body mass index, and systolic blood pressure were fitted as continuous variables. Smoking was dichotomized into current smokers and non-smokers. Alcohol consumption was fitted as a dichotomized variable, with heavy drinking defined as  $>21$  units per week. Social class was dichotomized into nonmanual and manual occupations. Marital status was either currently married or not married. A chronic disease variable was created that indicated whether the men suffered from 1 or more of ischemic heart disease, diabetes, or respiratory disease or had retired on grounds of ill health. Men were deemed to have ischemic heart disease at baseline if they had self-reported angina, ECG-diagnosed myocardial infarction, or a history of myocardial infarction. Diabetes was self-reported. Chronic obstructive airways disease or asthma was inferred from use of a bronchodilator drug in the previous week.

### Results

A total of 2201 men completed the GHQ, of whom 22% scored in the mood disorder range of  $<4$  of 30. The median score was 1, and the interquartile range was 0 to 4, with a mean score of 3.1. There were 29 men who had had strokes before phase II, and these were excluded from the main analyses. An additional 48 men did not have a full set of measurements on all the risk factors used for adjustments and were also excluded. In the remaining cohort of 2124 men, 130 incident strokes were recorded, of which 17 were fatal and 113 nonfatal. Table 1 shows the characteristics of the men stratified by whether or not they suffered a stroke in the follow-up period. Men who had a stroke were slightly older and heavier, had higher systolic blood pressure, and were more likely to have a manual occupation and to be current smokers than those who did not suffer a stroke. They also tended to report more symptoms of anxiety and depression on the GHQ. Table 2 shows the relationship between presence or absence of psychological distress and a range of stroke risk factors. Men with psychological distress were more likely to

**TABLE 1. Caerphilly Study: Characteristics at Phase II of Men Who Did and Did Not Suffer a Stroke During 14-Year Follow-Up**

	Participants, n	Stroke		P
		No (n=2042)	Yes (n=130)	
Age, y	2172	56.8 (4.5)	58.7 (4.1)	<0.001
Body mass index, kg/m <sup>2</sup>	2140	26.4 (3.6)	26.6 (3.5)	0.70
Systolic blood pressure, mm Hg	2164	146.1 (22.7)	154.1 (23.9)	<0.001
GHQ score (maximum=30)	2172	1 (0–4)†	1 (0–5)†	0.58
Psychological distress (score ≥5)	2172	21.7%	27.7%	0.11
Manual occupation	2169	65.8%	75.4%	0.03
Heavy drinker (>21 units/wk)	2168	24.4%	23.9%	0.89
Current smoker	2168	42.8%	48.5%	0.21
Not married	2172	11.4%	16.9%	0.06
Suffering from chronic disease*	2172	40.5%	61.5%	<0.001
Preexisting ischemic heart disease	2172	28.8%	43.9%	<0.001
Diabetes	2171	3.2%	10.8%	<0.001
Respiratory disease	2172	4.4%	5.4%	0.58
Retirement due to ill health	2169	15.3%	27.7%	<0.001

Values are mean (SD) unless indicated otherwise.

\*One or more of ischemic heart disease, diabetes, respiratory disease, or retirement due to ill health.

†Median (interquartile range).

be current smokers, to be suffering from a chronic disease, and to have retired because of ill health compared with other men.

The rate of ischemic stroke was 7.25/1000 per year for those men with psychological distress, ie, a GHQ score of ≥5 of 30, compared with 5.15/1000 per year for those with a GHQ score of <5. The hazard ratio for all ischemic stroke was 1.45 (95% CI, 0.98 to 2.14) in a comparison of those men with psychological distress with the remainder. However, this ratio masks a marked difference in the relative risk of fatal

stroke of 3.36 (95% CI, 1.29 to 8.71) compared with that of nonfatal stroke of 1.25 (95% CI, 0.82 to 1.92), as shown in Table 3.

There was no increase in hazard ratio for TIA in those men with psychological distress compared with the remainder (0.63; 95% CI, 0.26 to 1.53), although an additional 47 men had to be excluded from analysis because they had suffered from a TIA before phase II.

Table 4 shows the results of multivariable analyses, which take into account the confounding effects of known risk

**TABLE 2. Caerphilly Study: Baseline Characteristics of Men Classified by GHQ Score at Phase II**

	Participants, n	GHQ Score		P
		<5 (n=1692)	≥5 (n=480)	
Age, y	2172	57.0 (4.5)	56.7 (4.5)	0.30
Body mass index, kg/m <sup>2</sup>	2140	26.5 (3.5)	26.2 (4.0)	0.14
Systolic blood pressure, mm Hg	2164	146.9 (22.4)	145.4 (24.4)	0.20
Manual occupation	2169	65.7%	68.7%	0.23
Heavy drinker (>21 units/wk)	2168	25.0%	22.2%	0.21
Current smoker	2168	41.9%	47.7%	0.02
Not married	2172	11.3%	13.1%	0.27
Suffering from chronic disease*	2172	38.0%	54.8%	<0.001
Preexisting ischemic heart disease	2172	27.6%	37.1%	<0.001
Diabetes	2171	3.5%	4.4%	0.36
Respiratory disease	2172	4.3%	4.8%	0.65
Retirement due to ill health	2169	12.4%	29.0%	<0.001

Values are mean (SD) unless indicated otherwise.

\*One or more of ischemic heart disease, diabetes, respiratory disease, or retirement due to ill health.

**TABLE 3. Caerphilly Study: Relationship Between GHQ Score and Fatal and Nonfatal Ischemic Stroke**

	Participants, n	All Strokes			Fatal Strokes			Nonfatal Strokes		
		No. of Strokes	Rate./ 1000/y	Hazard Ratio (95% CI)*	No. of Strokes	Rate./ 1000/y	Hazard Ratio (95% CI)*	No. of Strokes	Rate, /1000/y	Hazard Ratio (95% CI)*
GHQ <5	1659	94	5.15	1	9	0.49	1	85	4.66	1
GHQ ≥5	465	36	7.25	1.45 (0.98–2.14)	8	1.61	3.36 (1.29–8.71)	28	5.64	1.25 (0.82–1.92)
Total	2124	130	5.60		17	0.73		113	4.87	

\*Adjusted for age.

factors for stroke. Adjustment for body mass index, systolic blood pressure, smoking, heavy drinking, social class, and marital status did not have much effect on hazard ratios for all categories of ischemic stroke. Inclusion of these variables decreased the relative risk from 1.45 to 1.41 for all strokes, from 3.36 to 3.27 for fatal strokes, and from 1.25 to 1.22 for nonfatal strokes. However, attenuation in hazard ratios was found when adjustment was made for chronic disease (ie, 1 or more of ischemic heart disease, diabetes, chronic obstructive airways disease, or retirement due to ill health); the hazard ratios decreased from 1.45 to 1.28 for all strokes, from 3.36 to 2.63 for fatal strokes, and from 1.25 to 1.12 for nonfatal strokes. The final model, including all the variables, showed results similar to the model that only included chronic disease. The hazard ratio for fatal stroke after all adjustments was 2.56 (95% CI, 0.97 to 6.75).

When psychological distress symptoms were grouped by tertile of GHQ score, there was little evidence of any association with all and nonfatal ischemic strokes. However a graded and highly statistically significant response effect (trend  $P<0.0005$ ) was observed for fatal ischemic strokes,

and this effect persisted after controlling for confounding variables. For fatal strokes the hazard ratio for the middle tertile of GHQ was 2.94 (95% CI, 0.49 to 17.59), decreasing to 2.70 (95% CI, 0.45 to 16.31) after controlling for all confounding variables. The hazard ratio for the top tertile of GHQ was 8.06 (95% CI, 1.79 to 36.39), which decreased to 6.15 (95% CI, 1.37 to 29.46) after all adjustments.

## Discussion

In this study of a representative sample of middle-aged men, those with symptoms of psychological distress were over 3 times more likely to die of ischemic stroke than their nonsymptomatic counterparts after controlling for common stroke risk factors. This did not appear to be due to an effect of using a threshold to classify psychological distress since a graded response was also observed when the distribution of GHQ scores was analyzed in tertile groups. There was no evidence of an association between GHQ and nonfatal strokes and TIAs. Previous studies have reported positive associations between depressive symptoms and stroke mortality, but, to our knowledge, this is the first study to investigate the

**TABLE 4. Caerphilly Study: Relationship Between GHQ Score and Fatal and Nonfatal Ischemic Stroke Adjusted for Age, Risk Factors, and Chronic Disease Status**

				Hazard Ratio (95% CI)			
Stroke Category	Participants, n	No. of Strokes	Rate, /1000/y	Age	Age+Risk Factors*	Age+Chronic Disease†	Age+Risk Factors*+Chronic Disease†
All strokes							
GHQ <5	1659	94	5.15	1	1	1	1
GHQ ≥5	465	36	7.25	1.45 (0.98–2.14)	1.41 (0.96–2.08)	1.28 (0.87–1.88)	1.26 (0.85–1.85)
Total	2124	130	5.60				
Fatal strokes							
GHQ <5	1659	9	0.49	1	1	1	1
GHQ ≥5	465	8	1.61	3.36 (1.29–8.71)	3.27 (1.25–8.57)	2.63 (1.01–6.88)	2.56 (0.97–6.75)
Total	2124	17	0.73				
Nonfatal strokes							
GHQ <5	1659	85	4.66	1	1	1	1
GHQ ≥5	465	28	5.64	1.25 (0.82–1.92)	1.22 (0.79–1.87)	1.12 (0.73–1.72)	1.1 (0.71–1.69)
Total	2124	113	4.87				

\*Body mass index, systolic blood pressure, smoking, alcohol, social class, marital status.

†One or more of ischemic heart disease, diabetes, respiratory disease, or retirement due to ill health.



association of psychological distress with both fatal and nonfatal strokes and with TIA.

### Strengths and Limitations

The Caerphilly Study is a large, population-based, long-term cohort that has achieved excellent participant compliance since its inception. Because of the methods used to collect stroke data, it is likely that there was near-complete ascertainment of incident strokes.<sup>17</sup> Data were collected on both fatal and nonfatal events, and strokes were classified into ischemic and hemorrhagic subtypes.<sup>20</sup> The GHQ was measured before onset of stroke and was also validated in this population. A wide range of risk factors, including prevalent cardiovascular disease, was controlled for in the analyses.

Limitations of the study included the fact that only male participants were recruited into the initial study, precluding examination of these relationships in women. Any bias introduced by loss to follow-up or lack of data on baseline risk factors is likely to be small because both of these were minimal. There may have been some misclassification of stroke type, but this too is likely to be small,<sup>20</sup> and any effect on our findings has been negligible. Use of self-reported chronic disease status may also have led to potential bias, although large population-based studies have indicated that self-reports of diabetes and ischemic heart disease are likely to be accurate.<sup>21,22</sup> We only used the GHQ at baseline, and reassessment would have provided a more powerful means of examining the relationship between persistent psychological distress and stroke. Although the use of a standardized clinical interview would have provided a more powerful means of examining the relationship between clinically relevant psychological distress and stroke, in common with most epidemiological studies, the use of a standardized interview schedule was beyond our resources for a study of 2200 men. However, a validation exercise was undertaken, as described previously.<sup>19</sup>

The explanation for the association between psychological distress and stroke is likely to be complex. It may be associated causally (on the etiologic pathway) with the adoption of unhealthy behaviors such as smoking, unhealthy diet, or lack of exercise, which in themselves increase the risk of stroke. There is evidence that depression increases the likelihood of smoking and reduces physical activity, both risk factors for stroke.<sup>23–25</sup> We adjusted for smoking and alcohol consumption, both risk factors for stroke, but it is possible that misclassification of these exposures has resulted in a degree of residual confounding. Psychological distress, although not directly linked to stroke, may be related to physiological risk factors for stroke such as hypertension, elevated cholesterol, or glucose intolerance. In our study there was no evidence that this was the case, and adjustment for physiological factors did not attenuate the associations observed. Furthermore, if biological factors were important mediators, a relationship with both fatal and nonfatal stroke would be expected.

Psychological distress may be a mediating factor between exposure to adverse social circumstances and stroke. These adverse circumstances might include social isolation and exposure to situations of low perceived control both at work

and at home. Lower socioeconomic status may, in turn, be an antecedent of these adverse social circumstances. However, adjustment for both marital status and social class did not have much effect on the hazard ratios observed. Psychological distress may be a consequence of personality characteristics, such as hostility, that also relate independently to higher stroke risk through chronic physiological hyperreactivity in stressful occupational and domestic contexts. Further analyses of personality characteristics and stroke are planned.

There is evidence in this cohort that men are more likely to suffer psychological distress if they have chronic ill health. For example, 34% of the men who had pre-phase II strokes, 28% of the men with prevalent ischemic heart disease, 25% of diabetics, 24% of men with chronic obstructive airways disease, and 40% of men who had retired because of ill health scored  $\geq 5$  on the GHQ compared with 22% of cases in the cohort overall. It would seem to be a reasonable assumption that men who perceived that their health had deteriorated or had long-term poor health would be more likely to suffer from psychological distress. Since ischemic heart disease<sup>26</sup> and low forced expiratory volume in 1 second,<sup>27</sup> which is associated with chronic airways disease, are both powerful risk factors for stroke, it is possible that the association between GHQ score and stroke is confounded by chronic disease status. Depression is now increasingly recognized as a risk factor for CHD,<sup>4,5,28</sup> and it is possible that the associations observed in our study reflect a prior increased risk of CHD in depressed men, who then go on to develop stroke as a consequence of CHD. However, it is not possible to determine whether the depressive symptoms reported at phase II occurred before or after chronic disease. Furthermore, although controlling for prevalent chronic disease attenuated the hazard ratios observed, they remained large and are consistent with findings from other studies that have also controlled for coexistent disease.<sup>8,11</sup> Because of the small numbers of deaths from ischemic stroke, further analyses excluding those men who died or suffered a cardiovascular event in the 2 years after administration of the GHQ were not performed. However, studies that have done this have reported little attenuation in the magnitude of risk observed.<sup>8,11</sup>

In our study the association of psychological distress with all ischemic stroke is not as strong as that reported in NHANES, although it is broadly consistent with those findings.<sup>11</sup> However, NHANES did not report analyses of nonfatal and fatal stroke separately, nor was stroke subtype defined. Our findings support the hypothesis that psychological distress is a risk marker for fatal but not nonfatal ischemic stroke, suggesting that distress has its effects on survival rather than acting as a primarily etiologic factor. It is possible that men with psychological distress suffered more severe strokes and therefore were more likely to die from the stroke. Alternatively, they may have suffered the same degree of damage at the stroke event, but their case fatality was worse, either through direct effects of psychological distress, associated risk factors for case fatality, or poorer access to medical care. Although the role of medication was not examined in this study, there is evidence that men who are on antidepressant medication may be at increased risk of cardiovascular disease.<sup>29</sup> Psychologically distressed men may be

more likely to ignore health promotion advice and to have poor compliance with any prescribed medical regimen for hypertension or diabetes or after a myocardial infarction.<sup>30</sup>

Small basal ganglia lesions have been shown to be significantly associated with depressive symptoms.<sup>31</sup> It is possible that the men suffering mild asymptomatic cerebral infarcts would become depressed as a result of the infarct. However, our analysis of TIAs, which tend to be recurrent, found no association between psychological distress and TIA, which suggests that this is an unlikely explanation for the association. Other mechanisms have been proposed, but we are unable to examine those in the present study. Psychological distress may lead to an elevated risk of stroke through increased adrenergic activity,<sup>5</sup> production of specific neuroendocrine and immunologic effects,<sup>32,33</sup> platelet activation or alteration,<sup>29</sup> or lipid metabolism,<sup>10</sup> but none of these hypotheses would explain a relationship only with fatal stroke. Further work should attempt to characterize the underlying psychiatric states more accurately so that relationships between ischemic stroke and minor and major depressive illness can be examined.

## Conclusions

The positive association between psychological distress and fatal ischemic stroke is not readily explained. Psychological distress is debilitating, and the finding that it may also increase risk of fatal stroke, one of the leading causes of mortality, indicates the need to better understand the mechanisms of this effect and also to improve primary prevention interventions for psychological distress in later life. Since there appears to be a graded association, those individuals who suffer minor distress are also likely to benefit from successful interventions.

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