Self-Reported Stress and Risk of Stroke
The Copenhagen City Heart Study

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Background and Purpose—Lay people often mention stress as one of the most important risk factors for stroke. Stress might trigger a cerebrovascular event directly or could be associated with higher levels of blood pressure or an unfavorable lifestyle. To examine these possibilities, we analyzed the association between self-reported stress frequency and intensity and risk of stroke.

Methods—Data from the second examination, 1981 to 1983, of participants in the Copenhagen City Heart Study were analyzed with Cox regression after a mean of 13 years of follow-up. A total of 5604 men and 6970 women were included, and 929 first-ever strokes occurred, of which 207 (22%) were fatal within 28 days after onset of symptoms. The stress frequency categories were never/hardly ever, monthly, weekly, or daily. The stress intensity categories were never/hardly ever, light, moderate, or high.

Results—Subjects with high stress intensity had almost a doubled risk of fatal stroke compared with subjects who were not stressed (relative risk [RR], 1.89; 95% CI, 1.11 to 3.21). Weekly stress was associated with an RR of 1.49 (95% CI, 1.00 to 2.23). There was no significant effect of stress in analyses of nonfatal strokes. Subjects who reported to be stressed often were more likely to have an adverse risk factor profile.

Conclusions—Self-reported high stress intensity and weekly stress were associated with a higher risk of fatal stroke compared with no stress. However, there were no significant trends, and the present data do not provide strong evidence that self-reported stress is an independent risk factor for stroke. (Stroke. 2003;34:856-862.)

Key Words: Denmark ■ epidemiology ■ stress ■ stroke

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n population surveys on the knowledge of stroke risk factors, stress is one of the most frequently mentioned factors, often before smoking and hypertension.1–5 The existing literature on the association between stress and risk of stroke is inconclusive, with some studies showing that there is a relation6–8 and others indicating that there is none.9 There are different possible biological mechanisms by which psychological stress may increase risk of stroke. One is related to behavior in which active coping has been related to increased catecholamine release and sympathetic activation, which may either directly or indirectly affect the vascular system, eg, via an effect on the blood pressure. Previous studies have addressed the association between stress and changes in blood pressure levels.10–13 Another possibility for an association between stress and risk of stroke might be related to behavioral differences such as smoking, physical activity, and alcohol consumption or to socioeconomic status (SES).14 Stressed subjects may be more likely than nonstressed subjects to have an adverse risk factor profile, which could explain an increased risk of stroke. Psychological stress has also been associated with the progression of atherosclerotic changes of the carotid artery.15,16 and preliminary findings on the effect of stress reduction indicated that it could decrease carotid atherosclerosis in hypertensive blacks.17 These results suggest that stress might be a potential modifiable risk factor for stroke.

The examination of the relationship between stress and risk of stroke is often hampered by relatively small sample sizes and the lack of consensus on how stress should be defined or measured,18 and some of the studies have presented results only for middle-aged men.6,8 In the present study, data from men and women participating in the Copenhagen City Heart Study (CCHS) on the intensity and frequency of self-reported stress have been analyzed for all strokes, nonfatal stroke, and fatal stroke. As part of the analyses, we have compared the risk factor profiles of the different stress groups. Furthermore, SES is a well-established risk factor for stroke.19–22 Previous studies have indicated that low SES may enhance the effect of stress,16,23 therefore, we have also examined the possibility of an interaction between SES and stress level.

Subjects and Methods

Population
The CCHS is a prospective observational study that was initiated in 1976 when 19 698 subjects living in Østerbro and Nørrebro in...
Copenhagen were invited to participate in the first study examination. In 1981 to 1983 and 1991 to 1994, additional study examinations were done. The response rates at the 3 examinations were 70%, 67%, and 60%, respectively. Fewer than 2% of the population was of nonwhite origin. In the present study, data from participants at the second examination were used with follow-up until 1997. There were a total of 12,698 eligible subjects 20 to 98 years of age. In total, 70 persons (0.5%) were lost to follow-up; of these, 69 were due to immigration, and there was no information for 1 person. A detailed description of the CCHS has previously been published.24

Self-Reported Stress

At the second study examination, participants were asked about their levels of stress in terms of intensity and frequency. In the questionnaire, stress was exemplified as the sensation of tension, nervousness, impatience, anxiety, or sleeplessness. Participants were asked to report their stress intensity given the following 4 possibilities: never/hardly ever stressed or, if stressed, light, moderate, or high intensity. The participants were also asked to report their stress frequency given the following 4 possibilities: never/hardly ever stressed and, if they were stressed, monthly, weekly, or daily.

Socioeconomic Status

The number of years of education (<8, 8 to 11, and ≥12 years) was used as a measure of SES. In preliminary analyses, we found that years of education provided a better fit of the model than income and that simultaneous adjustment for both education and income did not improve the statistical model significantly. Therefore, we included only years of education in the final model.

Covariates

The following variables were assumed to confound the analyses: sex; tobacco smoking (never smoker, ex-smoker, or smoker of 1 to 14, 15 to 24, or ≥24 g/d); body mass index (<20, 20 to 24, 25 to 29, or ≥30 kg/m²); physical activity in leisure time (physically active or light physical activity <2 h/wk, light physical activity 2 to 4 h/wk, light physical activity >4 h/wk, more exhausting physical activity 2 to 4 h/wk, and exhausting physical activity >4 h/wk); systolic blood pressure (continuous); antihypertensive treatment (yes/no); weekly alcohol intake exceeding the Danish National guidelines (a maximum of 14 U/wk for women and 21 U/wk for men); forced expiratory volume in 1 second (FEV₁) in percentage of expected according to age, sex, and height (continuous);25 history of a myocardial infarction before the second health examination (yes/no); and diabetes mellitus (yes/no).

Outcome

Identification of possible stroke events was obtained through linkage of a personal identification number to 2 national registers (the National Patient Register and Cause of Death Register),26 which contain complete data on all hospital admissions in Denmark and causes of death for all deceased subjects who resided in Denmark. Both registers have consistently used the International Classification of Disease (ICD) codes. Patient files and/or discharge letters covering admissions for participants who were registered with cerebrovascular disease (ICD, 9th revision, codes 430 through 438; ICD, 10th revision, codes I60 through I69 and G45) were retrieved, and stroke was diagnosed according to the World Health Organization definition: sudden onset of focal (or at times global) neurological symptoms lasting ≥24 hours or leading to death of presumably vascular origin.27 Type of stroke was based on available information, such as neuroimaging results, lumbar puncture, and necropsies. In addition, at each of the 3 CCHS examinations in 1976 to 1978, 1981 to 1983, and 1991 to 1994, participants were asked if they had suffered a stroke. If they answered positively, they were examined further, and information was collected from the general practitioner.

Statistical Analysis

Subjects with stroke before the start of the study were excluded (n=124). Cox regression analyses, with age as the underlying time axis, were used to estimate the association between self-reported stress intensity and frequency and risk of all, fatal, and nonfatal stroke. Subjects who never/hardly ever were stressed were used as the referent category. The initial analyses included adjustment for age and sex; subsequently, tobacco smoking, body mass index, physical activity in leisure time, systolic blood pressure, antihypertensive treatment, and weekly alcohol intake were entered into the model. In final analyses, further adjustment was done, including FEV₁, history of myocardial infarction, and diabetes mellitus. Fatal stroke refers to events in which the patients died within the first 28 days after onset of stroke symptoms. Analyses were made with the SAS/STAT statistical software, version 8.2.28 Comparisons of categorical variables were done by use of the χ² test, and continuous variables were compared by use of Wilcoxon’s rank-sum test. Fisher’s exact test was used to compare stroke type and stress level.

Results

During follow-up, there was a total of 929 first-ever strokes: 456 (49%) in women and 473 (51%) in men. Of these, 207 (22%) were fatal. There were 396 patients (43%) with ischemic stroke, 67 (7%) with intracerebral hemorrhage, and 34 (4%) with subarachnoid hemorrhage; in 432 (47%), the type of stroke was unknown.

Self-Reported Stress and Baseline Characteristics

There were significant differences in risk factor profiles between stress intensity and frequency groups (Table 1). The proportion of women increased in the highly stressed groups. Subjects in the more stressed groups were more likely to smoke, to have a low income, to be less physically active, to have a higher intake of alcohol, and to be on antihypertensive treatment compared with the less stressed groups. Although the differences between groups with regard to body mass index and mean systolic blood pressure were statistically significant, there was no clear trend. The proportion of subjects reporting to have diabetes mellitus did not differ significantly. There was no significant difference between type of stroke and level of stress intensity (P=0.33) or frequency (P=0.49).

Self-Reported Stress and Risk of Stroke

In analyses of self-reported stress frequency and intensity adjusted for age and sex, there was a tendency toward higher estimates of relative risk (RR) of stroke in the more stressed groups (Table 2). There was a significantly increased risk of stroke among subjects reporting daily stress. For the remaining stress categories, there were no significant associations. Further adjustment for confounding variables attenuated the estimates, especially in the high stress groups, and none of the results were statistically significant. Additional adjustment for history of myocardial infarction, FEV₁, and diabetes mellitus had almost no effect on the estimates and did not change the overall results.

Self-Reported Stress and Risk of Nonfatal Stroke

In the present study, 78% of the stroke patients survived the initial 28 days after onset of stroke symptoms. Thus, they constituted the majority of all stroke events, and the results of analyses between self-reported stress intensity and frequency and risk of nonfatal stroke resembled those of all strokes combined (Table 3). In analyses adjusted for age and sex, the RR estimates increased with increasing stress level and were
highest in subjects reporting a daily level of stress, but none of the results were statistically significant. Further adjustment for confounding variables, including chronic diseases, attenuated the estimates and had no effect on the overall results.

Self-Reported Stress and Risk of Fatal Stroke

There were 207 patients (22%) with a first-ever stroke who died within the first 28 days after onset of stroke symptoms. We reexamined the data with regard to the association with self-reported intensity and frequency of stress and risk of having a fatal stroke (Table 4). In analyses adjusted for age and sex only, the risk of fatal stroke was higher for those with a high level of stress (RR, 1.79; 95% CI, 1.07 to 2.99) compared with subjects who reported never or hardly ever having stress. Only weekly stress was significantly associated with a higher risk of fatal stroke compared with the finding in subjects who reported never or hardly ever being stressed. It should be noted that the estimate for daily stress indicated that there might be a higher risk of stroke, but there were only a few events, and the nonsignificant result may be due to low statistical power. In analyses adjusted for confounding variables, there were few changes in the estimates, and the risk of fatal stroke remained statistically significant for a high stress level and for a weekly feeling of stress, also when controlling for chronic diseases.

**Interactions and Trend Analyses**

There were no significant interactions between sex and stress intensity for all strokes (P=0.60), fatal stroke (P=0.61), or nonfatal stroke (P=0.80). Also, there were no statistically significant interactions between sex and stress frequency for all strokes (P=0.71), fatal stroke (P=0.69), or nonfatal stroke.

We also tested for possible interaction between the 2 measures of stress and level of education in analyses controlled for sex and risk factors. The tests for interaction between frequency of stress and educational level were significant for all stroke (P=0.02) and nonfatal stroke.
In the present study, self-reported weekly stress and high stress intensity were significantly associated with an increased risk of fatal stroke, whereas for the remaining stress categories, there were no significant associations. We did not find a statistical association between self-reported stress and risk of all strokes and nonfatal strokes. There were no significant trends between level of stress and risk of stroke. Subjects with high stress intensity who were frequently stressed had the most unfavorable risk factor profile.

The CCHS is a large, prospective, population-based, cohort study. Linkage of personal identification number to central registers enabled identification of all hospital admissions for stroke and all deaths caused by stroke. During the entire follow-up period, admission to health facilities was free of charge. Results from the Danish Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study have shown that 94% of all patients with nonfatal stroke are hospitalized and that 96% of all stroke events were identified in the central registers.29 In the present study, interview of the participants at the study examinations made it possible to include nonfatal nonhospitalized stroke.

### Table 4. Stress Intensity and Frequency and Risk of Fatal Stroke

<table>
<thead>
<tr>
<th>Stress intensity</th>
<th>RR (95% CI) of Fatal Stroke</th>
<th>Age and Sex</th>
<th>Age, Sex, and Risk Factors*</th>
<th>Age, Sex, Risk Factors, and Chronic Disease†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal Strokes, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (n=4931)</td>
<td>91</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>Light (n=4521)</td>
<td>67</td>
<td>1.07 (0.78–1.48)</td>
<td>1.08 (0.77–1.49)</td>
<td>1.14 (0.82–1.59)</td>
</tr>
<tr>
<td>Moderate (n=2381)</td>
<td>31</td>
<td>1.01 (0.67–1.53)</td>
<td>1.01 (0.66–1.54)</td>
<td>1.04 (0.67–1.61)</td>
</tr>
<tr>
<td>High (n=716)</td>
<td>18</td>
<td>1.79 (1.07–2.99)</td>
<td>1.74 (1.03–2.95)</td>
<td>1.89 (1.11–3.21)</td>
</tr>
<tr>
<td>Stress frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never/hardly ever (n=6027)</td>
<td>112</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>Monthly (n=3442)</td>
<td>37</td>
<td>0.89 (0.61–1.30)</td>
<td>0.88 (0.60–1.29)</td>
<td>0.92 (0.62–1.35)</td>
</tr>
<tr>
<td>Weekly (n=2001)</td>
<td>36</td>
<td>1.46 (1.00–2.15)</td>
<td>1.49 (1.01–2.19)</td>
<td>1.49 (1.00–2.23)</td>
</tr>
<tr>
<td>Daily (n=1061)</td>
<td>21</td>
<td>1.28 (0.80–2.04)</td>
<td>1.25 (0.77–2.01)</td>
<td>1.33 (0.82–2.16)</td>
</tr>
</tbody>
</table>

*Body mass index, smoking, education, physical activity, alcohol, systolic blood pressure, antihypertensive treatment.  
†Acute myocardial infarction, FEV1, diabetes mellitus.
events that were not registered. A few nonfatal nonhospitalized stroke events may have remained unidentified, but the overall effect on estimates is likely to be negligible.

There is no consensus on how stress should be measured. Different studies using different definitions and methods have examined the relation between stress and stroke and reached different conclusions. In a Finnish study of 2303 middle-aged men followed up for 11 years, during which 113 first-time strokes occurred, elevations in blood pressure during the anticipation phase before a maximal exercise bicycle ergometer test relative to the average resting baseline blood pressure were considered a measure of cardiovascular activation in response to psychological and behavioral stress. Subjects with excessive reactivity had an almost doubled risk of stroke, and men who were high reactors and poorly educated had almost a 3-times-higher risk of stroke compared with better-educated, less reactive men. The same study found that there was an association between level of stress and intima-media thickening, and stress has also been associated with increased progression of carotid artery disease. A Swedish study of 238 hypertensive men with a mean follow-up period of 9.9 years, during which 43 experienced stroke, showed that poor adaptation to stress measured with a psychological stressor (the color-word test) was associated with a 3-times-higher risk of stroke. In a large intervention study of 7495 middle-aged men (47 to 55 years of age at baseline), stroke incidence was estimated during 11.8 years of follow-up in Göteborg, Sweden. Psychological stress was defined as feelings of tension or anxiety on a scale from 1 (never experienced stress) to 6 (feeling permanent stress during the last 5 days). Subjects with the highest level of stress had doubled risk of stroke compared with nonstressed subjects. The stress definition in the latter study is very similar to ours in that self-reported stress was used in the analyses. However, it is not surprising that there is divergence of the results between the studies because we included both men and women, used a larger age range, and had no intervention group. Furthermore, the Göteborg study did not provide separate results for fatal and nonfatal stroke.

A returning question in studies of stress and stroke is the validity of the stress markers. For example, the generalizability of reactions to laboratory challenges to reactions to everyday life stress exposures has been questioned. Additionally, the validity of self-reported stress is questionable. A high validity would necessitate that the interviewed subjects interpret the meaning of the questions identically and report identically. Stress could even refer to both physical and psychological stress. Although we have no proof of how the participants in the CCHS understood the stress questions, it is our belief that the majority would interpret it as referring to psychological and not physical stress because stress in the questionnaire was exemplified in psychological terms. However, it is likely that the perceived level of stress for the same exposure may differ from one person to another because individual expectations about what is stressful differs. Thus, what is actually measured is a complex conglomerate of both exposure to ‘stressors’ and the subject’s resources for dealing with and reporting it. We can therefore expect that as long as there is no established definition of stress, results from different studies are likely to differ considerably. The proportion of women increased markedly in the higher stress groups. It remains unknown whether this results because women are more exposed to stressors than men, they feel more stress given the same exposure, or they report the sensation of stress differently than men. Results from our study suggested that data from men and women could be combined in the analyses because the interaction tests between stress and sex were not significant. We acknowledge that this is a purely statistical approach to examine whether the effect of stress and risk of stroke are similar for men and women, and future studies may provide an opportunity to examine this relation in more detail.

Despite the problem with the validity of self-reported stress, it was clearly associated with a less favorable risk factor profile. Many of the considered confounding variables were both well-established risk factors for stroke and modifiable. Thus, by asking a simple question about stress intensity and frequency, it was possible to identify a group of subjects that potentially could benefit from intensified preventive efforts. The effect of controlling for the confounding variables resulted in estimates for different levels of stress and risk of all stroke that were attenuated, indicating that an association between self-reported stress and risk of stroke may be due, at least in part, to differences in risk factor profile. However, when we adjusted for the same variables in analyses with only fatal strokes as the end point, the estimates decreased only slightly and even increased for high stress and weekly stress. This may indicate that there could be an independent relation between self-reported stress intensity and frequency and risk of fatal stroke. However, there were no clear patterns in any of the analyses and no significant trends for either stress intensity or frequency. Also, there was no indication of a threshold, and residual confounding may be another potential explanation for the findings. Even if there is an association, only ~10% of the subjects with fatal stroke were in the highly stressed groups; thus, according to our data, self-reported stress cannot be regarded as an important risk factor for fatal stroke at the population level.

One of the main purposes of the study was to examine whether different levels of self-reported stress were associated with different levels of systolic blood pressure. If subjects feeling stressed were more likely to have higher
blood pressure levels than nonstressed subjects, this could explain some of the relationship. The mean systolic blood pressure values differed significantly for both stress intensity and frequency, but there was no clear trend between the stress groups. However, there was an increasing proportion of subjects on antihypertensive treatment, and that pattern was found for both stress intensity and frequency. From these data, it is not possible to address whether stressed subjects become hypertensive or hypertensive subjects become stressed, and the increase could also be explained by stressed people being more frequently in contact with health professionals and therefore more likely to undergo treatment for increased blood pressure. We reanalyzed data with and without systolic blood pressure and antihypertensive treatment, but the estimates remained almost the same and the overall results did not change (data not shown). Therefore, according to the present data, systolic blood pressure and antihypertensive treatment cannot explain the relation between self-reported stress and risk of stroke.

There are several possible explanations why stress may be associated with only a higher risk of fatal stroke. Subjects who experience stress may be more likely to have more severe strokes, which would increase the risk of death. Regrettably, in the present study, we have no information on severity of stroke. Another possibility is that stressed subjects who suffer stroke more often than nonstressed subjects are more susceptible to complications. However, the biological background for this is unclear. An animal model examining the relation between stress and stroke with male mice examined the expression of ischemia-induced Bcl-2 expression.33 The Bcl-2 protooncogene promotes cell survival and protects against apoptosis and cellular necrosis. The authors found that male mice that were stressed before occlusion of cerebral artery occlusion expressed 70% less Bcl-2 than unstressed mice after ischemia. Whether these findings would be similar in humans is unknown; however, they suggest that there may be (unidentified) biological mechanisms between stress and risk of stroke.

A previous study has shown that men with high reactivity to stress and little education were at greater risk of stroke than more educated men.23 Previous studies have shown that there is an inverse socioeconomic gradient for stroke incidence and mortality,14 and SES may be related to cardiovascular responses to stress.16,34 The effect of stress on risk of stroke could be moderated by the coping possibility and strategy used by the subject; stress in individuals who do not feel in control could be more harmful than stress that is self-inflicted or of which the person feels in control. Hence, some degree of psychological stress may even be perceived as a positive challenge if the person feels in control of the situation.35 More educated people will often be more in control of their jobs and consequently more likely to be able to cope with stressful situations in the job compared with people with low-control jobs; thus, the effect of stress may vary according to education level. That some level of stress may be beneficial is in agreement with the finding of an interaction between educational levels of self-reported stress frequency in the present study, showing a U-shaped relation between risk of stroke and stress in subjects with >11 years of education.

Several baseline characteristics and RR estimates showed a J-shaped relationship between levels of stress and risk of stroke. This could hypothetically indicate a systematic misclassification of stressed individuals into the “none” and “never” stressed groups. If that happened, it likely attenuated the difference between the referent category and the other stress levels. There are different possible explanations for stressed individuals being misclassified as not stressed. They might have felt that the definition of stress was not applicable to their situation, or they may have been unaware of their high levels of stress. In addition, underreporting of stress might be related to lifestyle and may differ between categories of risk factors, which provides an alternative explanation for the results between years of education and risk of stroke. Similar interaction tests for age (<65 or ≥ 65) and smoking (yes/no) were not significant (results not shown).

The categorization of stress intensity and frequency raises the issue of multiple comparisons because each stress group was compared with the referent category. A formal test for multiple comparisons was not made because the present results relate mainly to the pattern between self-reported stress and risk of stroke rather than between specific stress levels and risk of stroke.

In conclusion, in the present study, self-reported high stress and weekly stress were associated with a higher risk of fatal stroke. However, there were no significant trends, and the present data do not provide strong evidence that self-reported stress is an independent risk factor for fatal stroke. Even if such an association exists, the biological background is unclear. There was no significant association between stress and risk of all strokes and nonfatal strokes. Stressed subjects had a more unfavorable risk factor profile than subjects not reporting to be stressed; thus, asking a relatively simple question about perceived level of stress may identify subjects who could benefit from intensified prevention. Although level of systolic blood pressure differed significantly between the stress groups, it could not explain the association between stress and stroke.

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References

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