Lifestyle Factors and Risk of Cerebrovascular Disease in Women
The Copenhagen City Heart Study
Ewa Lindenstrøm, MD; Gudrun Boysen, MD, DMSc; Jørgen Nyboe, MSc

Background and Purpose: The purpose of the present analysis was to determine how lifestyle influences the risk of cerebrovascular disease in women participating in the Copenhagen City Heart Study.

Methods: A random sample of a white, lower and middle-class, urban population selected in 1976 was invited to two cardiovascular examinations at 5-year intervals. The present analysis was based on 7060 women invited to an initial examination from 1976 through 1978, aged 35 years or more, and without previous stroke or transient ischemic attack. At the initial examination, potential risk factors were recorded. The 265 first cases of stroke and transient ischemic attack were ascertained at a second examination 5 years later and through hospital records and death certificates through 1988. The Cox regression model was used to estimate the influence of the factors recorded on the risk of cerebrovascular disease.

Results: The relative risks of cigarette smoking and lack of physical activity were 1.4 and 1.45; 95% confidence limits, 1.02 to 1.94 and 1.01 to 2.08, respectively. The relative risk of daily consumption of tranquilizers was 1.25 (95% confidence limits, 0.96 to 1.62). No significant influence was found for number of cigarettes, body mass index, or alcohol intake. In postmenopausal women, there was a statistically significant interaction (P < .041) between smoking and hormone replacement therapy. Smokers receiving this therapy had a 28% lower risk of cerebrovascular disease than smokers not receiving it.

Conclusions: The statistically significant and equally potent effects on the risk of cerebrovascular disease were found for cigarette smoking and lack of physical activity. The risk associated with smoking seemed to be influenced by hormonal replacement therapy. (Stroke. 1993;24:1468-1472.)

KEY WORDS • Denmark • epidemiology • risk factors • women

The purpose of the present study was to analyze lifestyle factors in women and evaluate their independent, causal effect on cerebrovascular disease, defined as stroke or transient ischemic attack (TIA). In the past decade, several studies analyzing risk factors for stroke using multivariate analysis have been published. However, few of them clarify how these risk factors act specifically in women. Besides the lifestyle factors common to both sexes, we have also analyzed the use of oral contraceptives and hormone replacement therapy (HRT) and evaluated their influence on the risk of cerebrovascular disease. As a basis for the analysis, we have established a hierarchical model of risk factors indicating the way they influence each other. This model gives a clue as to which factors should be included simultaneously in the Cox regression model to evaluate the independent, causal effect of a given factor in a population.

Subjects and Methods
The analysis was based on an age-stratified random sample of a Danish urban population, the study outcome being first stroke or TIA cases during 12 years of follow-up. This work is part of a larger prospective study known as the Copenhagen City Heart Study (CCHS) and primarily designed as a cardiovascular survey. The study population and sampling procedure have been described previously.1 Briefly, the study population was chosen randomly but after age stratification from an area of Copenhagen served by Rigshospitalet, with approximately 90,000 inhabitants aged 20 years or more. Of 10,317 women invited by letter to an initial examination on a specific date between March 1, 1976, and March 31, 1978, 7712 attended. The eligibility criteria for the present analysis were no previous stroke or TIA, sufficient information about the lifestyle factors recorded, and age 35 years or more at the initial examination, as no events occurred below this age. The criteria were met by 7060 women. The study population was then invited to the second cardiovascular examination between April 6, 1981, and September 7, 1983 (it took about 2 years each time to examine all the responders). The procedure and the complete questionnaire used have been described.2

The outcome of the study was first stroke and TIA cases. The information about new cases until the end of 1988 was then obtained and analyzed. The methods of

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From Rigshospitalet, Department of Neurology (E.L.), Hvidovre Hospital, Department of Neurology (G.B.), and the Copenhagen City Heart Study (J.N.) (Denmark).

Correspondence to Ewa Lindenstrøm, MD, Department of Neurology, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
case ascertainment are detailed elsewhere. Briefly, the first-in-life stroke and TIA cases were identified through (1) the two cardiovascular examinations, at which the history was taken, supplemented by a thorough neurological assessment, (2) the National Patient Register, and (3) the National Health Service Register of Deaths. The National Patient Register provides information on all hospital admissions in Denmark, including patient and hospital unit identification, admission and discharge dates, and six-digit codes corresponding to all discharge diagnoses. For the participants diagnosed with codes 430 through 438 of the World Health Organization’s International Classification of Diseases (8th revision), hospital discharge letters were retrieved to identify those who had suffered an event. When necessary, all hospital records, as well as additional information from the patient’s general practitioner, family, or nursing home, were collected. Death certificates were retrieved from the National Health Service Register of Deaths in all cases in which stroke was registered as either an underlying or contributing cause of death.

Whenever possible, these certificates were supplied by information from other sources, as mentioned above. Altogether, 265 initial cases of stroke and TIA were identified. The stroke types included were cerebral infarction, intracerebral hemorrhage, and unspecified stroke; subarachnoid hemorrhage was excluded. The distinction between stroke, TIA, and retinal embolism was clinical, whereas classification of different stroke subtypes was based on cerebral computed tomographic scan or brain autopsy.

The details of case ascertainment results and the discussion about case completeness have been provided in our article about stroke incidence. Briefly, we believe that the cases recorded represent more than 80% of all the cases experienced by our cohort because of the complete ascertainment of fatal strokes, the nearly complete assessment of cases between the two exams, and the Registers’ function permitting ascertainment of approximately 62% of the remaining cases.

The selection of risk factors was based on data in the literature. A broad spectrum of factors believed to influence the risk of cerebrovascular disease was chosen, and each factor was tested in Cox regression models. For statistical analysis we used the Cox regression model. The risk factors analyzed in this article are the ones recorded at the first examination only.

We set up the variables in a hierarchical system after we had established a hypothesis concerning the direction of influences among them. Such a system is essential to identify confounders and to evaluate the causal influence of a potential factor on the risk of cerebrovascular disease. To eliminate the confounding influences, we have included in the model age, length of school education, and household income, because they influence the lifestyle factors in our model and proved to be independent, significant factors for cerebrovascular disease in a previous analysis. In the basic model, family history of stroke, marital status, and menopausal age were also tested, but as no significant contribution to the risk of cerebrovascular disease could be found, they were not included in the lifestyle factor analysis. The lifestyle variables were defined as current cigarette smoking, average number of cigarettes per day, daily consumption of alcohol, daily or nearly daily consumption of sleeping pills or tranquilizers, physical activity at leisure time, current use of oral contraceptives, current use of HRT, and body mass index (BMI) (kilograms per square meter). The criterion of physical activity used was more than 2 hours of intense activity or 4 hours of lighter activity per week; any lesser activity was classified as physical inactivity. All the variables except BMI were recorded from the questionnaire. Among these variables, we assume that there is no one-way influence of one variable on another, and therefore they were included simultaneously in the Cox model.

### Results

Altogether, 268 initial cerebrovascular events were recorded in respondents to the first examination during 12 years of follow-up; 265 of the events were in the 7060 eligible responders. Among the 265 initial cerebrovascular events were 76 cerebral infarctions, 11 intracerebral hemorrhages, 128 unspecified strokes, 48 TIsAs, and 2 retinal embolisms. In 2605 nonresponders, 123 cases were recorded: 31 cerebral infarctions, 12 intracerebral hemorrhages, 70 unspecified strokes, and 10 TIsAs.

The confounders for the lifestyle factors were age, length of school education, and household income. Table 1 shows the relative risk (RR) estimates and 95% confidence intervals (CI) for these factors resulting from the Cox regression before the lifestyle analysis and from the final model containing both the confounders and lifestyle factors.

The distribution of lifestyle factors among the 7060 women is depicted in Table 2. The RR estimates and corresponding 95% CI values are depicted in Table 3. Current cigarette smoking was a significant risk factor for cerebrovascular disease, the risk of smokers being 1.4 times that of nonsmokers. No significant relation could be established between the number of cigarettes smoked and the risk of cerebrovascular disease, the estimated RR increment per cigarette being nonsignificant. The average number of cigarettes per day was 10.2 among current smokers and 7.7 among smokers who later had a stroke or TIA.

Physical inactivity at leisure time was associated with a significantly higher risk of cerebrovascular disease. Women who consumed alcohol daily seemed to have a lower risk of cerebrovascular disease than nondaily.

### Table 1. Effect of Age, Length of School Education, and Household Income on Risk of Cerebrovascular Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model I RR 95% CI</th>
<th>Model II RR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.08 1.07-1.09</td>
<td>1.09 1.07-1.11</td>
</tr>
<tr>
<td>Length of school education</td>
<td>1.35 1.04-1.75</td>
<td>1.28 0.97-1.70</td>
</tr>
<tr>
<td>Household income</td>
<td>1.35 1.02-1.79</td>
<td>1.30 0.98-1.72</td>
</tr>
</tbody>
</table>
TABLE 2. Distribution of Lifestyle Risk Factors for Stroke Among 7060 Women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency in Women at Risk (n=7060)</th>
<th>Stroke Cases (n=265)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>57.8</td>
<td>4081</td>
</tr>
<tr>
<td>No</td>
<td>42.2</td>
<td>2979</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21.1</td>
<td>1490</td>
</tr>
<tr>
<td>No</td>
<td>78.9</td>
<td>5570</td>
</tr>
<tr>
<td>Daily alcohol intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12.5</td>
<td>883</td>
</tr>
<tr>
<td>No</td>
<td>87.5</td>
<td>6177</td>
</tr>
<tr>
<td>Daily consumption of tranquilizers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27.5</td>
<td>1942</td>
</tr>
<tr>
<td>No</td>
<td>72.5</td>
<td>5118</td>
</tr>
</tbody>
</table>

Drinking, although the protective effect of alcohol did not reach statistical significance. There was no significant interaction between smoking and daily drinking; i.e., the effect of smoking was the same in daily and nondaily drinkers. There also was no significant interaction between smoking and age, smoking and physical activity, or smoking and BMI.

Daily consumption of sleeping pills or tranquilizers showed a tendency to influence the risk of cerebrovascular disease.

BMI did not have any significant effect on the risk of cerebrovascular disease, the estimated RR increment per unit BMI being nonsignificant. The average BMI was 24.4 kg/m² among all the women and 25.4 kg/m² among subsequent cerebrovascular cases.

The analysis of oral contraceptives was based on 2344 premenopausal women, in whom 27 events occurred during 12 years of follow-up. Two of the events occurred among the 288 oral contraceptive users, and 25 events occurred among 2056 nonusers. The current users of oral contraceptives did not have significantly higher risk than nonusers (RR = 0.93; 95% CI, 0.67 to 1.48) when adjusted for the remaining lifestyle factors, age, length of school education, and household income. A possible interaction between smoking and oral contraceptive use could not be investigated because there were no smokers among oral contraceptive users with subsequent cerebrovascular events.

The effect of HRT was estimated among 47 16 postmenopausal women, in whom 238 events occurred during the 12 years of follow-up. We found a significant interaction between smoking and HRT in this group (P < 0.01), which means that the effect of HRT was different in smokers and in nonsmokers and vice versa. Thus, HRT seemed to have a protective effect among nonusers. Table 4 shows RR estimates and 95% CI values for different combinations of smoking and HRT use.

Discussion

The accuracy of the data assessed by the questionnaire at one examination might be discussed. On the other hand, large quality-control measures were undertaken. From a statistical point of view, the fact of finding significant associations between some of the factors (smoking, physical inactivity) and the risk of cerebrovascular disease suggests that the level of accuracy must have been adequate. Otherwise, a large standard error would result from many inaccurate data and no significant association would be likely to appear.

The effect of smoking on stroke risk is well documented in both women and men in other prospective studies. The Framingham study, for example, found a significant RR of 1.6 in female smokers using the Cox proportional hazards model and adjusting for several other risk factors. The risk of stroke increased with the number of cigarettes. Our analysis could not find an association between the number of cigarettes and the risk of cerebrovascular disease in women, although we found such an association for men and for the whole population (unpublished data), in which stroke risk grows by 1% with each cigarette. The importance of smoking for stroke risk has been confirmed in a recent Finnish study in which the decline in smoking was

TABLE 3. Relative Risk Estimates and 95% Confidence Intervals for Lifestyle Factors in 7060 Women

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Regression Coefficient</th>
<th>Relative Risk</th>
<th>SEM</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>0.32</td>
<td>1.40</td>
<td>0.15</td>
<td>1.02-1.94</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>Daily no. of cigarettes</td>
<td>0.00</td>
<td>1.00</td>
<td>0.01</td>
<td>0.98-1.03</td>
<td>NS</td>
</tr>
<tr>
<td>Physical inactivity at leisure time</td>
<td>0.37</td>
<td>1.45</td>
<td>0.15</td>
<td>1.01-2.08</td>
<td>&lt;.04</td>
</tr>
<tr>
<td>Daily alcohol intake</td>
<td>0.30</td>
<td>0.74</td>
<td>0.21</td>
<td>0.48-1.13</td>
<td>NS</td>
</tr>
<tr>
<td>Daily consumption of tranquilizers</td>
<td>0.22</td>
<td>1.25</td>
<td>0.13</td>
<td>0.96-1.62</td>
<td>&lt;.1</td>
</tr>
<tr>
<td>BMI</td>
<td>0.02</td>
<td>1.02</td>
<td>0.01</td>
<td>0.99-1.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

CI, confidence intervals; BMI, body mass index. Log likelihood: -2197.5. Shown are adjusted Cox regression model relative risks. Each risk factor has been adjusted for age, length of school education, household income, and the five remaining lifestyle factors.
TABLE 4. Distribution and Relative Risks of Hormone Replacement Therapy Use and Smoking Among Postmenopausal Women and Among Subsequent Cerebrovascular Cases

<table>
<thead>
<tr>
<th>Smokers (n=2659) Among WR (n=4716) Among CC (n=238)</th>
<th>Regression coefficient</th>
<th>Relative risk</th>
<th>SEM</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT users</td>
<td>668</td>
<td>11</td>
<td>-0.56</td>
<td>0.57</td>
</tr>
<tr>
<td>HRT nonusers</td>
<td>1991</td>
<td>123</td>
<td>0.41</td>
<td>1.50</td>
</tr>
<tr>
<td>Nonsmokers (n=2057)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRT users</td>
<td>370</td>
<td>13</td>
<td>0.01</td>
<td>1.01</td>
</tr>
<tr>
<td>HRT nonusers</td>
<td>1687</td>
<td>91</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

CI, confidence intervals; WR, women at risk; CC, cerebrovascular cases; HRT, hormone replacement therapy. Shown are Cox regression model relative risks relative to nonsmoking and nonuse of HRT, adjusted for the lifestyle factors, age, length of school education, and household income. Interaction coefficient for HTR and smoking: -0.32, P<.041, corresponding to risk reduction of 1 - e^(-0.32) = 0.78, ie, 28%.

Associated with a decline in stroke incidence. The proportion of female smokers in the CCHS is striking: more than 57%, probably one of the highest in the world.10 This could partly explain why the stroke incidence in Copenhagen, also in women, is so relatively high and has shown no declining trend.4

The effect of physical activity on stroke risk is much less documented. In a Finnish study,11 low physical activity at work was associated with increased risk of stroke in women, whereas low physical activity at leisure time had no such effect. We have chosen to study physical activity at leisure time to analyze this variable in all women (ie, working and nonworking). Selecting only working women would reduce the number of cases and make the results less representative of the study population. Nearly 80% of women in our study had little or no physical activity at leisure time, contributing to the "unhealthy" lifestyle pattern in this population.

Only 12.5% of all women were daily drinkers. A prospective study of female nurses in the United States12 showed that among middle-aged women moderate alcohol consumption decreased the risk of ischemic stroke. In another study, light to moderate consumption of alcohol was inversely associated with extracranial carotid arteriosclerosis in 261 symptomatic patients with cerebrovascular disease, 92 of whom were women.13 In our study, where the outcome was all initial strokes and TIs, daily alcohol consumption in women was associated with an RR of 0.74, but this was not significant (P<.15). Data are missing on how alcohol affects intracerebral hematoma in women, whereas in men even light drinking significantly increased the risk of hemorrhagic stroke.14

In our study, BMI did not show a significant independent effect on the risk of cerebrovascular disease in women, although such an effect was observed for both sexes combined.15 The results from the Framingham study16 are different, showing that in women with high BMI (fifth quintile) the RR of cerebrovascular accident was 1.6 (1.1 to 2.4). The proportional hazard model used, however, differed from ours by not including length of school education, income, or physical activity in the model. These factors are known confounders for BMI in women17 and could account for the effect of BMI found in the Framingham study. Other studies show that waist-to-hip ratio is a stronger predictor of stroke in women than BMI.18,19

The effect of daily consumption of sleeping pills or tranquilizers has not previously been discussed, and we have no clear explanation of its effect on the risk of cerebrovascular disease in our study. It is possible that certain side effects of tranquilizers could in some cases be misinterpreted as TIA. Another explanation could be that long-term use of tranquilizers can contribute to the pathophysiology of cerebrovascular disease.

In a cohort of more than 16 000 women followed for an average of 6.5 years, use of HRT proved not to be a significant factor for stroke according to univariate analysis.20 The Framingham study is the only large prospective study showing an elevated risk of cerebrovascular disease (initial stroke or TIA) among HRT users.21 In the logistic model, the RR associated with HRT was 2.27 (P<.01) after adjustment for other risk factors. It is interesting to notice that both blood lipid and BMI measures were more favorable in HRT users at baseline.

However, when the interaction between smoking and HRT was examined in a similar logistic regression model, the effect of HRT on stroke was only significant in nonsmokers. Our results show that HRT had a protective effect on cerebrovascular disease among smokers. In fact, the following conclusions can be drawn from Table 4: Smoking is a significant risk factor among postmenopausal women not using HRT compared with nonsmokers and nonusers of HRT. Among nonsmokers, use of HRT does not influence the risk of cerebrovascular disease. The RR estimate associated with smoking and simultaneous HRT use is nonsignificantly lower than in nonsmokers and nonusers of HRT. The interaction analysis has shown that among smokers HRT use significantly reduces the risk of cerebrovascular disease. The combination of smoking and HRT use cannot, of course, be recommended because of other known health hazards associated with smoking and possibly also with HRT. On the other hand, possible pathophysiological background and pharmacologic implications of this interaction might be interesting. Our results seem to suggest that a combination of HRT and some components of cigarette smoke might have a protective effect on cerebral circulation.
This interaction needs to be verified in another cohort before any clinical significance can be attributed to it. In a prospective study of more than 8000 women, a protective effect of HRT on death from stroke was found (RR = 0.53; 95% CI, 0.31 to 0.91), and it was not affected by adjusting for hypertension, BMI, smoking, alcohol, and exercise. A recent update of this study has also shown a protective effect of HRT on all-cause mortality after adjusting for other risk factors (RR = 0.79; 95% CI, 0.71 to 0.88). Unfortunately, the interaction between smoking and HRT was not analyzed in this or other studies. A case-control study from the United Kingdom examined the combined effect of HRT on stroke and myocardial infarction. In a multivariate analysis, HRT did not have a significant effect on the outcome. The recent results of an American cohort study have shown no effect of HRT on stroke in current users compared with nonusers (RR = 0.97; 95% CI, 0.65 to 1.45) adjusted for several other risk factors. It is clear that our analyses deal only with one issue: effect of ever using HRT on stroke. The duration of HRT has not been analyzed, nor the type of hormones used.

The effect of oral contraceptives on the risk of cerebrovascular disease was not analyzed previously in the CCHS. In the above-mentioned cohort study, oral contraceptive use was associated with an increase in the risk of subarachnoid hemorrhage but not of other strokes (RR = 0.6; 95% CI, 0.1 to 3.5) when adjusted for smoking. A multivariate analysis of a cohort of British women showed that the use of oral contraceptives had no significant effect on death from cerebrovascular disease compared with the use of the diaphragm or intrauterine devices. The effect of the use of low-estrogen oral contraceptives compared with intrauterine devices among women less than 40 years of age in Finland was analyzed. The RR of death from intracranial hemorrhage was 0.19 (95% CI, 0.05 to 0.70) among oral contraceptive users. The prospective studies of the effect of oral contraceptives on stroke risk usually contain a limited number of stroke cases and give RR estimates with very large confidence limits and thus inconclusive results. Case-control studies, on the other hand, do not usually permit accurate recording of the confounding factors and therefore can provide unreliable results. A long follow-up period in prospective studies can lead to more reliable conclusions. At least 20 years of follow-up will be necessary to record a sufficient number of stroke cases among women who were premenopausal at baseline. Data about cerebrovascular events in the CCHS cohort are still being recorded.

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