Combined Effects of Socioeconomic Position, Smoking, and Hypertension on Risk of Ischemic and Hemorrhagic Stroke

Helene Nordahl, MS, PhD; Merete Osler, MD, PhD; Birgitte Lidegaard Frederiksen, MD, PhD; Ingelise Andersen, MS, PhD; Eva Prescott, MD, PhD; Kim Overvad, MD, PhD; Finn Diderichsen, MD, PhD; Naja Hulvej Rod, MS, PhD

Background and Purpose—Combined effects of socioeconomic position and well-established risk factors on stroke incidence have not been formally investigated.

Methods—In a pooled cohort study of 68,643 men and women aged 30 to 70 years in Denmark, we examined the combined effect and interaction between socioeconomic position (ie, education), smoking, and hypertension on ischemic and hemorrhagic stroke incidence by the use of the additive hazards model.

Results—During 14 years of follow-up, 3,613 ischemic strokes and 776 hemorrhagic strokes were observed. Current smoking and hypertension were more prevalent among those with low education. Low versus high education was associated with greater ischemic, but not hemorrhagic, stroke incidence. The combined effect of low education and current smoking was more than expected by the sum of their separate effects on ischemic stroke incidence, particularly among men: 134 (95% confidence interval, 49–219) extra cases per 100,000 person-years because of interaction, adjusted for age, cohort study, and birth cohort. There was no clear evidence of interaction between low education and hypertension. The combined effect of current smoking and hypertension was more than expected by the sum of their separate effects on ischemic and hemorrhagic stroke incidence. This effect was most pronounced for ischemic stroke among women: 178 (95% confidence interval, 103–253) extra cases per 100,000 person-years because of interaction, adjusted for age, cohort study, and birth cohort.

Conclusions—Reducing smoking in those with low socioeconomic position and in those with hypertension could potentially reduce social inequality stroke incidence. (Stroke. 2014;45:2582-2587.)

Key Words: hypertension • smoking • socioeconomic position • stroke

A socioeconomic gradient in stroke and stroke risk factors have been observed in a variety of settings.\(^1,2\) It has been documented that some stroke risk factors may interact or act synergistically with each other.\(^3,5\) Because people in lower socioeconomic groups are frequently exposed to several risk factors and the effect of one of these factors on risk of stroke is likely to be stronger in the lower socioeconomic groups than in the higher—these people are more vulnerable.\(^6\) Addressing such differential vulnerability and interactions between risk factors are relevant to the public health and clinical agenda because it allow us to quantify in which subgroups intervention could potentially prevent the most cases.\(^7,8\)

The mechanisms driving social inequality in stroke have been described as being partly a result of differential exposure to well-established risk factors, such as hypertension and smoking, during a life course.\(^9,12\) In previous studies, authors have suggested that smoking has a larger effect on ischemic stroke, hemorrhagic stroke, and heart disease if high blood pressure is also present.\(^13,15\) However, much less attention has been given to the extent to which these risk factors interact with socioeconomic exposures.\(^4\)

In a pooled cohort study including 68,643 men and women, we examined the combined effects and interaction among socioeconomic position, smoking, and hypertension on ischemic and hemorrhagic stroke incidence.

Methods

Study Population

The cohort consortium, the Social Inequality in Cancer cohort study, combined questionnaire data on 83,006 participants from 7 existing population-based cohort studies from Denmark: the Copenhagen City Heart Study; the 1936 Cohort Study; Monica I, II, and III; the Diet Cancer and Health Study; the Inter99 Study. Detailed descriptions of this consortium and the enrolled studies have previously been described.\(^10\)
For the current study, we excluded 492 participants aged ≤29 years (assuming that some of these participants had not yet reached their final level of education); 4424 participants born before 1921 (information on education was unavailable); 1796 participants with missing information on education; 7020 participants with preexisting cardiovascular disease (defined as diagnosed before study entry in the Danish National Registry of Patients using the International Classification of Diseases [ICD], ICD8: 390–458; ICD10: 100–109, G45); and 631 participants with missing information on smoking or systolic blood pressure; leaving 68,643 participants aged 30 to 70 years for the analyses.

Outcomes
Information on stroke cases was obtained through linkage with the Danish National Registry of Patients and the Causes of Death Registry using the ICD-Eighth Revision from 1981 to 1994 and the Tenth Revision thereafter. The cases were classified as ischemic stroke (ICD8: 433–434; ICD10:163), unspecified stroke (ICD8: 436; ICD10:164), subarachnoid hemorrhagic stroke (ICD8: 430; ICD10:160) and intracerebral hemorrhagic stroke (ICD8: 431; ICD10:161). Participants with ischemic strokes and unspecified strokes were analyzed together because Krarup et al.17 in their validation study confirmed that the majority of the unspecified stroke diagnosis in the Danish National Registry of Patients was diagnosed as ischemic stroke in their clinical evaluations. To increase the power of the limited number of hemorrhagic stroke cases, patients with subarachnoid hemorrhage and intracerebral hemorrhage were combined for the analysis. Follow-up was from date of study entry until date of first primary diagnosis of fatal or nonfatal stroke, death, emigration, or end of follow-up (December 31, 2009). Fewer than 0.1% were lost to follow-up because of emigration.

Exposures
Socioeconomic position was assessed by linkage to the high-quality data from central and administrative registries using highest attained education, which was measured 1 year before study entry. Education was categorized in 3 groups: low (primary and lower secondary education), medium (upper secondary, vocational or technical education, as well as short-cycle higher nonuniversity programs), and high (medium-cycle university or nonuniversity programs, as well as long-cycle university programs). Information on smoking was based on questions covering smoking status and levels of current smoking, which were combined into a 4-category smoking variable: never smoker, former smoker, smoker of 1 to 15 g/d, and smoker of ≥16 g/d. Blood pressure was measured by trained nurses according to the World Health Organization guidelines. We constructed a 4-category variable for systolic blood pressure: <120 mm Hg, 120 to 139 mm Hg, 140 to 159 mm Hg, and ≥160 mm Hg. Hypertension was defined as systolic blood pressure ≥140 mm Hg.

Covariates
Other covariates included age, sex, cohort study, birth cohort (from 1921 to 1970 in 5-year intervals), alcohol intake (continuous in grams per day), physical activity in leisure time (sedentary, <2 hours/wk of light activity; light, 2–4 hours/wk of light activity or <2 hours/wk of high-level activity; moderate, >4 hours/wk of light activity or 2–4 hours/wk of high-level activity; and high, >4 hours/wk of high-level activity), and body mass index (≤18.5, 18.6–24.9, 25.0–29.9, or ≥30 kg/m²).

Statistical Analysis
The concept of differential vulnerability was defined as deviation from additivity of absolute effect analogous to assessing additive interaction in statistical terms.15,16 We applied the additive hazards model that was recently proposed as a technique to assess additive interaction in survival analyses.19
In this model, the hazard of ischemic and hemorrhagic stroke was modeled as a linear function of the exposure variables (ie, education, smoking, and hypertension) adjusted for confounders (ie, sex, cohort study, and birth cohort) plus an unspecified baseline hazard using age as the underlying time scale.20 The effect estimate was rate difference interpreted as the extra number of cases per 100,000 person-years at risk in a specific exposure category when compared with the reference. The analysis for ischemic stroke was stratified into men and women because of marked sex-based differences. For hemorrhagic stroke, men and women were analyzed together as we found no indication of sex-based differences.

The magnitude of the deviation from additivity (or additive interaction) was directly assessed by including product terms of the exposure variables.19 We also defined 4 combined exposure variables: education-by-smoking, education-by-hypertension, smoking-by-hypertension, and education-by-smoking-by-hypertension. These were entered one at a time into the model.

In sensitivity analyses, we (1) restricted analysis to patients with an ICD code for ischemic stroke only and for intracerebral hemorrhagic stroke only, (2) assessed study-specific effects by including the exposure-by-cohort interaction terms, (3) evaluated potential measurement error by applying different cutoff points for smoking and hypertension and by testing interactions using 4-category variables, (4) evaluated potential age-dependent effects of education, smoking, or hypertension by the use of standard techniques,21 (5) evaluated the influence of other health-related behaviors by adjusting for body mass index, alcohol intake, and physical activity.

Results
During 14 years of follow-up, we observed 2346 unspecified strokes and 1951 ischemic strokes, which were combined as ischemic strokes. Furthermore, we observed 776 hemorrhagic strokes (with 70% of these being diagnosed as intracerebral hemorrhages and the remaining as subarachnoid hemorrhages).

Smoking was clearly more frequent in those with low education, and the level of blood pressure was only slightly higher among those with low versus high education (Table 1). The main effects of education, smoking, and blood pressure on ischemic and hemorrhagic stroke are shown in Table 2. Clear educational differences were observed for ischemic stroke but only slightly for hemorrhagic stroke. In absolute terms among men, low versus high education was associated with 181 (95% confidence interval, 127, 235) extra cases per 100,000 person-years at risk of ischemic stroke. Correspondingly, among women there were 93 (56, 129) extra cases of ischemic stroke. Smoking and high blood pressure were markedly associated with incidence of both ischemic and hemorrhagic stroke.

As presented in Table 3, the combined effect of low education and current smoking was more than expected by the sum of their separate effects on ischemic stroke but negligible for hemorrhagic stroke. This was most pronounced among men, where the separate effect of having low education was associated with 42 (−5, 90) extra cases per 100,000 person-years at risk of ischemic stroke and the separate effect of being current smoker was associated with 112 (38, 186) extra cases. However, the combination of current smoking and low education was associated with 289 (238, 340) extra cases per 100,000 person-years at risk of ischemic stroke. Thus, 134 (49, 219) extra cases per 100,000 person-years at risk of ischemic stroke could be ascribed to the interaction between smoking and education. We could not confirm evidence of similar patterns among women. There was no clear evidence of interaction with respect to the combination of low education and hypertension on risk of ischemic stroke (men, P=0.89;
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women, *P*=0.05) or hemorrhagic stroke (*P*=0.53). However, the combined effect of current smoking and hypertension was more than expected by the sum of their separate effects on ischemic and hemorrhagic stroke. This was most pronounced among women, where 178 (103, 253) extra cases per 100 000 person-years at risk of ischemic stroke could be ascribed to the interaction between smoking and hypertension.

The combined effect of exposure to all 3 risk factors on ischemic stroke was associated with 566 extra cases among men and 438 extra cases among women when compared with no exposure (high education, no current smoking, and no hypertension), as presented in the Figure. This was more than expected from the sum of their separate effects, ie, among women 308 extra cases of ischemic stroke per 100 000 person-years (calculated as 438−[−10+107+33]).

The sensitivity analyses indicated (data not shown) (1) that restricting the analysis to patients with an ICD code for ischemic stroke only and for intracerebral hemorrhagic stroke only did not change the conclusions, (2) no notable interaction between cohort study and the 3 exposure variables, (3) that using 4-category variables for smoking and systolic blood pressure with different cutoff point did not affect the presented results, (5) no indication of age-dependent effects, (6) that adjusting for body mass index, alcohol intake, and physical activity did not change the conclusions.

**Discussion**

In agreement with other studies, our results demonstrate that low versus high education is associated with greater ischemic but not of hemorrhagic, stroke incidence, and that stroke risk factors are more prevalent in low educational groups. The present study provides further insight into the combined effects and interactions among socioeconomic position, smoking, and hypertension.

In previous studies, authors have suggested that the existence of an interaction between the 2 well-established risk factors, smoking and hypertension, in relation to stroke in general and hemorrhagic stroke. Our data confirmed this

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**Table 1. Characteristics of 68643 Participants From the SIC Cohort**

<table>
<thead>
<tr>
<th>Educational Level</th>
<th>Low (n=20867)</th>
<th>Medium (n=33670)</th>
<th>High (n=14106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=68643)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, %</td>
<td>53</td>
<td>63</td>
<td>50</td>
</tr>
<tr>
<td>Age at study entry, y; median (5%, 95% percentile)</td>
<td>54 (40, 63)</td>
<td>54 (40, 64)</td>
<td>53 (35, 63)</td>
</tr>
<tr>
<td>Tobacco smoking, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>34</td>
<td>28</td>
<td>35</td>
</tr>
<tr>
<td>Former smoker</td>
<td>26</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>Smoker (1–15 g/d)</td>
<td>21</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Heavy smoker (≥16 g/d)</td>
<td>19</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>Systolic blood pressure, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120 mm Hg</td>
<td>21</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>120–139 mm Hg</td>
<td>42</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>140–159 mm Hg</td>
<td>26</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>≥160 mm Hg</td>
<td>11</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Alcohol intake, g/d; median (5%, 95% percentile)</td>
<td>12 (0, 62)</td>
<td>9 (0, 61)</td>
<td>13 (0, 63)</td>
</tr>
<tr>
<td>Body mass index, kg/m²; mean (SD)</td>
<td>26 (4)</td>
<td>26 (5)</td>
<td>26 (4)</td>
</tr>
<tr>
<td>Sedentary leisure time*, %</td>
<td>17</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Cohort study, y; %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCHS, 1981–1983</td>
<td>10</td>
<td>50</td>
<td>38</td>
</tr>
<tr>
<td>1936-COHORT, 1981–1982</td>
<td>1</td>
<td>36</td>
<td>52</td>
</tr>
<tr>
<td>MONICA I, 1982–1984</td>
<td>5</td>
<td>37</td>
<td>51</td>
</tr>
<tr>
<td>MONICA II, 1986–1987</td>
<td>2</td>
<td>36</td>
<td>50</td>
</tr>
<tr>
<td>MONICA III, 1991–1992</td>
<td>3</td>
<td>34</td>
<td>54</td>
</tr>
<tr>
<td>DCH, 1993–1997</td>
<td>71</td>
<td>28</td>
<td>50</td>
</tr>
<tr>
<td>INTER99, 1999–2001</td>
<td>8</td>
<td>24</td>
<td>55</td>
</tr>
<tr>
<td>Pooled SIC cohort 1981–2001</td>
<td>100</td>
<td>30</td>
<td>49</td>
</tr>
</tbody>
</table>

CCHS indicates Copenhagen City Heart Study; DCH, Diet Cancer and Health study; INTER99, Randomized Nonpharmacological Intervention Study for Prevention of Ischemic Heart Disease; MONICA (I, II, III), Multinational Monitoring of Trends and Determinants in Cardiovascular Disease; and SIC, Social Inequality in Cancer cohort study.

*Sedentary leisure time: <2 h/wk of light activity.
interaction and showed that the combined effect of current smoking and hypertension exceeded the sum of their separate effects on incidence of both ischemic and hemorrhagic stroke. Interestingly, an equally important interaction between education and smoking on incidence of ischemic stroke was observed, suggesting that people, particularly men, in lower socioeconomic groups could be more vulnerable to the effect of smoking than those in higher socioeconomic groups in terms of ischemic stroke. This finding may be of benefit to the public health and clinical agenda because health interventions and preventive strategies should be aimed at patients or population subgroups in which the most cases could potentially be prevented.

In support of our findings, we have previously shown that the same level of smoking has different effects across socioeconomic groups in relation to death from cardiovascular disease.23 Such apparent differential vulnerability could be a consequence of clustering and mutual interaction between other active determinants.24 Although others have described the important role of smoking and hypertension as contributors to the social gradients in stroke,8–12 our data indicated only sparse differential exposure to hypertension across socioeconomic groups. Likewise, in previous trend studies during the 1980s and 1990s, no marked socioeconomic differences in blood pressure have been reported.25,26 Our results indicate that the combined effect of low socioeconomic position, current smoking, and hypertension exceeded the sum of their separate effects. However, the apparent vulnerability to the effect of smoking in the low socioeconomic group did not seem to be purely a consequence of clustering or mutual interaction with hypertension. Actually, the stronger effect of smoking in the low socioeconomic group seemed regardless of the presence of hypertension. In a US population-based study, Liu et al4 found a combined effect of socioeconomic position and chronic conditions, such as hypertension, heart problems, and diabetes mellitus, in relation to risk of stroke. Furthermore, they suggested potential cumulative effects of childhood social conditions, adulthood socioeconomic position, and adult chronic conditions on risk of stroke. Thus, to understand the role of differential vulnerability better, it might be particularly relevant to address the interaction between earlier exposures and those that occur later in life because the presence of risk factors during childhood has been shown to increase the risk of stroke.27 However, we were unable to apply a life course perspective because information on childhood socioeconomic circumstances was not available in the present study.

To our knowledge, this is the first cohort study to evaluate interactions among socioeconomic position, smoking, and hypertension in relation to stroke incidence comprehensively. The large population sample and long follow-up provided sufficient power to test the hypotheses of interaction even in subgroups of stroke. Furthermore, the linkage to nationwide register data allowed for nearly complete follow-up. However, some limitations of the present analysis should be pointed out. First, there may be variations in the quality of register data for some diagnostic subgroups of stroke, which could compromise the estimation of absolute risk measures. Two validation studies from Denmark have confirmed high predictive values (>80%) of the overall stroke and ischemic stroke diagnosis in Danish National Registry of Patients.17,28 However, Krarup et al17 showed that for unspecified stroke more than two thirds were diagnosed as ischemic stroke by clinical evaluators. Thus, in the current study, we combined ischemic and unspecified stroke
because we did not find any indication of different effects across these subgroups. Second, during the past decade, the diagnostic strategy and management of patients with stroke have undergone important changes, and improved hypertension control might have contributed to a reduction in stroke incidence.28,29 Therefore, we controlled for such potential calendar effects by adjusting for birth cohort in 5-year intervals. Third, we were able to control for several important potential confounders, but we are aware that these may not be sufficient to avoid residual confounding. Because our focus in this study was initiated by a specific interest in mechanisms driving social inequality in stroke, we defined both behavioral risk factors (eg, alcohol intake and physical activity) and biological risk factors (eg, diabetes mellitus and atrial fibrillation) as intermediate variables rather than

Table 3. RD per 100 000 Person-Years at Risk of Ischemic Stroke (2005 Cases in Men, 1608 Cases in Women) and Hemorrhagic Stroke (776 Cases in Men and Women Together) Associated With 2-Way Combined Effects of Education, Smoking, and Hypertension, Among 68 643 Participants From the Social Inequality in Cancer Cohort

<table>
<thead>
<tr>
<th>Combined effects of education and smoking</th>
<th>Ischemic Stroke</th>
<th>Hemorrhagic Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>High education and no smoking</td>
<td>200 0 (Ref.)</td>
<td>0 (Ref.)</td>
</tr>
<tr>
<td>Low education and no smoking</td>
<td>710 42 (−5, 90)</td>
<td>651 23 (−11, 57)</td>
</tr>
<tr>
<td>High education and current smoking</td>
<td>139 112 (38, 186)</td>
<td>85 156 (91, 221)</td>
</tr>
<tr>
<td>Low education and current smoking</td>
<td>956 289 (238, 340)</td>
<td>760 231 (192, 270)</td>
</tr>
</tbody>
</table>

P value for interaction

No. of extra cases because of interaction

Combined effects education and hypertension

High education and no hypertension

No smoking and no hypertension

Current smoking no hypertension

No smoking and hypertension

Current smoking hypertension

P value for interaction

No. of extra cases because of interaction

CI indicates confidence interval; Ref, reference category; and RD, rate difference.

Figure. Rate difference per 100 000 person-years at risk of ischemic stroke (2005 cases in men and 1608 cases in women) associated with 3-way combined effects of education, smoking, and hypertension, among 68 643 men and women from the Social Inequality in Cancer cohort adjusted for age, cohort study, and birth cohort.
confounders of the education–stroke relationship. Fourth, the observed interactions between education and smoking in this study may be partly explained by the crude categorization of the smoking variable, which might result in an interaction if the residual exposure to smoking within each category depends on education. Another explanation of the interaction is education-dependent under-reporting of smoking or smoking- and education-dependent residual confounding by unobserved variables. However, our sensitivity analysis showed that the observed interaction was robust to the use of a 4-category smoking variable tested with different cutoff points for heavy smoking.

These caveats considered, the public health message of the current study is that targeted interventions with a given reduction in smoking among people from lower socioeconomic groups would yield a greater reduction in ischemic stroke than interventions targeting people from higher socioeconomic groups. Similarly, universal interventions (eg, legislation or taxes) with the same reduction of smokers in both groups would have the strongest effect on ischemic stroke in people from lower socioeconomic groups.

Conclusions

We showed that the combined effect of socioeconomic position and smoking exceeded the sum of their separate absolute effect on risk of ischemic stroke, particularly among men. We also found evidence of an interaction between smoking and hypertension on risk of both ischemic and hemorrhagic stroke. Because both the prevalence and the effect of smoking and hypertension are socially skewed, reducing smoking in lower socioeconomic groups may be partly explained by the crude categorization of the smoking variable, which might result in an interaction if the observed interaction between education and smoking exceeded the sum of their separate absolute effects. However, our sensitivity analysis showed that the observed interaction was robust to the use of a 4-category smoking variable tested with different cutoff points for heavy smoking.

Acknowledgments

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Disclosures

None.

References


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