Cigarette Smoking and Other Risk Factors for Silent Cerebral Infarction in the General Population

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Background and Purpose—Silent cerebral infarctions (SCIs) have a prevalence between 10% and 40% in the transient ischemic attack population and have been associated with increased mortality and morbidity; however, little is known about the prevalence and risk factors for SCI in the general population. This report focuses on the role of cigarette smoking and other risk factors for SCI in the general population.

Methods—MRI scans were performed on 1737 participants selected from the general population as part of the Atherosclerosis Risk in Communities Study. Smoking status and other major cerebrovascular risk factors were assessed, and associations between smoking status and SCIs were established with the use of ANCOVA.

Results—Overall, the prevalence of SCI in this population aged 55 to 70 years was 11%. Cigarette smoking had an ordered association ($P=0.029$) with the presence of SCI, with the odds ratio (OR) of nonsmoking participants exposed to environmental tobacco smoke being 1.06 (95% confidence interval [CI], 0.64 to 1.75) times as great as for nonsmokers not exposed; the OR of past smokers was 1.16 (95% CI, 0.74 to 1.83) times greater, and the OR of current smokers was 1.88 (95% CI, 1.13 to 3.13) times greater. An increased prevalence was also noted among black, older, and hypertensive participants.

Conclusions—This report is among the first to examine the risk factors for SCI in the general population and finds a relatively high overall prevalence (11%). There is an ordered relationship between increasing exposure to cigarette smoke and the presence of SCI that parallels the relationship between smoking and carotid atherosclerosis. The magnitude of the association with smoking is substantial compared with the effect of hypertension and other traditional cerebrovascular risk factors. The reduction in prevalence of SCI between current and past smokers and the trend that increased pack-years of smoking is related to increased prevalence of SCI are both additional arguments for smoking avoidance and cessation. (Stroke. 1998;29:913-917.)

Key Words: cerebral ischemia ■ cigarette smoking ■ diabetes mellitus ■ hypertension ■ magnetic resonance imaging ■ risk factors

Silent cerebral infarctions, or cerebral lesions present on radiological evaluations of the brain without corresponding clinical symptoms, were first noted as part of the evaluation of patients with TIA. More than 30 reports have described the prevalence of SCI in the TIA population, with estimates of the prevalence of SCI based on CT scans generally between 10% and 40%.1 In populations with cerebrovascular symptoms, the presence of SCIs has been associated with many “traditional” cerebrovascular risk factors including increasing age,2,3 stenosis of the carotid artery,2,4,5 hypertension,3,6 cigarette smoking,3 glucose intolerance,7 and atrial fibrillation.8,9 The presence of SCI lesions among those with cerebrovascular symptoms is important because it has been associated with higher rates of mortality10,11 and subsequent clinical cerebral infarctions.12,13

Although there has been a substantial investigation of SCI in the cerebrovascular symptomatic population, few reports have described the prevalence, risk factors, or outcome of SCI in the asymptomatic population.14 To address this shortcoming, the ARIC Study performed MRI in a subset of their cohort representing the general population. In this report we focus on the association of SCI with cigarette smoking.

Subjects and Methods

The ARIC Study is a prospective study investigating the cause and natural course of atherosclerosis and its clinical sequelae in four US communities.15 The baseline examination, conducted in 1987 through 1989, examined approximately 15 800 adults aged 45 to 65 years. Approximately 4000 adults were enrolled in each of four study areas: the northwest suburbs of Minneapolis, Minnesota; Washington County, Maryland, which includes Hagerstown; Forsyth County, North Carolina; and the northwest suburbs of Boston, Massachusetts.
North Carolina, which includes Winston-Salem; and Jackson, Mississippi. The Jackson center enrolled only black participants to allow more power to conduct racial comparisons. Follow-up examinations of the ARIC cohort were scheduled at 3-year intervals and are ongoing.

During 1993 and 1994, all cohort members 55 years and older at the Forsyth County and Jackson study sites were screened for eligibility for cerebral MRI examination (n=2877). Participants were excluded for safety reasons if they had (1) prior surgery on cerebrovascular aneurysms; (2) metal fragments in the eyes, brain, or spinal cord; (3) valvular prosthesis, cardiac pacemaker, cochlear implant, spinal cord stimulator, or other electric device; and (4) occupations associated with exposure to metal fragments. These exclusions removed few of the participants (2% of women, 6% of men, the majority because of occupations associated with exposure to metal fragments). Of those meeting the eligibility requirements, 75% of women and 79% of men agreed to participate in the MRI examination, for a total of 1934 MRI examinations. Since the focus of this report is the association of cigarette smoking with SCI, the following participants were excluded: (1) subjects with a self-report of a previously diagnosed clinical infarction in order to remove potential confounding with clinical strokes (n=46); (2) subjects who reported current cigar, cigarillo, or pipe smoking in order to remove potential effects of current smoking of tobacco products other than cigarettes (n=42); and (3) subjects who were younger than 55 years or did not have MRI reading or smoking status data available (n=109). Thus, 1737 participants were available for this analysis. Because the baseline examination dates were allocated randomly and reexamination visits were scheduled according to the anniversary date, selective sampling from the first 2 years of the 1993 to 1995 cohort reexamination does not affect the representativeness of the MRI subset of participants.

Details of the MRI scanning and image interpretation protocols used for this study have been published elsewhere. In brief, 1.5-T MR scanners (GE and Picker) were used. Axial images were angled to be parallel to the anterior commissure–posterior commissure line. The digitized data included, spin density/T2-weighted (repetition time, 3000 milliseconds; echo time, 30 and 100 milliseconds) and T1-weighted (repetition time, 500 milliseconds; echo time, 20 and 100 milliseconds) data, were evaluated at the MRI Reading Center on a Vortech Personal Display System (PDS-4) workstation. Focal cortical or deep gray structure abnormalities greater than 3 mm in diameter and exhibiting increased signal on both proton density and T2-weighted images were considered “infarctlike lesions.” Lesions in the cerebral white matter or in the brain stem had to meet the additional criterion of decreased T1-weighted signal. The κ statistic reflecting interrater reliability of lesion detection was estimated to be 0.71, and the κ statistic reflecting interreader reliability was estimated to be 0.78.

Participants’ smoking status was ascertained by a questionnaire and categorized into four strata. Current smokers were defined as those respondents who currently smoked cigarettes. Past smokers were participants who reported a history of smoking but were not currently smoking cigarettes. The remaining respondents, who reported neither current nor past cigarette use, were divided into two categories based on their exposure to ETS: (1) ETS smokers were defined as those who reported current exposure for 1 or more hours per week to ETS or “passive” smoke, and (2) nonsmokers were defined as those who reported no regular weekly exposure to ETS. The exposure to ETS was evaluated among nonsmokers by the following question: “During the past year, about how many hours per week, on average, were you in close contact with people when they were smoking? For example, in your home, in a car, at work, or in other close quarters?”

Cerebrovascular risk factors or lifestyle choices that differ among the smoking groups may underlie differences in the crude estimates of the prevalence of SCI among the smoking groups. As such, the “independent” effect of smoking was assessed by statistical adjustment with the use of logistic regression, in which adjustments were made for the impact of cerebrovascular risk factors and lifestyle choices. The cerebrovascular risk factors employed in this adjustment were hypertension (defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or self-reported antihypertensive medication use), HDL cholesterol concentration, triglyceride concentration, and diabetes (based on self-report of a physician diagnosis, hyperglycemic medication use, or fasting [8-hour] blood glucose level ≥7.8 mmol/L [140 mg/dL]). Additional adjustment was also made for lifestyle choices including dietary fat intake as indexed by the Keys score, reported leisure-time physical activity as assessed by an interviewer-administered questionnaire, BMI (calculated as weight in kilograms divided by the square of height in meters), and alcohol intake (with participants classified as current drinkers, past drinkers, or never drinkers).

In addition, regression analyses were used to relate the pack-years of cigarette exposure to the presence of SCI among past and current smokers and to relate the hours of ETS exposure to the presence of SCI among ETS smokers.

### Results

Of the 1737 participants, 444 (26%) were never smokers, 348 (20%) were ETS smokers, 651 (37%) were past smokers, and 294 (17%) were current smokers (Table 1). Overall, the prevalence of SCI was 11% (198/1737) and ranged from 9.5% among ETS smokers to 16% for current smokers. However, there were substantial differences in the risk factor and lifestyle composition of the population by smoking status, in that compared with the overall group (1) never smokers were less likely to be white or drink alcohol, less likely to have higher HDL levels, and more likely to be female; (2) ETS smokers were less likely to be current alcohol users and more likely to be hypertensive and to have higher BMI; (3) past smokers were less likely to be female and more likely to be white and past users of alcohol; and (4) current smokers were less likely to be hypertensive, diabetic, or obese and more likely to have low HDL levels, high triglyceride levels, and a high fat intake.

Table 2 provides the estimated OR for SCI across the smoking strata after adjustment for demographic factors and after further adjustment for cerebrovascular disease risk factors and lifestyle variables. In the model that adjusted for demographic factors only (“demographic” model), there was an ordered trend toward increasing odds with increasing exposure to cigarette smoking, with the odds of current smokers significantly above those of nonsmokers (95% CI, 1.35 to 3.36) and a significant trend across the smoking categories (P=0.001). In models that made further adjustment for cerebrovascular disease risk factors and lifestyle variables (“risk factor/lifestyle” model), the OR of SCI increased marginally for ETS smokers compared with the demographic model and decreased marginally for past and current smokers. However, the significance for the test of trend between smoking exposure and prevalence of SCI remained strong (P=0.029).
The impact of other risk factors on the prevalence of SCI is also provided in Table 2. The prevalence increased substantially with age (P<0.01), nonwhite race (P=0.01), and hypertension (P<0.01). The prevalence was not significantly associated with sex, diabetes, HDL level, triglyceride level, alcohol use, BMI, leisure-time physical activity, or Keys score.

Among current (n=294) and past (n=651) smokers, in the demographic model a 20-pack-year difference in smoking exposure was associated with a 20% (OR=1.20) increase in the odds of SCI (P=0.03). Further adjustment for risk factors and lifestyle factors marginally reduced the estimated impact of the 20-pack-year difference (OR=1.16), and the effect was now of only borderline statistical significance (P=0.09). The interaction between pack-years of smoking and smoking status (current versus past) was nonsignificant (P=0.37); hence, there was no indication in these data that the impact of pack-years differed between the current versus past smokers. Among ETS smokers, there was not a significant relationship between hours of exposure to ETS and the likelihood of SCIs (P>0.5, both models).

**Discussion**

Overall, the prevalence of SCI in this general population aged 55 to 70 years was 11% and as such represents a relatively common abnormality. Among the major cerebrovascular risk factors considered, current cigarette smoking and hypertension were significantly associated with prevalent SCIs. Current smoking and hypertension were both associated with an approximate doubling of the odds of SCI (1.88 for current smoking, 2.00 for hypertension). In addition, SCI was more prevalent among black participants (OR=1.64). The substantial impact of smoking as a risk factor for SCI is supported by its major role as a risk factor for clinical stroke.22 Given the substantial role of hypertension as a risk factor for clinical stroke,23 it is not surprising that it also substantially increases the risk for prevalent SCI.

Most important is the ordered relationship between increased exposure to cigarette smoke and the likelihood of SCI, increasing from never smokers (OR=1.00 as reference group), to ETS smokers (OR=1.06), to past smokers (OR=1.16), to current smokers (OR=1.88). Although the pairwise comparisons between adjacent pairs of smoking categories do not reach a level of statistical significance (P>0.05), there remains a highly significant trend across the smoking categories (P=0.029). This trend across smoking categories is remarkably similar to that previously observed between these smoking categories and carotid artery atherosclerosis, in which there were significant (P<0.05) increases in the carotid artery intimal-medial thickness between never smokers and ETS smokers, ETS smokers and past smokers, and past smokers and current smokers.24 We have also reported an ordered relationship between smoking exposure and the progression of carotid atherosclerosis,25 and we and others4,5 have previously reported that increased carotid artery atherosclerosis is a risk factor for the presence of SCI in TIA populations. In this population some of the SCIs are lacunar infarctions. It is possible that the risk factors for lacunar infarctions may differ from infarctions in the cortex; specifically, the association between carotid atherosclerosis and lacunar infarction has not been clearly established. Hence, the literature suggests that increased smoke exposure is related to atherosclerosis, but it does not necessarily associate increased atherosclerosis with increased prevalence of SCI.
The relationship between increased pack-years of smoking and increased prevalence of SCI was in the appropriate direction and reached statistical significance, indicating a dose relationship between smoking and the prevalence of SCI. This relationship was partially mediated by other risk factors but remained marginally significant after control for these factors. There was also no indication in these data that the impact of pack-years differed between past and current smokers, suggesting a chronic rather than an acute effect of smoking on the risk of SCI.

That there was not a significant relationship between hours of ETS exposure and the prevalence of SCI was expected. In our previous report of the relationship of smoking to carotid atherosclerosis, we observed only a very weak (but significant) relationship between carotid atherosclerosis and hours of ETS. While we suggested that exposure versus nonexposure to ETS can be reliably reported, we attribute the weakness of the association to the difficulty of quantifying a historical estimate of the average number of hours of ETS per week. The uncertainty in the answers to this question could introduce considerable measurement error, making the determination of the association more difficult. That the association between hours of ETS and carotid atherosclerosis is weak suggests that establishing a relationship with SCI would be difficult.

Both the ARIC Study and the Cardiovascular Health Study have recently reported the clinical correlates of "white matter disease" (total volume of periventricular and subcortical white matter signal abnormality on spin density–weighted axial images) in the general population. In the ARIC cohort, which included participants with an average age of 62 years, increasing age and hypertension were powerful predictors of the presence of white matter disease. The Cardiovascular Health Study, which was an elderly cohort (all older than 70 years at examination), found associations with increasing age, clinically silent stroke on MRI, systolic blood pressure, lower forced expiratory volume in 1 second (FEV\textsubscript{1}), and lower income, as well as an association with smoking (P<0.05). Since white matter disease almost certainly reflects ischemia, as does SCI, one could hypothesize that they share similar risk factors, which may be supported by these reports. However, the possibility of shared risk factors for SCI and white matter disease is currently an untested hypothesis that is beyond the scope of this report.

Some scientists (including those representing the tobacco industry) have suggested that differences in the health risk among smoking groups can be partially attributed to differences among the smoking categories in the prevalence of other risk factors, with smokers having a relatively adverse risk factor profile compared with nonsmokers. As such, since they are confounded with a higher prevalence of other risk factors, analyses focusing on the effect of smoking would provide biased results that would overstate the effect of smoking. In this report we controlled for the major cerebrovascular risk factors and lifestyle variables known to differ among smoking groups, and little effect on the magnitude of the estimated effect of the association with smoking was apparent. While it is possible that we failed to control for other important factors that would account for the effect of smoking, the relatively small effect of

### TABLE 2. Estimated ORs for Prevalence of Infarctlike Lesions

<table>
<thead>
<tr>
<th>Demographic Model*</th>
<th>Risk Factor/Lifestyle Model†</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>95% CI</td>
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<tr>
<td>Smoking</td>
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</tr>
<tr>
<td>Nonsmoker</td>
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</tr>
<tr>
<td>ETS smoker‡</td>
<td>1.03</td>
</tr>
<tr>
<td>Past smoker‡</td>
<td>1.32</td>
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<tr>
<td>Current smoker‡</td>
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</tr>
<tr>
<td>Demographic</td>
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</tr>
<tr>
<td>Age§</td>
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<tr>
<td>Nonwhite race</td>
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<tr>
<td>Female sex</td>
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<tr>
<td>Risk factors</td>
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<tr>
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<td>Diabetes</td>
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<td>HDL</td>
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<tr>
<td>Triglycerides</td>
<td>0.97</td>
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<tr>
<td>Lifestyle factors</td>
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<tr>
<td>Alcohol use</td>
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<td>Never use</td>
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<tr>
<td>Past use‡</td>
<td>1.37</td>
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<tr>
<td>Current use‡</td>
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</tr>
<tr>
<td>BMI</td>
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<tr>
<td>Leisure-time activity</td>
<td>0.88</td>
</tr>
<tr>
<td>Keys score</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*The demographic model represents estimates from a logistic regression with smoking, age, race, and sex in the model.
†The risk factor/lifestyle model represents estimates from a logistic regression with smoking, age, race, sex, hypertension, diabetes, HDL, triglycerides, alcohol use, BMI, leisure-time activity, and Keys score in the model.
‡OR expressed relative to nonuse.
§OR expressed for a 10-year difference.
||OR expressed for a 1 SD difference (HDL, 19.6 mg/dL; triglycerides, 91.3 mg/dL; BMI, 5.2 kg/m²; leisure-time activity score, 0.59; Keys score, 9.4).
adjustment for the major cerebrovascular risk factors suggests that such factors are unlikely to account for the association of smoking with SCIs.

Another potential weaknesses of the report is the possibility that nonparticipants (randomly selected potential participants declining the evaluations) in the ARIC Study could potentially bias the results of the study. However, for this to be of concern for this report, the likelihood of participation would have to be associated with both smoking and the prevalence of SCI. While it is possible that smokers and nonsmokers would have differential survey response rates, it is difficult to conceive of a mechanism whereby those with and without a silent disease would differentially participate in the study. SCIs and smoking were both measured with some error. However, this error would tend to bias results toward the null hypothesis of no association and as such would lead to understating the strength and magnitude of associations reported herein. Finally, the ARIC Study strove to be a population-based study representative of the general population. Although it is unlikely, it is possible that there are geographic differences in the association between smoking and SCI that are not reflected in the four study communities. Finally, the ARIC Study failed to include substantial Asian, native American, or Hispanic representation, and as such the results reported herein are restricted to black and non-Hispanic white populations.

The clinical implications of SCI remain unclear. As described above, in the cerebrovascular symptomatic population these lesions have been related to higher rates of mortality\textsuperscript{10,11} and subsequent clinical cerebral infarctions.\textsuperscript{12,13} One could infer that these lesions may be associated with a poor prognosis in the general population as well. However, there have been no prospective studies of the impact of SCI on the long-term mortality and morbidity of the general population. The long-term follow-up of participants in both the ARIC Study and the Cardiovascular Health Study\textsuperscript{28} will address these issues.

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References

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