

# Smokeless Tobacco as a Possible Risk Factor for Stroke in Men

## A Nested Case-Control Study

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**Background and Purpose**—Snuff and other forms of smokeless tobacco are widely used in some populations. Whereas the detrimental cardiovascular effects of smoking are well documented, possible health hazards associated with the use of smokeless tobacco remain controversial. The purpose of this study was to explore whether the use of snuff, a smokeless tobacco product, increases the risk of stroke in men.

**Methods**—In a nested case-control study (1 case and 2 matched controls without cardiovascular disease), information on tobacco habits was collected through population risk factor surveys. During follow-up, first-ever fatal and nonfatal strokes occurring among 25- to 74-year-old participants were identified in a population-based stroke register. The study was restricted to men (276 cases, 551 controls).

**Results**—The unadjusted odds ratio for stroke in regular cigarette smokers compared with men who never used tobacco was 2.21 (95% CI, 1.29 to 3.79). When never-smoking regular snuff dippers (excluding ex-smokers) were compared with men who never used tobacco, the unadjusted odds ratio was 1.05 (95% CI, 0.37 to 2.94). The odds ratio for never-snuffing smokers versus never-smoking snuff users was 2.90 (95% CI, 0.92 to 9.1). After adjustment for multiple cardiovascular risk factors, the odds ratio for having a stroke was 1.74 (95% CI, 0.85 to 3.54) in regular smokers and 0.87 (95% CI, 0.41 to 1.83) in regular snuff users.

**Conclusions**—Whereas regular smoking doubles the risk of stroke in men, snuff use is not associated with any apparent excess risk. Chemical moieties produced by burning tobacco are probably the most important contributors to smokers' excess risk of atherothrombotic disease, including stroke. (*Stroke*. 2003;34:●●●-●●●.)

**Key Words:** case-control studies ■ cigarette smoking ■ stroke ■ tobacco, smokeless

Cigarette smoking is pandemic, affecting large proportions of the populations worldwide. In contrast, use of smokeless tobacco is endemic, largely restricted to certain geographical areas such as North America, the Scandinavian countries, India, Bangladesh, southeast Asia, and parts of Africa.<sup>1</sup>

Of the commercially available forms of smokeless tobacco, snuff is probably the most widespread. It constitutes pulverized tobacco that is most often moist and taken orally, either in a loose form or in tea bag–like small packages (sachets) placed between the gum and the chin or under the upper lip.

Cardiovascular and other health hazards associated with the use of moist snuff are poorly documented.<sup>1</sup> Three studies performed in Sweden have consistently demonstrated a much lower risk of myocardial infarction and sudden death among snuff users than among cigarette smokers.<sup>2–4</sup> Whereas no excess risk at all for myocardial infarction was observed in snuff users in 2 of the studies,<sup>2,4</sup> the third study showed a 40% higher risk of cardiovascular death in snuff dippers compared with nonusers of tobacco.<sup>3</sup>

Nothing is known about the influence of smokeless tobacco on the risk of stroke. The present study was initiated to

resolve this issue. A nested case-control study design with matched controls was used. Within cohorts of people who had been examined for cardiovascular risk factors, including tobacco habits, participants who later suffered a stroke were identified. Contrary to conventional case-control studies, risk factor data collection is prospective in the nested study design. A population-based stroke register was used to identify participants in the survey who later suffered a fatal or nonfatal stroke. Because few women were snuff users, the study was restricted to men. The cohorts were relatively young, and the mean age of patients at the time of stroke was also low (mean age, 59 years).

### Patients and Methods

This population-based study covered 25- to 74-year-old people in the 2 northernmost counties in Sweden, a population with a high prevalence of snuff dipping<sup>5</sup> in a sparsely populated area with 8 acute-care hospitals. Because few middle-aged and elderly women in this population are snuff users (see Results), the study was restricted to men. It was a substudy performed within the Northern Sweden Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Project<sup>6</sup> and the Västerbotten Intervention Project (VIP).<sup>7</sup>

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The study was approved by the ethics committee at Umeå University; the computerized patient database was approved by the National Computer Data Inspection Board. Informed consent was obtained at the time of the risk factor surveys (see below), and if a stroke occurred, informed consent was obtained from patients and matched control subjects.

### Collection of Baseline Risk Factor Information

In this nested case-control study, cases and controls were obtained from 2 cohort studies, the Northern Sweden MONICA Project and VIP. In the MONICA Project, 2000 to 2500 randomly selected samples of 25- to 74-year-old inhabitants of 2 Swedish counties (Norrbotten and Västerbotten; target population, 316 015 in 1999) stratified by age and sex were invited to health surveys in 1986, 1990, 1994, and 1999.<sup>6</sup> All participants responded to detailed questionnaires, including items on tobacco habits. The mean participation rate in the 4 surveys was 77.2%. Previous analyses of nonparticipants in the Northern Sweden MONICA surveys have shown that the prevalence of smoking has been somewhat higher in nonparticipants than in participants.<sup>5</sup>

VIP started in 1985. All men and women in Västerbotten County are invited to a health examination the years they turn 30, 40, 50, and 60 years of age.<sup>7</sup> Between 1985 and September 2000, ≈66 300 individuals attended the health examinations, which used a simplified form of the MONICA questionnaires. Overall, the participation rate in VIP is 60%. Information on tobacco habits in VIP nonparticipants is not available.

The VIP risk factor survey protocol was designed as a simplified version of the MONICA protocol<sup>7</sup> with fewer questions but identical wording. There were also fewer response alternatives. The questionnaires from the MONICA and VIP surveys were harmonized for the purposes of the present study. For both cigarette smoking and snuff use, each participant was categorized into present user, former user, and never user. A regular cigarette smoker was defined as a person smoking ≥1 cigarette daily, and a regular snuff dipper took snuff at least once daily. A former user had quit smoking or snuffing at least 1 month previously.

The participants also responded to a number of other questions on cardiovascular risk factors; those used in the present analyses are given in the Results section. Blood pressure was measured twice in patients in the sitting position after 5 minutes of rest (with a random-zero sphygmomanometer in the MONICA Project and with a regular sphygmomanometer in VIP), and analyses of blood samples included determination of total serum cholesterol.

### Ascertainment of Stroke Events During Follow-Up

All cases of stroke, fatal and nonfatal, occurring in and out of hospital were recorded from 1985 to September 2000 in a standardized manner using World Health Organization (WHO) definitions and the MONICA methodology described in detail elsewhere.<sup>8,9</sup> The present study was restricted to first-ever events of stroke in subjects who did not have cancer during the follow-up. The number of subjects with confirmed or suspected stroke not included in the Northern Sweden MONICA register because of refusal after information has averaged 6 per year (0.6%).

Possible cases of stroke were validated with the MONICA criteria.<sup>8,9</sup> Criteria for diagnosis and classification of stroke have been described in detail elsewhere.<sup>8,9</sup> Subjects who died within 28 days of stroke onset were recorded as fatal cases. Of the 276 cases of stroke in the present study, 264 (96%) either have undergone a CT scan or, if fatal, have been subjected to an autopsy. Subtyping of stroke into brain infarction, intracerebral hemorrhage, and subarachnoid hemorrhage followed the criteria previously used in the WHO MONICA Project. In the present study, patients with subarachnoid hemorrhage were excluded.

Consistency over time was ensured by regular centralized quality control<sup>9</sup> and by the same personnel (K.A., B.S.) overseeing the abstracting and recording of data since 1985.

### Selection of Control Subjects

Controls without a history of cardiovascular disease or cancer were selected from the MONICA and VIP cohorts. For each stroke case, 5 matched control subjects were selected. Matching was by sex, age ( $\pm 2$  years), geographical area, year of baseline examination, and cohort (MONICA and VIP). Each control subject received a questionnaire with items on any cardiovascular events that had occurred since the baseline survey. As a first choice, the first 2 control men selected were used in the analyses. If one of them did not respond, the third (or occasionally the fourth) selected person was used as control. A substitute for the first 2 selected subjects was used in 13 of the 344 case-control triplets (3.8%).

### Statistical Analyses

Both crude odds ratios (ORs) and multiple-adjusted ORs with their 95% confidence intervals (CIs) were calculated by means of conditional logistic regression, which takes the advantage of matching the subjects (2 controls for each case) into account. In the multiple logistic regression analyses, 2 models were used, with all stroke patients analyzed together. To deal with the problem of mixed tobacco use, all snuff dippers were excluded in the first model, and all smokers were excluded in the second model. In addition to tobacco habits, the variables included as independent variables were elevated blood pressure (defined in the tables), diabetes, serum cholesterol levels, level of education, and marital status, all at the time of the baseline screening. The statistical package SPSS, version 11.0, was used for all calculations.

### Results

In the MONICA and VIP cohorts, the total number of subjects with a documented first stroke was 473. Only 2 of 197 women with stroke were snuff users at baseline, and 4 women were former snuff users. It was therefore not meaningful to analyze the impact of snuff use in women. The present study was restricted to the 276 male stroke patients and their 551 controls. Information on tobacco habits at baseline was missing for 55 subjects (30 cases, 25 controls). The proportion with missing data on tobacco habits was similar in single (3.9%) and married/cohabitant (4.8%) men. It was higher in men with a low level of education (5.9%) than in men with secondary school (0.8%) and university (1.9%) levels of education.

The mean age at the risk factor survey was 54.8 years (95% CI, 53.8 to 55.7) in the men who subsequently suffered a first stroke and 54.7 years (95% CI, 54.0 to 55.3) in their matched controls. At the time of the index stroke event, their mean age was 59.2 years (95% CI, 58.2 to 60.2). Thus, the average time span from baseline to stroke was 4.5 years (95% CI, 4.1 to 4.8).

Characteristics of the stroke patients are shown in Table 1. In this relatively young group of stroke patients, the proportion with cardioembolic stroke was low, few had serious ischemic heart disease, and the 28-day case fatality was <10%.

When both cigarette smoking and snuff use are common in a population, the classification of tobacco habits becomes complex. Of the 167 smokers in the study, 26 were concomitantly using snuff. In study subjects from the MONICA cohort with more detailed information on tobacco habits, the cigarette consumption in men who concomitantly used snuff was lower (mean, 10.0 cigarettes daily; 95% CI, 8.8 to 11.3) than in men who were exclusive smokers (mean, 13.4 cigarettes daily; 95% CI, 12.5 to 14.3). Within the group of

**TABLE 1. Characteristics of the 276 Male Stroke Patients for Whom Complete Information on Tobacco Habits was Available at Baseline**

Patient Characteristics	n (%)
Stroke subtype*	
Brain infarction without cardiac source of embolism	183 (66)
Brain infarction with cardiac source of embolism	33 (12)
Intracerebral hemorrhage	47 (17)
Undetermined	13 (5)
Concomitant disorders	
Hypertension	109 (40)
Diabetes	34 (13)
Atrial fibrillation	29 (11)
History of myocardial infarction	3 (1)
Impaired level of consciousness during hospitalization	25 (9)
Case fatality at 28 d	22 (8)

\*Diagnosis based on CT scan in 261 out of 276 patients (95%).

smokers, the proportion of high consumers ( $\geq 15$  cigarettes daily) was lower in those who concomitantly used snuff (27%) than in those who were exclusive smokers (45%).

Snuff is often used as an aid to quit or reduce smoking. Of the 121 regular snuff users in the present study, 26 (21%) were also smoking, 53 (44%) were ex-smokers, and 42 (35%) were exclusive snuff users (ie, had never smoked regularly).

In univariate analyses, stroke patients and control subjects with various combinations of present and former tobacco use were compared, and the risk of stroke was calculated in relation to never users of tobacco. An OR of 1.00 for any group of tobacco consumers means that the risk of stroke is equal to that in never users of tobacco.

The prevalence of smoking was higher among men who later suffered a stroke than among age-matched control subjects (Table 2). In contrast, the prevalence of regular snuff dipping was similar in cases and controls (Table 2).

Compared with never users of tobacco, the OR for stroke was 1.86 (95% CI, 1.13 to 3.05) among all smokers. After

**TABLE 2. Univariate Comparisons of Tobacco Habits Between 25- to 74-Year-Old Male Patients With First-Ever Stroke and Matched Control Men and ORs for Stroke Based on Conditional Logistic Regression Analyses (Taking Case-Control Matching Into Account)**

	Stroke Patients (n=276), n (%)	Controls (n=551), n (%)	OR (95% CI)
Never users of tobacco	85 (30.8)	210 (38.1)	1.00
Smokers*	67 (24.2)	102 (18.6)	1.86 (1.13–3.05)
Snuff users†	30 (10.8)	65 (11.8)	1.16 (0.60–2.22)
Other tobacco categories‡	64 (23.2)	149 (27.0)	—
Incomplete information on tobacco use	30 (10.8)	25 (4.5)	—

OR for those who never used tobacco is 1.00.

\*Including former and present snuff users.

†Including ex-smokers.

‡For example, occasional smokers and men who previously used cigarettes and/or snuff but are not present tobacco users.

**TABLE 3. Univariate Comparisons of Baseline Characteristics at Risk Factor Survey Between 25- to 74-Year-Old Male Patients With Stroke and Matched Control Men and OR for Stroke Based on Conditional Logistic Regression Analyses Taking Case-Control Matching Into Account**

	Stroke Patients (n=276), n (%)	Referents (n=551), n (%)	OR (95% CI)
Not married or cohabitant*	55 (21.1)	90 (18.3)	1.23 (0.84–1.81)
Level of education†			
Primary school	184 (71.9)	371 (70.9)	1.12 (0.69–1.83)
Secondary school	40 (15.6)	80 (15.3)	1.09 (0.60–1.99)
University	32 (12.5)	72 (13.8)	1.00 (referent)
Previously diagnosed diseases			
Blood pressure elevation‡	137 (50.6)	162 (29.5)	2.88 (2.04–4.06)
High cholesterol levels§	111 (41.4)	205 (38.0)	1.20 (0.88–1.63)
Diabetes	25 (9.9)	13 (2.5)	4.30 (2.11–8.78)

\*Includes men who were never married, divorced, or widowed or otherwise living single; information missing for 15 cases and 9 controls.

†Information missing for 20 cases and 28 controls.

‡Systolic blood pressure  $\geq 160$  mm Hg and/or diastolic blood pressure  $\geq 95$  mm Hg and/or treatment with antihypertensive drug(s); information missing for 5 cases and 2 controls.

§ $\geq 6.5$  mmol/L; information missing for 8 cases and 12 controls.

||Information missing for 23 cases and 21 controls.

exclusion of men with concomitant use of snuff from the group of smokers, the OR was 2.21 (95% CI, 1.29 to 3.79).

The OR for stroke was 1.16 (95% CI, 0.60 to 2.22) in all nonsmoking snuff users (including ex-smokers) and 1.05 (95% CI, 0.37 to 2.94) in nonsmoking snuff users who had never been smokers. Compared with the risk in never-smoking snuff users, the risk was higher among smokers (excluding concomitant snuff users), but the difference did not reach statistical significance (OR, 2.90; 95% CI, 0.92 to 9.1).

Men with stroke differed from control men in several aspects other than tobacco habits (Table 3). A somewhat lower proportion of cases were married or cohabitant, but the level of education did not differ between cases and controls. Before the first stroke, cases more often had elevated blood pressure and high serum cholesterol, and the prevalence of diabetes was higher.

Conditional logistic regression models were used to analyze the predictive value of various tobacco habits, independent of confounding factors, on the risk of stroke. Because the univariate analyses indicated that smoking was a much stronger risk factor for stroke than snuff use, we used separate regression models for smoking and use of snuff so as not to miss a small adverse effect of snuff use. All variables included in the models are given in Table 4.

When snuff dippers were excluded (model A in Table 4), elevated blood pressure and diabetes were significant independent determinants of stroke. The OR for smoking was 1.74, but the difference between cases and controls did not reach statistical significance. In a corresponding model (model B) in which smokers were excluded, only elevated blood pressure emerged as a statistically significant predictor of



**TABLE 4. Conditional Logistic Regression Analysis of Independent Predictors of Stroke Excluding Men Who Were Snuff Users (Model A) or Smokers (Model B) at Baseline. 261 valid case-control triplets in Model A and 219 in Model B**

Variable	OR (95% CI)	
	Model A	Model B
Elevated blood pressure*	6.98 (3.04–16.0)	3.93 (1.86–8.29)
Low level of education	0.54 (0.18–1.60)	0.72 (0.25–2.10)
Not married or cohabitant	1.38 (0.57–3.36)	1.23 (0.48–3.15)
Diabetes	9.85 (1.57–61.9)	2.16 (0.56–8.30)
Serum cholesterol	1.28 (0.64–2.58)	0.99 (0.51–1.94)
Regular smoking	1.74 (0.85–3.54)	—
Regular use of snuff	—	0.87 (0.41–1.83)

There were 261 valid case-control triplets in model A and 219 in model B.

\*For definition, see Table 3.

stroke. The OR associated with the use of snuff was 0.87 (Table 4).

### Discussion

Compared with never users of tobacco, smoking men had ORs for stroke of 1.86 to 2.21 in this study, depending on how smoking was categorized. This closely coincides with the 1.8-fold excess risk in meta-analyses of previous studies on the relationship between smoking and stroke in men.<sup>10</sup> Our observations do not exclude the possibility that snuff users may also have had an excess risk, because the CI of the OR included the possibilities of a lower risk and a considerably increased risk compared with nonusers of tobacco. However, snuff users consistently had an OR close to 1 (and a much lower numerical risk than smokers). Among possible confounding factors, the presence of well-known risk factors for stroke (elevated blood pressure and diabetes) predicted an increased risk of stroke. This indicates that the present study design, patient sample, and selection of matched controls were valid.

### Methodological Aspects

The strength of the present nested case-control design compared with a conventional case-control design is that information on risk factors is collected before the event. This eliminates the risk of recall bias when patients who have suffered a serious event like stroke are interviewed and ensures that information also is available in severely affected and deceased subjects. The drawback is that lifestyle, including tobacco habits, may change from the time of the baseline data collection to the time of the event, which would tend to dilute the strength of any existing correlation, resulting in lower ORs. The time from baseline to the stroke event averaged 4.5 years. This reduces the likelihood that many participants have drastically changed their lifestyles, particularly because mean age at baseline was 55 years, an age when tobacco habits are relatively stable. Few participants reported a history of ischemic heart disease at the time of the risk factor survey, and an ECG was not obtained. Therefore, it was not possible or meaningful to include cardiac variables

(ischemic heart disease or atrial fibrillation) in the regression models.

The stroke cases and the controls were obtained from 2 different study cohorts, VIP and MONICA. VIP was modeled on the MONICA study, although in a simplified version. This made responses to the questionnaires easy to harmonize. The procedures for blood pressure recordings and cholesterol measurements differed slightly between the 2 studies. Because matching was done within the cohorts (a case from the MONICA cohort was matched with 2 controls from MONICA, and a case from the VIP cohort was matched with 2 controls from VIP), this should not influence the comparisons between cases and controls.

Of the original set of case-control triplets, 19% (52 triplets) were excluded from analyses because information on tobacco habits was missing in at least 1 of the subjects. The proportion that was married or cohabitant was similar among excluded and included cases and controls, whereas a somewhat higher proportion of excluded patients had a low level of education. Because level of education was not a predictor of stroke in the present analyses, the influence of the small number of missing data on tobacco habits (ie, missing case-control triplets) should be negligible. It should be noted that the use of conditional logistic regression, which creates wider CIs than unconditional analyses, and the limited numbers of some of the variables in the regression models made the CIs of the ORs generally wide.

The participation rate in the cohorts on which this nested case-control study was based ranged from 60% to 82%. In the northern Sweden risk factor surveys, tobacco use is somewhat more common among nonresponders.<sup>2</sup> Because in this nested case-control study nonparticipation probably would be of similar magnitude in cases and their matched controls, it is unlikely that this would have affected the estimated stroke risk in various tobacco categories.

### Risk of Stroke in Snuff Users

The present results suggesting a more pronounced risk increase in smokers than in snuff users are in agreement with those obtained on the risk for myocardial infarction in 3 previous studies on the relationship between snuff use, smoking, and myocardial infarction.<sup>2–4</sup> Two of these, both case-control studies performed within the framework of the Northern Sweden MONICA Project, showed a high risk of stroke in smokers but no excess risk in snuff users.<sup>2,4</sup> The third study, a cohort study among construction workers followed up for 12 years, showed an 85% excess risk of cardiovascular death among smokers, whereas regular snuff users had a 40% excess risk.<sup>3</sup> Thus, both major manifestations of atherothrombotic disease, myocardial infarction and stroke, show the same relationship to tobacco consumption, namely a marked excess risk in smokers and no or modest risk increase in snuff users. Our study did not have the power to explore whether snuff use had different associations with the risk of particular subtypes of stroke.

### Smoking Versus Snuffing: Possible Mechanisms

The apparent difference in risk for stroke between cigarette smoking and snuff dipping provides, along with the previous

observations on myocardial infarction, important information on how the effects of smoking on cardiovascular risk are mediated. Some tobacco components are better absorbed through airways than through the buccal mucosa. Other components of tobacco smoke are produced when tobacco is burned.<sup>11</sup> Among the  $\approx 2500$  chemical substances identified in tobacco smoke, tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons are candidates for etiological agents for cardiovascular disease.<sup>12,13</sup> Although the compositions of smokeless tobacco and tobacco smoke are different, it should be noted that tobacco-specific nitrosamines can also be absorbed to a considerable extent from snuff.<sup>12</sup>

Common to cigarette smoke and snuff is nicotine. Plasma levels of nicotine are as high in snuff dippers as they are in smokers, and nicotine addiction seems to be as common in snuff users as in smokers.<sup>14</sup> In tissue culture and experimental animal models, exposure to high concentrations of nicotine has been shown to have adverse effects on a number of physiological and biochemical processes involved in atherosclerosis.<sup>15</sup> However, 2 studies that have used ultrasound to investigate intima-media thickness and other signs of atherosclerosis in the carotid arteries have observed that regular snuff dippers, in contrast to smokers, do not have more carotid arterial disease than nonusers of tobacco.<sup>16,17</sup> It thus appears that nicotine is a minor contributor to stroke or myocardial infarction (and probably to atherothrombotic mechanisms in general). It is more likely that moieties specific to tobacco smoke are more important to mediate the excess risk.

It is controversial whether there are any chronic hemodynamic effects of snuff dipping. Like smoking, snuff causes an immediate rise in heart rate and blood pressure.<sup>18</sup> Differences in resting blood pressure levels between snuff dippers and nonusers of tobacco were suggested in a study based on data from the 1970s,<sup>19</sup> but this has not been confirmed in more recent studies.<sup>20–22</sup>

The present results from Sweden cannot be extrapolated to other countries without caution. In Sweden, smokeless tobacco is now prepared without traditional smoke drying, whereas in the United States snuff is produced by fermentation, resulting in differences in the content of tobacco-specific nitrosamines.<sup>1</sup> In countries in which snuff is homemade or various additives are used, snuff may contain exceedingly high concentrations of tobacco-specific nitrosamines.<sup>1</sup>

### A Complicated Message

The present findings on stroke, together with our observations on myocardial infarction,<sup>2,4</sup> would suggest that from a cardiovascular perspective, the deleterious effects of snuff dipping are considerable less than those of cigarette smoking.

This is a complicated message. On one hand, snuff may be used as an aid to quit smoking, what has been labeled a harm reduction strategy. Sweden, where snuff use now is more common in men than smoking, has the lowest prevalence of smoking in Europe (and the lowest lung cancer rates).<sup>23</sup> On the other hand, there is often heavy addiction to nicotine among snuff dippers, and the success rate among people who try to quit using snuff is no better than that among cigarette smokers.<sup>24</sup> It has also been argued that use of smokeless

tobacco may serve as a gateway to smoking among young people.<sup>25,26</sup> When benefits and risks of access to smokeless tobacco are balanced against each other, legal authorities in different countries have come to different conclusions.

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