Smokeless Tobacco and the Risk of Stroke

Maria-Pia Hergens, PhD,[a] *Mats Lambe, MD, PhD,*[b] *Göran Pershagen, MD, PhD,*[a,c] *Andreas Terent, MD,*[d] *and Weimin Ye, MD, PhD*[b]

Background: In Sweden, use of smokeless tobacco (oral moist snuff) is common among adult men. Research on cerebrovascular effects associated with long-term use of snuff is limited and inconclusive. We aimed to study whether long-term use of snuff affects the risk of stroke.
Methods: Information on tobacco use was collected by questionnaire among Swedish construction workers attending health check-ups between 1978 and 1993. In total, 118,465 never-smoking men without a history of stroke were followed through 2003. We used the Inpatient Register and Causes of Death Register to identify subsequent morbidity and mortality from stroke and its subtypes (ischemic, hemorrhagic, and unspecified stroke). Relative risk estimates were derived from Cox proportional hazards regression model.
Results: Almost 30% of the nonsmoking men had ever used snuff. Overall, 3248 cases of stroke were identified during follow-up. Compared with nonusers of tobacco, the multivariable-adjusted relative risks for ever-users of snuff were 1.02 (95% confidence interval; 0.92–1.13) for all cases and 1.27 (0.92–1.76) for fatal cases. Further analyses on subtypes of stroke revealed an increased risk of fatal ischemic stroke associated with current snuff use (1.72; 1.06–2.78), whereas no increased risk was noted for hemorrhagic stroke.
Conclusion: Snuff use may elevate the risk of fatal stroke, and particularly of fatal ischemic stroke.

(*Epidemiology* 2008;19: 794–799)

Oral moist snuff ("snus") is a type of smokeless tobacco widely used in Sweden. In 2004, 22% of men were daily snuff users, and the prevalence is steadily increasing.[1] Stroke is one of the leading causes of disability and death in Western countries, with tobacco smoking being a well-known risk factor.[2,3] Possible associations between snuff use and stroke have been investigated only to a limited extent.

Submitted 9 August 2007; accepted 24 March 2008.
From the [a]Institute of Environmental Medicine, Karolinska Institutet; [b]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet; and [c]Department of Occupational and Environmental Health, Stockholm County Council, Stockholm, Sweden; and [d]Department of Medical Sciences, Uppsala University Hospital, Uppsala, Sweden.
Supported by an unrestricted grant from Swedish Council for Working Life and Social Research.
Supplemental material for this article is available with the online version of the journal at www.epidem.com; click on "Article Plus."
Correspondence: Maria-Pia Hergens, PhD, MEB, Nobelsväg 12, SE 171 77, Stockholm, Sweden. E-mail: maria-pia.hergens@ki.se.

ISSN: 1044-3983/08/1906-0794
DOI: 10.1097/EDE.0b013e3181878b33

Snuff consists of ground tobacco leaves that are pasteurized through a heating process. One of the constituents of snuff, nicotine, has direct cardiovascular effects through sympathicoadrenal activation.[4] The effects include increases in heart rate, systolic blood pressure, cardiac stroke volume, and coronary blood flow. Nicotine also induces vasoconstriction.[5,6] Animal studies show that nicotine may induce arrhythmias.[7] Results from the few epidemiologic studies on long-term use of snuff and the risk of stroke seem inconsistent.[8–11] One Swedish study found evidence of an increased risk of cerebrovascular mortality among snuff users,[10] whereas no such increase in risk was found in 2 later studies; 1 nested case-control study from northern Sweden[9] and 1 Swedish cohort study.[12] One American cohort study found no association between snuff use and risk of stroke,[8] whereas a subsequent US-based cohort study showed an increased risk of stroke among smokeless tobacco users but not among exclusive users of snuff.[11] None of these studies divided stroke into subtypes. Such a subdivision could be of importance, considering the different etiologies of hemorrhagic stroke and ischemic stroke.

We performed a prospective cohort study to assess the association between snuff use and the risk of stroke, with an emphasis on different types of stroke.

METHODS

Setting

This cohort has previously been described in detail.[13] In brief, the Swedish Construction Industry's Organization provided outpatient medical services to construction workers in Sweden from 1969 through 1993. This included preventive health service to all workers in the industry at stationary or mobile clinics staffed by nurses and doctors. About 80% of the construction workers attended at least 1 health check-up.[14] Information on medical history and working environment, and detailed smoking (from 1971) and snuff dipping history (from 1978), was obtained by questionnaires.

The Cohort

Exposure information was drawn from first visits starting in 1978 because data on tobacco use were incomplete before 1978. To minimize misclassification we used information on smoking (cigarettes, pipes, or cigars) from all check-ups between 1971 and 1993 to exclude participants who reported smoking daily at any time during this period. In all,

122,346 male workers who had never smoked daily were registered between 1978 and 1993. Using the unique national registration number, all subjects could be followed through record linkage to the nationwide Causes of Death Register, the Inpatient Register, and the Migration Register. We excluded 3881 men for the following reasons: inconsistent birth dates or personal identifiers (134); insufficient exposure data on snuff consumption (35); a history of stroke before entry (131); missing information on area of domicile, weight, or height (1830); and other inconsistencies (1751). The final study population comprised 118,465 men.

Follow-Up

The National Board of Health and Welfare has collected data since 1965 on individual hospital discharges in the Inpatient Register, described in detail elsewhere.[15] The proportion of the Swedish population covered by this register increased from 60% in 1969 to 85% in 1983, and to 100% in 1987, and thereafter. Each record contains up to 8 discharge diagnoses. The Causes of Death Register, which is also held by the National Board of Health and Welfare, includes information on date of death and underlying and contributory causes of death. Discharge diagnoses and death causes are coded according to the Swedish revision of 7th International Classification of Diseases (ICD-7) before 1969, ICD-8 from 1969 through 1986, ICD-9 from 1987 through 1996, and ICD-10 since 1997. We identified incident cases and subjects dying from ischemic, hemorrhagic and unspecified stroke using the Inpatient Register (as main diagnosis) and Causes of Death Register (as underlying cause). Stroke patients who survived fewer than 28 days after first admission were considered fatal cases. Stroke and its subtypes were derived in accordance with methods used in a previous study[16] (for details, see eTable, available with the online version of this article). Hemorrhagic stroke included both nontraumatic intracranial hemorrhage, and subarachnoid hemorrhage. Ischemic stroke included occlusion in both precerebral and cerebral arteries, cerebral thrombosis, and cerebral embolism, as well as transient cerebral ischemia. Ill-defined cerebrovascular diseases were categorized as unspecified stroke.

Information on Snuff Dipping and Other Risk Factors

Questionnaires provided information on amount of snuff used (g/wk), duration of snuff dipping, and time since cessation of snuff dipping. Regular snuff use was defined as consumption of at least 1 g/d for at least 1 year. Former snuff users were defined as those who had stopped using snuff more than 1 year before enrollment. The mean consumption among current snuff users was 23 g/d. We used snuff information only from the first registered visit. (Later visits varied in number and timing and were subject to self-selection; also, the number of repeated visits was age dependent.) Current users were divided into 4 groups according to amount of daily snuff intake in g/d; <12.5 g/d, 12.5–24.9 g/d, 25.0–49.9 g/d and 50 or more g/d.

Body mass index ([BMI]; weight [kg]/height [m]^2) was calculated using information from the first health check-up in 1978. Area of domicile at baseline was determined by linkage to the Total Population Register and the Register of Domestic Migration. We grouped the residence areas of participants into the northern, middle, and southern parts of Sweden. No information was available on other possible confounders, such as alcohol use and physical activity.

Statistical Analysis

Coverage of the Inpatient Register differed among counties over time. For subjects who lived in a county without coverage (or with incomplete coverage) before 1987, cohort entry was reset to the date at which the Inpatient Register had full coverage. Also, to exclude prevalent cases of stroke, we defined the date of complete coverage by the Inpatient Register as 2 years after the Register had actually achieved complete coverage. Each cohort member contributed person-years from the entry date until the date of first stroke diagnosis, death, emigration out of Sweden, the date for moving into a county without (or with incomplete) coverage by the Inpatient Register, or the end of year 2003, whichever occurred first. The incidence rate was standardized to the total person-years experienced by all participants, using 5-year age categories.

The associations between snuff dipping and risk of stroke were estimated by hazard ratios (presented as relative risks [RRs] with 95% confidence intervals [CIs]) derived from the Cox proportional hazards regression model with adjustment for attained age (as time scale),[17] BMI, and region of residence. Assumption of proportional hazards for snuff dipping and covariates was examined by the method of Shoenfeld′s partial residuals; there was no indication of violation of the assumption for any of the variables checked in regression models.[18] To assess potential influence of selection bias, a sensitivity analysis was performed by excluding the first 5 years of follow-up.

Kaplan–Meier cumulative survival curves (all causes of death or deaths due to stroke) among those who had experienced a nonfatal ischemic stroke were plotted for ever-users of snuff and never-users, with follow-up through 2003. The log-rank test was used to examine the difference of survival curves between the 2 groups. The relative risks of mortality from all causes or stroke were similarly derived from the Cox proportional hazards regression model described above.

All analyses were conducted in SAS statistical software, version 9.1 (Cary, NC). This study was approved by the Regional Ethics Committee of Umeå University.

RESULTS

Twenty-nine percent of these never-smoking men had used snuff, with the highest proportion in the youngest group

TABLE 1. Baseline Characteristics of 118,465 Never-Smoking Male Workers in the Swedish Construction Workers Cohort, Registered From 1978–1993

Characteristics	N	(%)	Snuff Use (%)		
			Never	Former	Current
Total	118,465	(100)	71	2	27
Age at entry (y)					
<35	80,667	(68)	64	2	34
35–44	17,628	(15)	82	3	16
45–55	11,184	(10)	89	1	10
55+	8986	(8)	88	1	11
BMI[a] (weight/height^2)					
<20	7610	(6)	71	1	28
20–24	71,647	(61)	72	2	26
25–30	34,148	(29)	69	2	28
30+	5060	(4)	68	1	31
Region					
North	32,815	(28)	68	2	29
Middle	61,682	(52)	71	2	27
South	23,968	(20)	74	2	25

[a]Adjusted to age distribution at entry.

(<35 years). Snuff users in general had a higher BMI than nonusers, and snuff prevalence was highest in northern Sweden (Table 1).

During an average of 18 years (>2 million person–years) of follow-up, 3248 subjects had ischemic, hemorrhagic, or unspecified stroke as a primary cause of death or primary discharge diagnosis. Among them, 2283 (70%) had ischemic stroke, 550 (17%) hemorrhagic stroke, and 415 (13%) stroke of unspecified type. The proportion of unspecified stroke decreased during the follow-up, from 16% in 1987 to 8% in 2003. This may have been the result of introduction of new diagnostic tools, such as computed tomography scanning. The average age at diagnosis was 66, 59, and 66 years among patients with ischemic, hemorrhagic, and unspecified stroke, respectively.

Table 2 provides relative risks of all types of stroke taken together, as well as stroke subtypes, for categories of snuff use. The overall relative risk of stroke among ever-users of snuff was 1.02 (95% CI = 0.92–1.13). There was an indication of an elevated risk for fatal stroke (1.27 [0.92–1.76]), which was mainly driven by an excess risk among current snuff users (1.38 [0.99–1.91]). Further analyses on subtypes of stroke showed that the excess risk was primarily confined to ischemic stroke among ever-users of snuff (1.63 [1.02–2.62]). Among former snuff users, a tendency toward decreased risk was observed for all subtypes of stroke. Further analyses among current snuff users showed no clear evidence of a dose response effect (Table 3). Sensitivity analyses excluding the first 5 years of follow-up confirmed

TABLE 2. Standardized Incidence Rates and Relative Risks of Stroke (Hemorrhagic, Ischemic, Unspecified Stroke, and All Cerebrovascular Diseases) for Snuff Users Compared With Nonusers of Tobacco Among 118,465 Never-Smoking Swedish Construction Workers

	Never-Users[a]			Ever-Use			Former Use			Current Use		
	No. Cases	SIR	RR	No. Cases	SIR	RR (95% CI)	No. Cases	SIR	RR (95% CI)	No. Cases	SIR	RR (95% CI)
All types of stroke												
All	2805	152	1.00	443	173	1.02 (0.92–1.13)	31	104	0.72 (0.50–1.02)	412	182	1.05 (0.95–1.17)
Nonfatal	2569	139	1.00	398	154	1.00 (0.89–1.11)	30	100	0.75 (0.53–1.08)	368	161	1.02 (0.91–1.14)
Fatal	236	13	1.00	45	19	1.27 (0.92–1.76)	1	5	0.30 (0.04–2.11)	44	21	1.38 (0.99–1.91)
Ischemic stroke												
All	1979	106	1.00	304	122	1.03 (0.91–1.16)	20	72	0.68 (0.44–1.06)	284	129	1.07 (0.94–1.22)
Nonfatal	1887	101	1.00	282	112	1.00 (0.88–1.13)	19	67	0.67 (0.43–1.06)	263	118	1.04 (0.91–1.18)
Fatal	92	5	1.00	22	10	1.63 (1.02–2.62)	1	5	0.82 (0.12–5.93)	21	11	1.72 (1.06–2.78)
Hemorrhagic stroke												
All	474	26	1.00	76	25	0.86 (0.67–1.10)	8	21	0.90 (0.45–1.82)	68	26	0.85 (0.65–1.10)
Nonfatal	378	21	1.00	60	19	0.82 (0.62–1.08)	8	21	1.10 (0.54–2.21)	52	19	0.77 (0.57–1.04)
Fatal	96	5	1.00	16	6	1.05 (0.61–1.80)	0		—	16	7	1.17 (0.68–2.01)
Unspecified stroke												
All	352	19	1.00	63	26	1.22 (0.93–1.61)	3	11	0.66 (0.21–2.06)	60	28	1.35 (1.02–1.80)
Nonfatal	304	16	1.00	56	22	1.25 (0.93–1.67)	3	11	0.69 (0.22–2.14)	53	24	1.31 (0.98–1.77)
Fatal	48	3	1.00	7	3	1.03 (0.47–2.31)	0		—	7	4	1.14 (0.51–2.54)

Number of person-years was 1,524,553 for never-users, 590,925 for ever-users; 43,474 for former users, and 547,452 for current users.

[a]Reference category.

SIR indicates incidence rate (per 100,000 person-years), standardized to the age distribution of person-years experienced by all study participants using 5-year age categories; RR, relative risk derived from Cox proportional hazards regression model; adjusted for age (age at follow-up was used as time scale), BMI (weight [kg]/height [m]^2, categorized into <20, 20–24.9, 25–29.9, and ≥30) and region of residence (north, middle, and south part of Sweden).

TABLE 3. Standardized Incidence Rates and Relative Risks of Stroke (Hemorrhagic, Ischemic, Unspecified Stroke, and All Cerebrovascular Diseases) for Current Snuff Users by Amount Used, Compared With Nonusers of tobacco Among 118,465 Never-Smoking Swedish Construction Workers

	Snuff Use (g/d)											
	<12.5			12.5–29.9			25–49.9			≥50		
	No. Cases	SIR	RR (95% CI)	No. Cases	SIR	RR (95% CI)	No. Cases	SIR	RR (95% CI)	No. Cases	SIR	RR (95% CI)
All types of stroke												
All	150	182	1.08 (0.92–1.27)	175	185	1.11 (0.95–1.29)	58	164	1.06 (0.82–1.38)	29	174	1.13 (0.78–1.64)
Nonfatal	133	161	1.05 (0.88–1.25)	155	162	1.07 (0.91–1.26)	53	150	1.05 (0.80–1.38)	27	161	1.13 (0.77–1.66)
Fatal	17	21	1.42 (0.86–2.32)	20	24	1.57 (0.99–2.49)	5	14	1.24 (0.51–3.03)	2	12	1.16 (0.29–4.69)
Ischemic stroke												
All	106	129	2.11 (1.10–4.07)	117	128	1.66 (0.80–3.44)	40	120	0.66 (0.09–4.76)	21	130	3.28 (0.79–13.6)
Nonfatal	96	117	1.05 (0.85–1.28)	109	118	1.08 (0.89–1.31)	39	116	1.15 (0.83–1.58)	19	118	1.19 (0.76–1.88)
Fatal	10	13	2.11 (1.10–4.07)	8	10	1.99 (0.80–3.44)	1	5	0.66 (0.09–4.76)	2	12	3.28 (0.79–13.6)
Hemorrhagic stroke												
All	20	23	0.79 (0.51–1.24)	31	26	0.92 (0.64–1.33)	11	22	0.83 (0.45–1.52)	6	24	0.91 (0.40–2.05)
Nonfatal	15	17	0.73 (0.44–1.23)	23	18	0.82 (0.53–1.25)	8	17	0.70 (0.35–1.42)	6	24	1.05 (0.47–2.37)
Fatal	5	6	1.05 (0.43–2.59)	8	8	1.43 (0.69–2.96)	3	5	1.56 (0.46–4.99)	0		—
Unspecified stroke												
All	24	30	1.39 (0.92–2.10)	27	30	1.46 (0.98–2.17)	7	21	1.16 (0.55–2.47)	2	20	0.75 (0.19–3.03)
Nonfatal	22	27	1.49 (0.97–2.30)	23	25	1.42 (0.93–2.18)	6	17	1.11 (0.49–2.50)	2	20	0.81 (0.20–3.27)
Fatal	2	3	0.78 (0.19–3.21)	4	5	1.71 (0.62–4.76)	1	5	1.65 (0.22–12.06)			—

these results, and showed a relative risk of 1.71 (1.06–2.77) for fatal ischemic stroke among ever-users of snuff.

Kaplan–Meier survival curves among those who experienced a nonfatal ischemic stroke during follow-up, either from any cause or from stroke, are shown in Figures 1 and 2. Compared with nonusers, snuff users had a higher probability of dying from either all causes (P value from log-rank test = 0.08) or stroke (P value from log-rank test = 0.02). With multivariable analyses, the relative risk for mortality from all causes was 1.32 (1.07–1.65) for ever-users of snuff compared

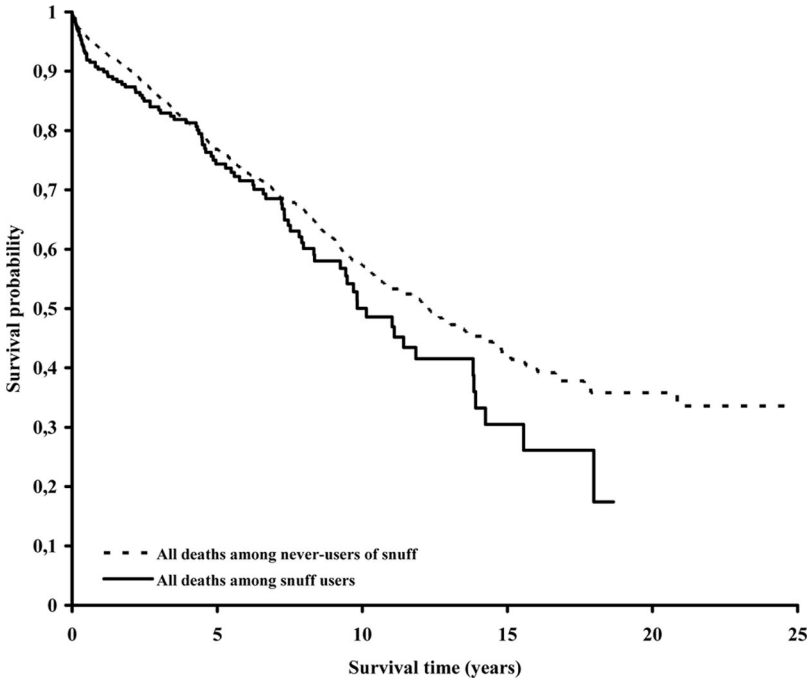

FIGURE 1. Kaplan–Meier survival curves for all deaths among male never-smoking Swedish construction workers with prior nonfatal ischemic stroke, stratified by snuff use at baseline.

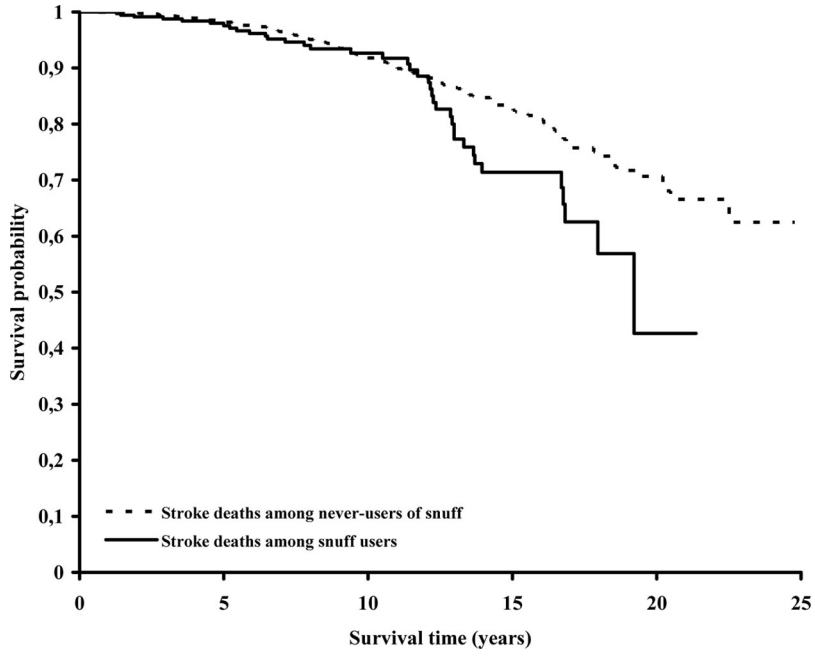

FIGURE 2. Kaplan–Meier survival curves for stroke deaths among male never-smoking Swedish construction workers with prior nonfatal ischemic stroke, stratified by snuff use at baseline.

with nonusers of tobacco. The corresponding relative risk for mortality from stroke was 1.52 (1.01–2.29).

DISCUSSION

We found no evidence of an overall elevated risk of stroke or nonfatal stroke among snuff users. However, there was an increased risk for fatal ischemic and unspecified stroke among snuff users. Our finding of no overall excess risk of stroke among snuff users is in line with 2 previous studies in Sweden.[9,12] We observed an elevated risk for fatal stroke among snuff users and also found evidence that the effect was strongest for fatal ischemic stroke among current snuff users. Results from previous studies of the association of snuff use with cerebrovascular death are inconclusive; 2 studies showed an increased risk,[11,19] whereas 2 did not.[8,12] Only 1 previous study looked separately at former and current snuff users,[11] with stronger effects among current users. None of the previous studies has subdivided stroke into subtypes. Our results did not indicate an increased risk of hemorrhagic stroke among snuff users, corroborating negative findings from a recently published Swedish study on snuff use and subarachnoid hemorrhage.[20]

Differences in etiology between hemorrhagic and ischemic stroke could help explain our results. Smoking is a well-known risk factor for stroke, and this effect seems more consistent for ischemic stroke.[3,21] A rapid decline in excess risk following cessation of smoking has suggested an acute effect from tobacco. This is supported by our data, in which the increased risk was confined to current users of snuff. We found some evidence of decreased risk for stroke among former snuff users. This may reflect negative confounding if more health cautious men quit snuff use.

Biologic mechanisms by which snuff might cause fatal ischemic stroke are not implausible. Results from animal studies show that nicotine can induce cardiac arrhythmias.[7] About 20% of all strokes are cardioembolic strokes, and atrial fibrillation is a risk factor for this type of ischemic stroke.[22,23] Cardiac embolization may explain the observed differences of risk between ischemic and hemorrhagic stroke. Also, results from in vitro studies suggest that nicotine opens the blood brain barrier, which could increase the severity of the stroke by allowing postischemic brain edema.[24] A previous study on snuff use and myocardial infarction also found an increased risk of fatal myocardial infarction, but not nonfatal cases.[25]

This study is the largest study to date on the possible association between snuff use and stroke risk. Disease-related misclassification of exposure was not an issue because data on exposure and outcome were collected from independent sources in a prospective manner. Follow-up was virtually complete, which diminishes the influence of selection bias, and the restriction of our study subjects to never-smokers minimized the risk of confounding by smoking.

Some weaknesses of our study should also be pointed out. Although use of the Inpatient Register in combination with the Causes of Death Register is an efficient way to identify cases of stroke,[26] this may lead to inclusion of nondefinite events, ie, false positives.[27] However, there is no reason to believe that misclassification of disease would differ between exposure groups (snuff users and nonusers). If anything, misclassifica-

tion would lead to a dilution of associations. Studies of stroke subtypes can be difficult due to misclassification.[27] By using only first events of stroke we decreased this problem. Further, our data suggested differential effects of snuff on risks of hemorrhagic and ischemic stroke, which allayed such a concern. Our analyses were based on the baseline information, because health status (eg, early symptoms of stroke) and exposure status (eg, snuff use) might correlate with the likelihood of obtaining later check-ups.

During extended follow-up, misclassification of exposure is a concern; tobacco use can change. Snuff users who had never smoked could be more inclined than never-users of tobacco to take up smoking during follow-up. However, previous sensitivity analysis suggests this concern is of limited influence.[28] We had information only on daily smoking; snuff users may be occasional smokers to a larger extent than never-users of tobacco. However, the observed differential associations between snuff use and risk of stroke subtypes (ischemic vs. hemorrhagic or nonfatal vs. fatal) allayed this concern, in that smoking is a risk factor for all types of stroke. Further, no excess risk of lung cancer was observed among never-smoking snuff users, as compared with nonusers of tobacco.[29] Alcohol is an important risk factor for stroke, especially hemorrhagic stroke.[30] The lack of association between snuff use and hemorrhagic stroke suggests that confounding from alcohol is unlikely to have had an important influence. Our study base consisted of male construction workers, which reduced the risk of confounding by sex, socioeconomic status, or education. Confounding by dietary and other life style factors is possible, but this would have to affect mainly fatal ischemic stroke to explain our results.

In conclusion, our results suggest that use of Swedish moist snuff is associated with an increased risk of fatal ischemic stroke. Considering the increasing prevalence of snuff use in Sweden, this association deserves to be pursued further.

REFERENCES

1. National Public Health Report. Stockholm: National Board of Health and Welfare; 2005.
2. Shinton R. Lifelong exposures and the potential for stroke prevention: the contribution of cigarette smoking, exercise, and body fat. *J Epidemiol Community Health*. 1997;51:138–143.
3. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. *BMJ*. 1989;298:789–794.
4. Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. *J Am Coll Cardiol*. 1997;29:1422–1431.
5. Fant RV, Henningfield JE, Nelson RA, et al. Pharmacokinetics and pharmacodynamics of moist snuff in humans. *Tob Control*. 1999;8:387–392.
6. Westman EC. Does smokeless tobacco cause hypertension? *South Med J*. 1995;88:716–720.
7. Mehta MC, Jain AC, Mehta A, et al. Cardiac arrhythmias following intravenous nicotine: experimental study in dogs. *J Cardiovasc Pharmacol Ther*. 1997;2:291–298.
8. Accortt NA, Waterbor JW, Beall C, et al. Chronic disease mortality in a cohort of smokeless tobacco users. *Am J Epidemiol*. 2002;156:730–737.
9. Asplund K, Nasic S, Janlert U, et al. Smokeless tobacco as a possible risk factor for stroke in men: a nested case-control study. *Stroke*. 2003;34:1754–1759.
10. Bolinder G. *Long-Term use of Smokeless Tobacco. Cardiovascular Mortality and Risk Factors* (Thesis), Karolinska Institute, 1997.
11. Henley SJ, Thun MJ, Connell C, et al. Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). *Cancer Causes Control*. 2005;16:347–358.
12. Haglund B, Eliasson M, Stenbeck M, et al. Is moist snuff use associated with excess risk of IHD or stroke? A longitudinal follow-up of snuff users in Sweden. *Scand J Public Health*. 2007;1–5.
13. Nyren O, Bergstrom R, Nystrom L, et al. Smoking and colorectal cancer: a 20-year follow-up study of Swedish construction workers. *J Natl Cancer Inst*. 1996;88:1302–1307.
14. Bolinder GM, Ahlborg BO, Lindell JH. Use of smokeless tobacco: blood pressure elevation and other health hazards found in a large-scale population survey. *J Intern Med*. 1992;232:327–334.
15. Ye W, Ekstrom AM, Hansson LE, et al. Tobacco, alcohol and the risk of gastric cancer by sub-site and histologic type. *Int J Cancer*. 1999;83:223–229.
16. Lawlor DA, Smith GD, Leon DA, et al. Secular trends in mortality by stroke subtype in the 20th century: a retrospective analysis. *Lancet*. 2002;360:1818–1823.
17. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol*. 1997;145:72–80.
18. Shoenfeld D. Partial Residuals for the Proportional hazards regression model. *Biometrika*. 1982;69:239–241.
19. Bolinder G, Alfredsson L, Englund A, et al. Smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers. *Am J Public Health*. 1994;84:399–404.
20. Koskinen LO, Blomstedt PC. Smoking and non-smoking tobacco as risk factors in subarachnoid haemorrhage. *Acta Neurol Scand*. 2006;114:33–37.
21. Hankey GJ. Smoking and risk of stroke. *J Cardiovasc Risk*. 1999;6:207–211.
22. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983–988.
23. Falk RH. Atrial fibrillation. *N Engl J Med*. 2001;344:1067–1078.
24. Hawkins BT, Brown RC, Davis TP. Smoking and ischemic stroke: a role for nicotine? *Trends Pharmacol Sci*. 2002;23:78–82.
25. Hergens MP, Alfredsson L, Bolinder G, et al. Long-term use of Swedish moist snuff and the risk of myocardial infarction amongst men. *J Intern Med*. 2007;262:351–359.
26. Merlo J, Lindblad U, Pessah-Rasmussen H, et al. Comparison of different procedures to identify probable cases of myocardial infarction and stroke in two Swedish prospective cohort studies using local and national routine registers. *Eur J Epidemiol*. 2000;16:235–243.
27. Stegmayr B, Asplund K. Measuring stroke in the population: quality of routine statistics in comparison with a population-based stroke registry. *Neuroepidemiology*. 1992;11:204–213.
28. Zendehdel K, Nyren O, Luo J, et al. Risk of gastroesophageal cancer among smokers and users of Scandinavian moist snuff. *Int J Cancer*. 2008;122:1095–1099.
29. Luo J, Ye W, Zendehdel K, et al. Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet*. 2007;369:2015–2020.
30. Hillbom M, Juvela S, Numminen H. Alcohol intake and the risk of stroke. *J Cardiovasc Risk*. 1999;6:223–228.