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Snus (Swedish smokeless tobacco) use and risk of stroke: pooled analyses of incidence and survival

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Abstract. Hansson J, Galanti MR, Hergens M-P, Fredlund P, Ahlbom A, Alfredsson L, Bellocco R, Engström G, Eriksson M, Hallqvist J, Hedblad B, Jansson J-H, Pedersen NL, Trolle Lagerros Y, Östergren P-O, Magnusson C (Karolinska Institutet, Stockholm; Stockholm County Council, Stockholm; Karolinska Institutet, Stockholm, Sweden; University of Milano-Bicocca, Italy; Karolinska Institutet, Stockholm; Lund University, Malmö; Umeå University, Umeå; Uppsala University, Uppsala; Umeå University, Umeå; Karolinska Institutet, Stockholm; Lund University, Malmö, Sweden). Snus (Swedish smokeless tobacco) use and risk of stroke: Pooled Analyses of Incidence and Survival. *J Intern Med* 2014; **276**: 87–95.

Background. Snus is a moist smokeless tobacco product with high nicotine content. Its use has a short-term effect on the cardiovascular system, but the relationship between snus use and stroke is unclear.

Objective. The aim of this study was to assess the associations between use of snus and incidence of and survival after stroke, both overall and according to subtypes.

Methods. Pooled analyses of eight Swedish prospective cohort studies were conducted, including 130 485 men who never smoked. We estimated hazard ratios (HRs) with 95% confidence intervals (CIs) of incidence and death after diagnosis using Cox proportional hazard regression models and case fatality and survival using logistic regression and Kaplan–Meier methods, respectively.

Results. No associations were observed between the use of snus and the risk of overall stroke (HR 1.04, 95% CI 0.92–1.17) or of any of the stroke subtypes. The odds ratio (OR) of 28-day case fatality was 1.42 (95% CI 0.99–2.04) amongst users of snus who had experienced a stroke, and the HR of death during the follow-up period was 1.32 (95% CI 1.08–1.61).

Conclusion. Use of snus was not associated with the risk of stroke. Hence, nicotine is unlikely to contribute importantly to the pathophysiology of stroke. However, case fatality was increased in snus users, compared with nonusers, but further studies are needed to determine any possible causal mechanisms.

Keywords: smokeless tobacco, snus, stroke.

Introduction

Snus is a moist smokeless tobacco product. Although this type of smokeless tobacco has only recently been introduced in the USA [1], it has a long tradition of use amongst Scandinavians. In particular, the prevalence of snus use is high amongst Swedish men, where the use of snus exceeds that of cigarettes (20% vs. 12%) [2]. In light of this growing trend in snus use, there is a need to clarify its health effects. The nicotine yield from snus use is equivalent to that of cigarette smoking [3, 4], and its use triggers vascular constriction and affects both heart rate and blood pressure [4]. Evidence suggests that snus use may be associated with hypertension [5–8] and fatal myocardial infarction [9], but not with ischaemic heart disease overall [6, 9–17]. Few

studies have investigated the relationship between use of snus and stroke, particularly with regard to subtypes of stroke. To date, there is no evidence to suggest any increased risk of either incident stroke overall [15–19], or haemorrhagic or ischaemic stroke specifically [19]. Relationships between the use of snus and fatal stroke, however, are reported to vary between subtypes of disease. Although no increased risk of fatal haemorrhagic stroke has been found, both the risk of and fatality after ischaemic stroke seem to be augmented [19]. The aim of the present study was to add to the existing body of evidence by investigating several aspects of the relationship between snus use and stroke in men, using the largest available sample to date. Specifically, we assessed the association between use of snus and risk of and survival after stroke, both overall and by subtype.

Methods

Setting and participants

The Swedish Collaboration on Health Effects of Snus Use is a national pooling project. Briefly, Swedish prospective studies with information on snus use and cigarette smoking were eligible for inclusion. In total, eight studies [9, 20–26] contributed data, with periods of recruitment ranging from 1978 to 2004. Details of the individual studies have been reported previously [10]. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Data collection

Self-reported tobacco use and self-reported or measured height and weight [to calculate body mass index (BMI)] were ascertained from each study, whilst self-reported level of education was available and collected from all studies except one [9]. We have previously presented further details of the data collection [10]. Outcome was assessed via record linkage to the National Inpatient Register [27] and the Cause of Death Register [28] using subjects' personal identification numbers [29]. These registers cover virtually all inpatient care and deaths in Sweden since 1987 and 1961, respectively. For each hospital admission and death, information was obtained about the primary and secondary admission diagnoses and underlying causes of death [coded according to the International Classification of Diseases (ICD) 30].

Statistical analyses

The associations between snus use and incident stroke, and overall survival after stroke, were estimated using Cox proportional hazard regression models. Study-specific and pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using attained age or age at diagnosis as the time scale. The supremum test [31] was used to assess the proportionality assumption, and the Kaplan–Meier method was used to estimate and plot the survival distribution after first stroke amongst current and noncurrent snus users. Differences in survival were assessed using the log rank test. Case fatality (defined as the probability of death within 28 days of diagnosis) amongst incident cases of stroke during follow-up was estimated using logistic regression models and presented as the odds ratio (OR) and corresponding 95% CI. We adjusted for BMI, and then additionally for educational level in separate analyses in the subsample in which this information was available [20–23, 25, 26, 32]. Analyses of case fatality and risk of death were also adjusted for year of diagnosis. Analyses were stratified by study and conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). We tested for heterogeneity across the studies using I^2 statistics.

Use of snus was primarily classified as current and noncurrent use at baseline. Where information was available, current use was further categorized according to duration (<20 or ≥20 years) [9, 21, 23, 26] and extent of use (less than four, four to six or seven or more cans per week) [9, 20–23, 26]. Information on former snus use was also available in six cohorts [9, 21–24, 26]. Smoking was considered as use of any type of smoked tobacco (cigarettes, pipe and cigars), regardless of timing. BMI was categorized according to the World Health Organization classification [33], and educational level as primary school, upper secondary school or university.

The end-point during follow-up was first ever stroke, which was defined as ICD codes I60–I61 (haemorrhagic), I63 (ischaemic) and I64 (unspecified) in ICD-10th edition, 430–431; 434 and 436 in ICD-9th edition and corresponding codes in the 8th and 7th edition. Main and secondary diagnoses as well as the underlying cause of death were considered. Participants with a history of stroke (defined as a main or secondary diagnosis of stroke according to the National Inpatient Register) were

censored at baseline. Subjects were recruited from 1978 to 2004, and the duration of follow-up was 5–29 years. Each participant contributed person-years to the analysis from the date of entry in the individual study until diagnosis of stroke, death or the end of follow-up, whichever occurred first. In analyses of ischaemic stroke, haemorrhagic or unspecified strokes led to censoring, and *vice versa*.

Analyses were restricted to men who had never smoked, and noncurrent snus users served as the reference group. Additional analyses were performed excluding the Construction Workers Cohort, as participants in this study constituted 76% of the sample. In subanalyses, we also restricted the length of follow-up to a maximum of 10 years to investigate whether a potential misclassification of exposure over time attenuated the associations. Further, we stratified the analyses by period of recruitment (1978–1984 or 1985–2004) to determine whether the findings were dependent on changes in diagnostic methods or types of snus use marketed over time. To test the influence of the inclusion of secondary diagnoses of stroke according to the National Inpatient Register, we also conducted an analysis with only primary admissions and underlying causes of death as end-points. Lastly, we assessed the impact of including former snus users in the reference group by analysing current snus users versus never users of tobacco (also excluding former snus users).

Results

The basis of the analytical sample is shown in Fig. 1. A total of 130 485 men without a history of smoking or of prior stroke at baseline were included in the study; 32 542 (25%) of them reported current use of snus. At baseline, snus users were younger than noncurrent snus users (mean age 28 and 37 years, respectively). Further baseline characteristics are shown according to snus use in Table 1 and according to cohort in Table 2. Overall, 2934 new cases of stroke were observed during a total of 2 266 921 person-years of follow-up (mean follow-up time 17 years), including 1953 cases of ischaemic stroke, 581 of haemorrhagic stroke and 400 of unspecified stroke. Mean age at diagnosis was 62 and 68 years amongst current and noncurrent snus users, respectively ($P < 0.0001$).

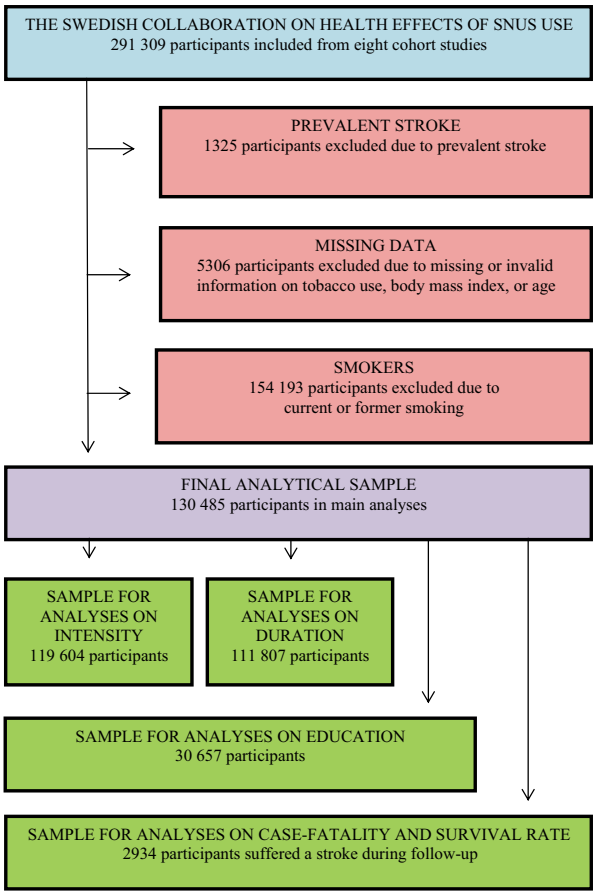

Fig. 1 *Basis of analytical samples.*

Pooled and study-specific HRs of stroke overall according to snus use at baseline are presented in Fig. 2. After adjustment for age and BMI, the HR of stroke overall was 1.04 (95% CI 0.92–1.17). There were no significant associations between snus use and risk of ischaemic stroke (HR 1.06, 95% CI 0.91–1.23), haemorrhagic stroke (HR 0.94, 95% CI 0.73–1.22) or unspecified stroke (HR 1.10, 95% CI 0.78–1.54). There were no significant differences between the results from the various studies with regard to any of the subtypes of stroke (data not shown) or overall ($I^2 = 32\%$). Restriction of follow-up to 10 years resulted in almost identical results compared with the main analyses (HR 1.00, 95% CI 0.80–1.25 for all types of stroke combined). Similar null associations were noted in subgroups defined by period of recruitment and in analyses restricted to outcomes determined as primary admission diagnoses or underlying causes of death (data not

Table 1 *The study population*

	Snus use		
	Noncurrent use	Current use	All
Participants, *n* (%)	97 942 (75)	32 542 (25)	130 485
Construction Workers Cohort (CWC)	70 310 (71)	28 998 (29)	99 308
Malmö Diet and Cancer Study (MDCS)	3082 (98)	74 (2)	3156
Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA)	1574 (83)	317 (17)	1891
National March Cohort (NMC)	6633 (94)	413 (6)	7046
Scania Public Health Survey (Scania PHS)	2366 (86)	394 (14)	2760
Stockholm Public Health Survey (Sthlm PHS)	4634 (85)	812 (15)	5446
Screening Across the Lifespan Twin Study (SALT)	6499 (88)	870 (12)	7369
Work, Lipids and Fibrinogen Study (WOLF)	2845 (81)	664 (19)	3509
Mean age at recruitment, years	37	28	35
Mean age at diagnosis, years	68	62	68
Person-years of follow-up, *n*	1 682 752	584 168	2 266 920
Cases of stroke, *n*	2630	304	2934
Ischaemic stroke	1758	195	1953
Haemorrhagic stroke	510	71	581
Unspecified stroke	362	38	400

shown). With never tobacco users as the reference group, the HR of overall stroke amongst current users was 1.01 (95% CI 0.89–1.14) based on 291 exposed cases; amongst former users, the HR was 0.88 (95% CI 0.64–1.22) based on 39 exposed cases. In additional subanalyses excluding the Construction Workers Cohort, the age- and BMI-adjusted HR for stroke was 1.13 (95% CI 0.79–1.60). This sample allowed additional adjustment for educational level, which also had only a marginal effect on the HR (HR for overall stroke, after adjustment for age, BMI and education: 1.10, 95% CI 0.78–1.57).

There was no evidence of any dose–response relationships with risk of incident stroke according to either extent or duration of snus use (Table 3). Amongst those individuals who experienced a stroke, there was no statistically significant difference in the crude survival rates between current snus users and noncurrent users (log rank test, $P = 0.30$) during the first 10 years of follow-up after a stroke diagnosis (Fig. 3) nor when followed for total time of follow-up (data not shown). The risk of death following a stroke, after adjustment for age, BMI and year of diagnosis, was increased amongst snus users (HR 1.32, 95% CI 1.08–1.61) based on 115 deaths amongst exposed cases. This increase was observed both for ischaemic (HR 1.29, 95% CI 1.00–1.67) and haemorrhagic strokes (HR 1.76, 95% CI 1.16–2.67), but did not persist after exclusion of the Construction Workers Cohort, based on 10 exposed cases. The OR for 28-day case fatality was 1.42 (95% CI 0.99–2.04) for overall stroke, based on 41 exposed cases. After exclusion of the Construction Workers Cohort, and adjustment for age, BMI and year of diagnosis, OR was 1.43 (95% CI 0.52–3.92), based on five exposed cases and was slightly increased by including educational level in the model.

Discussion

Use of snus was not associated with risks of incident ischaemic, haemorrhagic or unspecified stroke in this pooled analysis including over 130 000 men. Our null finding is in agreement with previous reports of no association between use of snus and incident stroke combined [15–19], as well as of haemorrhagic and ischaemic stroke [19]. Case fatality was increased amongst snus users in our analysis, but this increase was attenuated over time. Few studies have investigated the relationship between snus use and

Table 2 *The included cohorts*

Study	Participants (*n*)	Current snus users (%)	Mean age at recruitment (years)	Mean age at diagnosis (years)	Person-years of follow-up	Mean time of follow-up (years)	Cases of stroke (*n*)	Cases of fatal stroke (*n*)
Construction Workers Cohort (CWC)	99 308	29	30	66	2 000 601	20	2112	43
Malmö Diet and Cancer Study (MDCS)	3156	2	59	71	41 069	13	207	3
Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA)	1891	17	46	68	21 249	11	59	1
National March Cohort (NMC)	7046	6	49	74	64 212	9	233	9
Screening Across the Lifespan Twin Study (SALT)	7369	12	56	66	59 122	8	153	9
Stockholm Public Health Survey (SthlmPHS)	5446	15	46	71	27 361	5	63	3
Scania Public Health Survey (Scania PHS)	2760	14	45	74	21 660	8	81	0
Work, Lipids and Fibrinogen Study (WOLF)	3509	19	40	55	31 646	9	26	0
All studies	130 485	25	35	68	2 266 920	17	2934	68

stroke fatality [15, 19, 34]. Two of these studies were not able to demonstrate any statistically significant increased risk amongst snus users, but these findings were based on small sample sizes [15, 34]. In an update of one of these studies, an increased risk of fatal ischaemic stroke was found with a higher probability of dying amongst snus users than nonusers after an ischaemic stroke [19].

We identified cases of stroke through national registers [27, 28]. Although diagnostic information from these sources is generally considered to be highly valid [27], there has been criticism of the classification of stroke subtypes [35], and suggestions that further validations are needed [36]. Any such misclassification is likely to be nondifferential with regard to exposure, however, and is of little concern in this study, as findings were similar regardless of stroke subtype. Although snus use is relatively stable [37], misclassification of current exposure could be expected to increase over time primarily due to cessation but also to new onset of use. Because the timing of exposure to smoked tobacco is known to be of great importance with regard to the effect on the cardiovascular system [38], we conducted a subanalysis in which we restricted follow-up to 10 years to minimize exposure misclassification. Findings from this analysis, however, did not differ from the main results. Furthermore, there was no evidence of any associations between snus use and risk of stroke in sensitivity analyses excluding either the Construction Workers Cohort or all former snus users, or in analyses stratified according to period of recruitment.

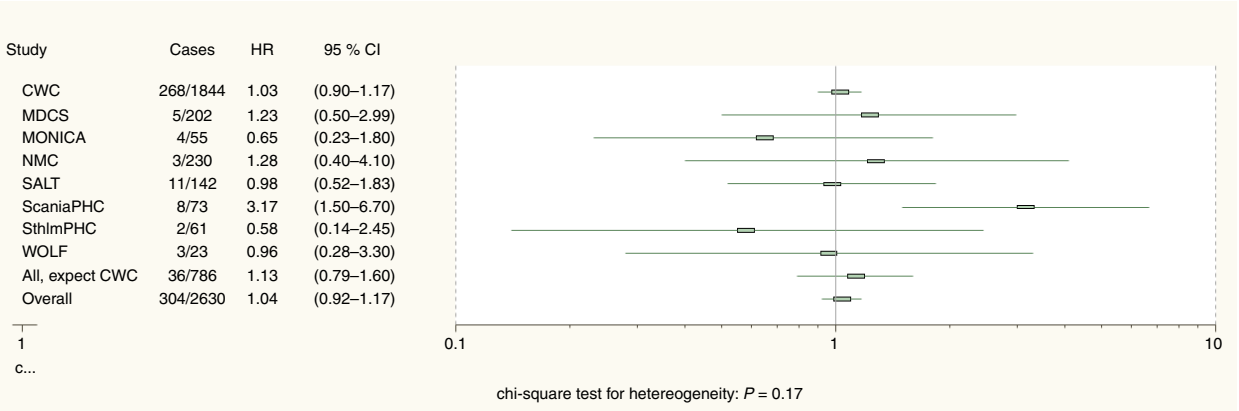

Fig. 2 *Study-specific and pooled estimated hazard ratios (HRs) and 95% confidence intervals (CIs) of stroke during follow-up amongst never smokers who used snus at baseline versus nonsnus users*

Table 3 *Pooled estimated hazard ratios (HRs) and 95% confidence intervals (95% CIs) of stroke (ischaemic, haemorrhagic, unspecified and all stroke) according to extent and duration of snus use at baseline*

	All types of stroke		Ischaemic stroke		Haemorrhagic stroke		Unspecified stroke	
	Cases	HR (95% CI)[c]	Cases	HR (95% CI)[c]	Cases	HR (95% CI)[c]	Cases	HR (95% CI)[c]
Extent of snus use[a]								
Reference	2496	1.00	1657	1.00	492	1.00	347	1.00
<4 cans/ week	235	1.05 (0.92–1.20)	151	1.06 (0.89–1.26)	52	0.95 (0.71–1.27)	32	1.16 (0.81–1.68)
4–6 cans/ week	26	1.00 (0.67–1.47)	16	1.02 (0.62–1.68)	8	1.02 (0.51–2.07)	2	0.75 (0.19–3.01)
≥7 cans/ week	14	0.72 (0.42–1.22)	6	0.54 (0.24–1.26)	5	0.78 (0.32–1.90)	3	1.52 (0.49–4.79)
Duration of snus use[b]								
Reference	2064	1.00	1374	1.00	418	1.00	272	1.00
<20 years	130	0.98 (0.81–1.18)	76	1.01 (0.79–1.29)	44	0.99 (0.71–1.38)	10	0.79 (0.41–1.51)
≥20 years	152	1.05 (0.89–1.23)	103	1.05 (0.85–1.28)	24	0.89 (0.59–1.35)	25	1.26 (0.83–1.89)

[a]Based on the CWC, MDCS, MONICA, NMC, SALT and WOLF cohorts; [b]based on the CWC, MONICA, SALT and WOLF cohorts; [c]adjusted for age and BMI.

The strengths of this study include its prospective design and large sample size, which enabled analyses of specific subtypes of stroke to be conducted and dose–response relationships to be evaluated. The study limitations include restriction of the population to men. This was necessary due to the small number of exposed women, and lack of opportunity to investigate the influence of all potential confounders. A second limitation is that the Construction Workers Cohort contributes a large proportion of cases, thus potentially influencing the overall results. However, we conducted analyses after exclusion of this cohort and demonstrated essentially the same results. Snus users differ, to varying degrees according to time periods and settings, from non-tobacco users with regard to certain lifestyle and social characteristics. Snus use has been associated with smoking [17, 37], alcohol consumption and low intake of fruit and vegetables [39]; however, results of studies investigating the association between snus use and being overweight or obese [6, 7, 32, 40, 41], as well as the level of physical activity [39, 42], are conflicting. Snus use has also been associated

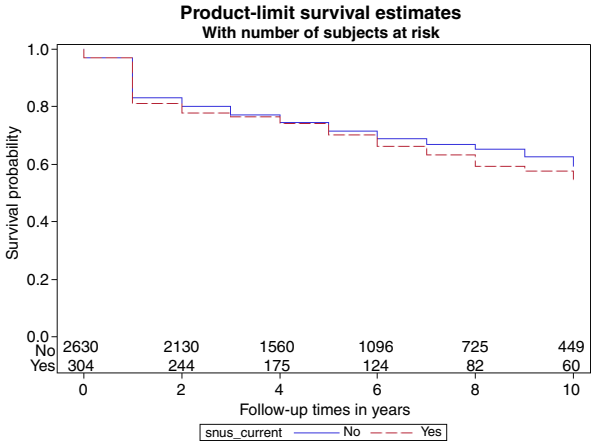

Fig. 3 *Kaplan–Meier survival distribution in current and noncurrent snus users who experienced a stroke (log rank test:* $P = 0.30$).

with low socio-economic position [37, 39]. Some of these variables are known risk factors for ischaemic and haemorrhagic stroke [43], and higher incidence and case-fatality rates of stroke have been reported amongst lower socio-economic groups [44]. Hence, these factors could be considered possible confounders. We were able to account for the effects of age, smoking, BMI and, to some extent, socio-economic position (using educational level as a proxy). We considered the possibility that BMI acts as a mediator in any potential association between snus use and stroke, and that adjustment would induce bias. However, inclusion of BMI did not materially change the results. To avoid potential confounding by smoking, all analyses were restricted to never smokers.

Confounding by socio-economic or lifestyle factors may explain our finding of an increased case-fatality rate. For example, low educational level [45] and self-reported financial strain [46] have been associated in Swedish studies with refraining from seeking healthcare. These socio-economic characteristics are, more common amongst snus users than nonusers of tobacco [37, 39]. However, the possibility of a true negative impact of snus use on stroke survival cannot be excluded. Exposure to nicotine is usually continuous amongst snus users. It is possible that the haemodynamic effects of this continuous exposure may explain the increased risk of mortality after stroke observed in this study and the previously reported increased mortality after acute myocardial infarction [47].

The levels of nicotine yield from snus use and cigarette smoking are similar [3, 4], and the relationship between smoking and risk of stroke is well established [43]. If nicotine was indeed an important contributor to the pathophysiology of smoking-related stroke, a similar impact on stroke incidence would be expected from the use of snus. Our findings thus indicate that other substances are more likely to have a causal role in the pathway between smoking and stroke. In conclusion, we found no association between the use of snus and risk of incident stroke. Case fatality seemed to be increased amongst snus users, and this association was strongest during the first weeks after diagnosis, nevertheless confounding as an explanation of the relationship cannot be ruled out.

Conflict of interest statement

The authors have no competing interests to declare.

Acknowledgements

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