Use of Scandinavian Moist Smokeless Tobacco (Snus) and the Risk of Atrial Fibrillation

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Background: Snus is a smokeless tobacco product, widely used among Swedish men and increasingly so elsewhere. There is debate as to whether snus is an acceptable "harm-reduction" tobacco product. Since snus use delivers a dose of nicotine equivalent to cigarettes, and has been implicated in cardiac arrhythmia because of associations with sudden cardiovascular death, a relation with atrial fibrillation is plausible and important to investigate.

Methods: To assess the relation between use of snus and risk of atrial fibrillation, we carried out a pooled analysis of 7 prospective Swedish cohort studies. In total, 274,882 men, recruited between 1978 and 2004, were followed via the National Patient Register for atrial fibrillation. Primary analyses were restricted to 127,907 never-smokers. Relative risks were estimated using Cox proportional hazard regression.

Results: The prevalence of snus use was 25% among never-smokers. During follow-up, 3,069 cases of atrial fibrillation were identified. The pooled relative risk of atrial fibrillation was 1.07 (95% confidence interval = 0.97–1.19) in current snus users, compared with nonusers.

Conclusion: Findings from this large national pooling project indicate that snus use is unlikely to confer any important increase in risk of atrial fibrillation.

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Snus is a moist smokeless tobacco extensively used by Swedish men (with a prevalence at around 20%), and to a lesser extent, but increasingly, also by women.[1,2] A rise in smokeless tobacco use has been reported from Norway[3] (a non-European Union country with no ban) and the United States.[3,4] In the United States and the European Union, there is an ongoing debate regarding snus as a product with the potential to reduce the risk associated with tobacco smoke.[5,6] In the wake of increasing use and the public health debate, it is important to study the possible health risks of snus use. The nicotine absorbance from snus is equivalent to that from cigarettes, but without the toxic combustion yields from smoking.[7] So far, the evidence suggests a moderate increase in risk of cardiovascular death among snus users[8] but no associations with acute myocardial infarction and stroke.[8,9] Findings for snus use and hypertension are conflicting,[10,11] but the lone existing longitudinal study showed a moderate increase in risk.[12] Atrial fibrillation/flutter (AF), the most common cardiac arrhythmia, is a risk factor for cardiovascular disease, particularly for ischemic stroke.[13–16] Risk factors for AF, in addition to age and male sex, include chronic heart disease, hypertension, diabetes, obesity, and smoking.[17–23] To date, there are no studies on snus use and risk of AF. Experimental studies in both humans and animals indicate that nicotine acutely increases the heart rate,[24,25] possibly through sympathicoadrenal-activating pathways.[26] These data, together with the epidemiologic evidence that snus use may increase case fatality in acute myocardial infarction and ischemic stroke, may indicate a role of snus use in the development of cardiac arrhythmias including AF. The long tradition and high prevalence of snus use in Sweden, coupled with the opportunity of near-complete follow-up via nationwide health data registers, makes Sweden a unique setting to explore health effects of smokeless tobacco. We

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report here on the association between snus use and risk for AF, based on a pooling project comprising the near-complete prospective data in Sweden.

METHODS

Study Population

Data from already established prospective Swedish cohort studies were pooled. The following criteria were applied for inclusion of studies: prospective design, reasonable sample size and duration of follow-up, and availability of relevant exposure information (including current use of snus, current and past smoking, and other key risk factors for cardiovascular diseases). Women were not included, due to their low prevalence of snus use. In total, 9 studies were identified, of which all but 2[27,28] joined the collaborative group for the study of snus use and AF. The collaborative pooling project and included cohorts are described in detail elsewhere.[29] The period of recruitment ranged from 1978 to 2004. Further details about the cohorts are provided in Table 1.

Baseline Information

Information about current snus use and smoking (current, former, and never) was available in all cohorts from either self-administrated questionnaires or structured telephone interviews (Table 1). Other covariates of interest were body mass index (BMI) (available in all cohorts), and educational level (available in all cohorts except the Construction Worker Cohort). BMI was categorized as <18.5; 18.5–24.9; 25–29.9; or ≥30 kg/m^2. Achieved level of education was self-reported and categorized as primary school, upper secondary school, or university.

Follow-up

The national registration number, the unique personal identifier assigned to all Swedish residents, enabled follow-up through record linkages to the nationwide Causes of Death Register and the National Patient Register held by the National Board of Health and Welfare. From 1961, the National Board of Health and Welfare compiled a complete register for causes of death coded according to the International Classification of Diagnoses (ICD-7–ICD-10). The National Patient Register covers all public in-patient care in Sweden and reached complete nationwide coverage in 1987.[30] It contains dates of admissions and discharges, with primary and secondary discharge diagnoses, coded according to the ICD.

Study participants were followed from baseline until the date of a first hospitalization with atrial fibrillation (as main or secondary diagnosis), death from any cause, emigration from Sweden (Construction Workers Cohort), or end of follow-up, whichever occurred first. The outcome, first hospitalization with atrial fibrillation, or flutter (including paroxysmal, persistent, and permanent) was ascertained via the National Patient Register, as hospitalizations for the following diagnoses: ICD-7: 433.12, 433.13; ICD-8: 427.92; ICD-9: 427D; and ICD-10: I48. Ethical approval was given by the research ethics board at Karolinska Institutet, Stockholm, Sweden.

Statistical Analysis

Hazard rate ratios measuring the associations between snus use and AF were estimated using Cox proportional hazards models. Proportional hazard assumptions were confirmed by Supremum test for hazard assumptions.[31] Snus use was categorized as current and noncurrent. Primary analyses was confined to never-smokers (of cigarettes, cigars, or pipe), to avoid potential confounding. In secondary analyses, the risks of AF according to any tobacco use (classified as current and former snus use or smoking, as well as mixed tobacco use) were investigated. All analyses used attained age (continuous) as the underlying time variable,[32] and estimates were further adjusted for BMI and achieved level of education when available.

Prior to the pooling the studies were tested for heterogeneity using the $\chi 2$ test.[33] All analyses were specified a priori, stratified by study within the models and conducted in SAS statistical software, version 9.1 (Cary, NC).

RESULTS

The analytical sample used for the primary analyses, restricted to never-smokers, consisted of 127,907 men with a total of 1,676,363 person-years of follow-up. Prevalence of current snus use was 25%. The mean age among current snus users was somewhat lower than among smokers and nonusers of tobacco. During follow-up, 3069 cases of AF were identified, 425 including among exclusive current snus users (Table 2).

There was no clear association between current snus use and risk of AF (overall pooled hazard ratio = 1.10 [95% confidence interval = 0.99–1.23]), and, although estimates differed, there was little heterogeneity among studies (Figure). Neither exclusion of the largest study (Construction Workers Cohort) nor adjustment for BMI or education changed risk estimates materially (eTable 1, http://links.lww.com/EDE/A826).

Table 2 shows relative risks for AF according to timing of snus use and smoking. Current and former smoking, but not snus use, was weakly associated with AF.

DISCUSSION

Findings from this large national pooling project do not support any important association between use of snus and risk of AF. Auxiliary results indicated a weak increase in AF risk among smokers. This is the first study on the association of snus use with the risk of AF, although previous studies have examined the effect of smoking, with conflicting results. Two studies reported weak associations, similar to our findings,[18,27] whereas 1 study found a 50% relative increase in AF risk among smokers[17] after adjusting for several risk factors. Nicotine increases the heart rate in the short-term,[25] although long-term effects on heart rate and arrhythmia have not been studied. These findings, along with evidence of increased

TABLE 1. Description of Studies Included in The Swedish Collaboration on Health Effects of Snus Use—Never-smokers

Study	Study Population	No. of Male Study Participants	Mean Age at Recruitment (Years)	Year of Recruitment	No. Person-years	Exclusive Current Snus Users (%)	Snus Information Available			Data Collection
							Duration	Amount	Former	
The Stockholm Public Health Cohort	Population-based, Stockholm County[a]	5,507	46	2002	27,233	14.8	NA	NA	Yes	Questionnaire
The Scania Public Health Cohort	Population-based, Skåne County	2,760	45	1999–2000	21,526	14.2	NA	NA	NA	Questionnaire
The National March Cohort	Participants of national charity-walk for cancer	7,364	50	1997	67,949	5.7	NA	Yes	Yes	Questionnaire
Work, Lipids, and Fibrinogen study	Employees, Väster-Norrland, Jämtland, and Stockholm County	3,532	40	1992–1998	31,857	18.9	Yes	Yes	Yes	Questionnaire, physical exam, blood sample
Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases	Population-based, Norrbotten and Västerbotten County	1,917	46	1986–2004	21,356	16.6	Yes	Yes	Yes	Questionnaire, physical exam, blood sample
Construction Workers Cohort	Employees within the construction industry, national	99,366	30	1978–1993	2,038,872	29.2	Yes	Yes	Yes	Questionnaire/nurse, physical exam
Swedish Twin Register	Twins born in Sweden1926–1958	7,470	56	1998–2002	57,704	11.8	Yes	Yes	Yes	Structured telephone interviews

NA, Not available.
[a]Stratified simple random sample.

TABLE 2. Association of Snus Use with Atrial Fibrillation, Stratified by Smoking Status, in the Pooled Data (n = 274,882)

Tobacco Exposure					
Smoking	**Snus**	**No. Cases**	**HR (95% CI)[a]**	**HR (95% CI)[b]**	**HR (95% CI)[c]**
Never	Noncurrent use[d]	3,069	1.00	1.00	1.00
	Current use	425	1.10 (0.99–1.22)	1.07 (0.97–1.19)	0.97 (0.71–1.33)
Current	Noncurrent use	3,009	1.04 (0.99–1.09)	1.08 (1.03–1.14)	1.16 (1.01–1.33)
	Current use	564	1.13 (1.03–1.23)	1.12 (1.03–1.23)	1.13 (0.82–1.56)
Former	Noncurrent use	2,865	1.12 (1.07–1.18)	1.10 (1.04–1.15)	1.11 (1.01–1.21)
	Current use	661	1.11 (1.02–1.21)	1.09 (1.00–1.19)	1.05 (0.87–1.28)

HR indicates the relative risk derived from Cox proportional hazards regression model; CI, confidence interval.
[a]Adjusted for age.
[b]Adjusted for age and BMI.
[c]Adjusted for age, BMI, and education (in a subsample the Construction Workers Cohort is excluded).
[d]Reference category.

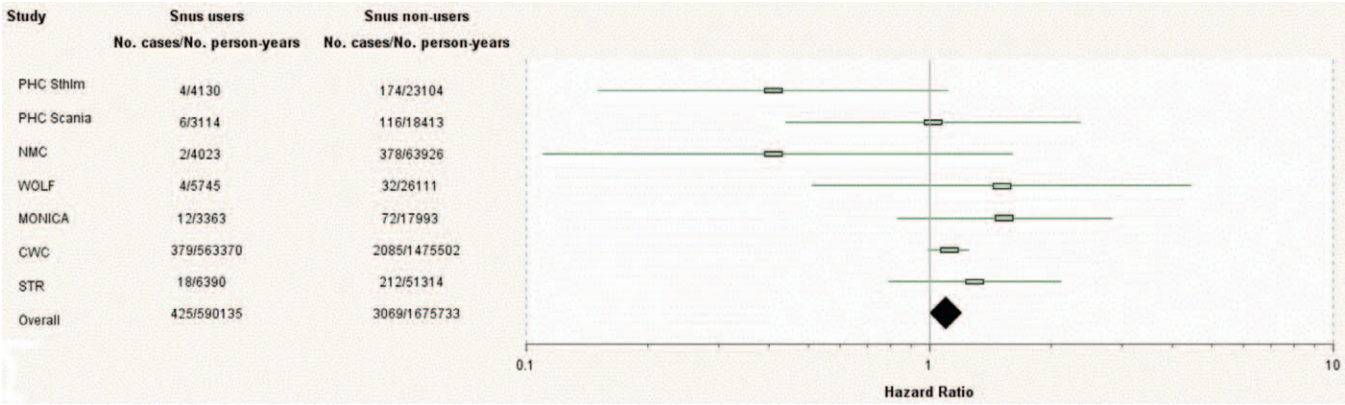

FIGURE. Study-specific and pooled estimated hazard ratios (HRs) and 95 percent confidence intervals (CIs) of atrial fibrillation among never-smokers, according to use of snus at baseline, in the Swedish collaboration on health effects of snus use. $\chi 2$ test for heterogeneity, $P = 0.28$. PHC_Stockholm indicates The Stockholm Public Health Cohort; SPHC, The Scania Public Health Cohort; NMC, The National March Cohort; CWC, Construction Workers Cohort; STR, Swedish Twin Register; WOLF, Work, lipids, and fibrinogen study; and MONICA, World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases study.

case fatality in myocardial infarction and stroke among snus users,[34] have raised concerns of an increased risk of cardiac arrhythmias in relation to snus. However, our study could not confirm any strong relation with AF.

The prospective design of this study precludes recall bias and minimizes risk of reverse causality. The large sample size allowed for analyses restricted to never-smokers and strict control of confounding by smoking. The National Patient Register does not enable complete ascertainment of AF, but a recent study showed high reliability for estimations of AF prevalence using the National Patient Register.[35] AF can be treated in the outpatient setting and may remain undetected in some patients. Using the National Patient Register for case ascertainment may therefore potentially lead to selection bias, if snus users are at increased (or decreased) risk of hospitalization for any cause. However, looking at the general perceived health among exclusive snus users, this does not seem to be the case.[36] Another factor that could have underestimated the risk among snus users would be if the snus use is affected by an outpatient diagnosis of AF prior to baseline, resulting in former users of snus with higher risk of AF being included in the nonusers group. We found no reports on changes regarding the use of snus after AF diagnosis, although 1 study[37] has found that smoking cessation was more common after intervention among patients with coronary heart disease. Although our findings are adjusted for important potential confounding factors, residual confounding may still be of concern. However, our null finding at least precludes any strong association between snus use and risk of AF.

Findings from this large national pooling project indicate that snus use is unlikely to confer any important increase in risk for AF.

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