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Long-term use of Swedish moist snuff and the risk of myocardial infarction amongst men

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Abstract. Hergens M-P, Alfredsson L, Bolinder G, Lambe M, Pershagen G, Ye W (Karolinska Institutet; Stockholm County Council; and Karolinska University Hospital; Stockholm, Sweden). Long-term use of Swedish moist snuff and the risk of myocardial infarction amongst men. *J Intern Med* 2007; **262:** 351–359.

Background. The scientific evidence on cardiovascular risks associated with long-term use of snuff is limited and inconclusive. The use of this smokeless tobacco has increased in recent decades, and adverse health effects associated with snuff use could be of great public health concern.

Objective. We aimed to study whether long-term use of snuff affects the risk of myocardial infarction.

Design. Between 1978 and 1993 all construction workers in Sweden were offered repeated health check-ups by the Swedish Construction Industry's Organization for Working Environment Safety and Health. A cohort was created with information on tobacco use and other risk factors, collected through questionnaires.

Setting. In total, 118 395 nonsmoking men without a history of myocardial infarction were followed through 2004. Information on myocardial infarction morbidity and mortality was obtained from national registers. Relative risk estimates were derived from Cox proportional hazards regression model, with adjustment for age, body mass index and region of residence.

Results. Almost 30% of the men had used snuff. In total, 118 395 nonsmoking men without a history of myocardial infarction were followed through 2004. The multivariable-adjusted relative risks for ever snuff users were 0.91 (95% confidence interval, 0.81–1.02) for nonfatal cases and 1.28 (95% confidence interval, 1.06–1.55) for fatal cases. Heavy users (≥50 g day^{-1}) had a relative risk of fatal myocardial infarction of 1.96 (95% confidence interval, 1.08–3.58). Snuff use increased the probability of mortality from cardiovascular disease amongst nonfatal myocardial infarction patients.

Conclusion. Our results indicate that snuff use is associated with an increased risk of fatal myocardial infarction.

Keywords: case fatality, cohort, myocardial infarction, relative risk, Swedish moist snuff.

Introduction

The prevalence of oral moist snuff use is increasing in Sweden and other regions, partly as a result of increasing restrictions on smoking. Sweden has a long tradition of oral use of moist snuff. In recent decades the consumption of snuff has more than doubled and today approximately 20% of adult men in Sweden are daily users [1]. The high prevalence of exposure together with the possibility of almost complete

follow-up in population-based health registers makes Sweden a unique setting for studies of possible associations between snuff dipping and adverse health effects.

The hazardous cardiovascular effects from tobacco smoking are well documented. Nicotine is one of the substances in tobacco known to affect the cardiovascular system. Several studies show that snuff users are exposed to similar or higher doses of nicotine than smokers, and generally demonstrate higher levels of serum cotinine, the primary metabolite of nicotine [2]. Comparable serum concentrations of nicotine have been reported in Swedish and American snuff users [2,3]. Acute cardiovascular effects from nicotine exposure include increases in heart rate, systolic blood pressure, cardiac stroke volume and coronary blood flow as well as vasoconstriction [3,4]. Findings in a recent study indicate that snuff dipping can cause endothelial dysfunction, a risk factor for myocardial infarction [5].

Results from the few studies available on long-term cardiovascular effects amongst users of smokeless tobacco are ambiguous. Some studies suggest that blood pressure is elevated amongst snuff users compared with nonusers [2,6–8], whilst other studies could not confirm these findings [9,10]. Results from the few epidemiological studies on snuff and the risk for myocardial infarction also appear inconsistent [11–15].

Based on a large database generated by a linkage between an extended cohort of construction workers with detailed information on snuff use [11], and several nationwide health registers on morbidity and mortality, the aim of this study was to examine possible associations between oral use of Swedish moist snuff and the risk of fatal and nonfatal myocardial infarction.

Materials and methods

Setting

The Construction Industry's Organization for Working Environment Safety and Health provided outpatient medical services to construction workers in Sweden from 1969 to 1993. The organization was a venture launched jointly by trade unions and the Swedish Construction Employers Association. About 25% of the construction workers did not attend any health check-up. There is no information as to why they did not attend or whether those who did not attend differed from the examined workers [7]. The basic follow-up units included stationary and mobile clinics, typically staffed by a few nurses and a physician. The main activity was preventive health check-up, offered to all blue-collar and white-collar workers in the building industry through regular personal invitations and advertisements at virtually all major building sites. Before each visit, the workers completed a questionnaire with approximately 200 items, including health history and working environment as well as detailed smoking and snuff dipping history. The answers were double-checked by a nurse to minimize misunderstandings and inconsistencies. Beginning with visits in 1971, data from these health check-ups were computerized.

The cohort

During the period 1971–1974 exposure information on snuff use was limited to ever or never use and between 1975 and 1978, no information about tobacco use was registered. For this reason, our analyses were based on exposure information from the first visit after 1978 to 1993. To minimize confounding, we used information on smoking (cigarettes, pipes or cigars) from all check-ups between 1971 and 1993 to exclude participants registered as having smoked daily at any time during this period. Out of 122 346 never-smoking male subjects registered during the period 1978 to 1993, 3951 were excluded for the following reasons: inconsistent birth dates or personal identifiers ($n = 134$); a previous history of myocardial infarction ($n = 244$); death or emigration between first check-up and the reset entry date into the cohort ($n = 222$) and other inconsistencies ($n = 1525$). Another 34 individuals with insufficient exposure data on snuff consumption together with 1792 subjects with missing information on area of domicile, weight or height were deleted, leaving 118 395 men for final analyses.

Follow-up

The national registration number, a unique personal identifier assigned to all Swedish residents, was used for follow-up through record linkage to the nationwide Causes of Death Register, the Inpatient Register, the Acute Myocardial Infarction Register and the Migration Register. The Acute Myocardial Infarction Register, founded in 1987, was established by combining information from the Inpatient and Causes of Death Registers [16]. Acute myocardial infarction was coded according to the Swedish revision of International Classification of Diseases 9th (1987–1997) and 10th edition (from 1997) (ICD-9:410; ICD-10:I21:I22). Cases of myocardial infarction before 1987 were identified from both the Inpatient Register and Causes of Death Register and were coded according to the Swedish revision of ICD-7 before 1969 and ICD-8 from 1969 through 1986 (ICD-7:420.10:420.17; ICD-8:410). Since the death certificates in 2004 were not computerized, they were examined and coded by one of the authors (MPH) who was blinded to snuff use status of the dead subjects.

In Sweden, there are virtually no private inpatient care services, and residents use regional hospitals within the county of their domicile, except for unusual emergency situations. Counties started reporting to the Swedish Inpatient Register in different calendar years, and only since 1987 the Register achieved nationwide coverage. To exclude patients with an earlier diagnosis of myocardial infarction, we defined the date of complete coverage for each county-specific register as 2 years after the Register had actually achieved complete coverage. For subjects who lived in a county without coverage or with incomplete Inpatient Register coverage, cohort entry dates were reset to the date when the Inpatient Register became complete in that county.

Information on snuff dipping and other risk factors

For snuff dipping, information on amount of snuff use (g $week^{-1}$), duration of snuff dipping, and time since cessation of snuff use (years) was gathered. Regular snuff use was defined as using snuff at least 1 g day^{-1} for at least 1 year. Subjects who had stopped using snuff more than 1 year before enrolment were classified as former snuff users. Current users were divided into four groups according to amount of daily snuff intake: <12.5 g day^{-1}, 12.5–24.9 g day^{-1}, 25–49.9 g day^{-1} and 50 or more g day^{-1}. The mean consumption amongst ever snuff users was 22 g day^{-1}.

At the health examination height and weight were measured, allowing calculation of body mass index [BMI, weight(kg)/height(m)^2]. Area of domicile at baseline was established by linkage to the Total Population Register and the Register of Domestic Migration. No information on other possible confounders, such as alcohol and physical activity, was available.

Statistical analysis

Each cohort member contributed person-years from the entry date until the date of first myocardial infarction diagnosis, death, emigration out of Sweden, the date for moving into a county without or with an incomplete inpatient register, or the end of year 2004, whichever occurred first. Incidence rate was standardized to the total person-years experienced by all participants using 5-year categories. The cohort was also stratified into two age groups (35–45 and 55–65) to enhance comparability with a previous study [11]. To assess selection bias a sensitivity analysis was performed by excluding the first 5 years of follow-up.

The associations between snuff dipping and risk of myocardial infarction (fatal, nonfatal and total) were estimated by hazard ratios (presented as relative risks) 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 of proportionality for any of the variables checked in the regression models [18]. Kaplan–Meier cumulative mortality curves (all death causes or all cardiovascular death causes respectively) amongst

those who had experienced a nonfatal myocardial infarction were plotted for ever snuff users and never users with follow-up through 2003. The Log-rank test was used to examine the difference between two groups. All analyses were conducted in SAS statistical software, version 9.1 (Cary, NC, USA).

This study was approved by the Regional Ethics Committee of Karolinska Institutet.

Results

Between 1978 and 1993, 118 395 male workers who had never smoked entered the cohort at a mean age of 31.5 years. The mean age at enrolment varied between 33.3, 31.1 and 26.7 years amongst never, previous and current snuff users respectively. The mean duration of follow-up was 19 years with more than 2 million cumulative person-years. Close to 30% of the never-smoking men were ever snuff users with the highest proportion in the youngest age group. After adjusting for age, snuff use tended to be more common amongst overweight and obese men. Snuff consumption was slightly more common in northern Sweden (Table 1).

During follow-up, 3651 cases of acute myocardial infarction were identified (2810 nonfatal cases and 841 fatal cases). Compared with nontobacco users, no overall increased risk of acute myocardial infarction was observed amongst snuff users. The overall relative risk of myocardial infarction amongst ever snuff users was 0.99 (95% confidence interval 0.90–1.10) (Table 2). However, an excess risk of fatal myocardial infarction was observed amongst snuff users (relative risk = 1.28, 95% confidence interval 1.06–1.55). This excess risk was confined to current snuff users, and most evident amongst heavy users (50 g or more per day) (relative risk = 1.96, 95% confidence interval, 1.08–3.58) (Table 2). The age-adjusted incidence rate of fatal myocardial infarction amongst nontobacco users was 36 per 100 000 person-years, whilst the corresponding estimate was 70 per 100 000 person-years amongst heavy snuff users (50 g or more per

Table 1 Baseline characteristics of 118 395 never-smoking men in the Swedish construction workers cohort who were first registered from 1978 to 1993

		Snuff use (%)						
				Current				
Characteristics	*n*(%)	Never	Former	Total	<12.5 g day^{-1}	12.5–24.9 g day^{-1}	25–49.9 g day^{-1}	≥50 g day^{-1}
Age at entry (years)								
<35	80 685 (68.0)	63.7	2.2	34.2	6.8	15.6	8.1	3.6
35–44	17 635 (14.9)	81.6	2.7	15.7	4.3	6.6	3.1	1.8
45–55	11 161 (9.5)	89.3	1.2	9.5	3.3	3.9	1.5	0.9
55+	8914 (7.6)	88.4	1.1	10.5	4.6	4.2	1.2	0.5
BMI[a] (weight/height^2)								
<20	7605 (6.4)	70.6	1.3	28.1	8.0	13.1	5.0	2.0
20–24	71 647 (60.5)	71.6	2.1	26.3	6.0	12.1	5.8	2.4
25–30	34 102 (28.8)	69.1	2.4	28.5	5.3	12.1	7.4	3.8
30+	5041 (4.5)	68.0	1.4	30.6	5.2	10.6	8.5	6.3
Region								
North	32 768 (27.7)	68.3	2.4	29.4	6.2	12.6	7.2	3.4
Middle	61 669 (52.0)	70.7	2.1	27.2	5.6	12.4	6.2	3.0
South	23 958 (20.3)	73.6	1.6	24.8	6.7	11.7	4.9	1.5
Total	118 395 (100)	70.6	2.1	27.3	6.0	12.3	6.2	2.8

[a]Adjusted for age distribution at entry.

Table 2 Standardized incidence rates and relative risks of myocardial infarction for snuff users compared with nontobacco users amongst male never-smoking Swedish construction workers

		All cases			Nonfatal			Fatal		
Snuff use	Person-years	Cases	SIR[a]	RR (95% CI)[b]	Cases	SIR[a]	RR (95% CI)[b]	Cases	SIR[a]	RR (95% CI)[b]
Never user	1 598 216	3198	163	Referent	2485	127	Referent	713	36	Referent
Ever user	624 046	453	167	0.99 (0.90–1.10)	325	117	0.91 (0.81–1.02)	128	51	1.28 (1.06–1.55)
Former user	45 793	37	118	0.76 (0.55–1.05)	27	84	0.70 (0.48–1.02)	10	34	1.00 (0.54–1.88)
Current user	578 253	416	173	1.02 (0.92–1.14)	298	121	0.94 (0.83–1.06)	118	53	1.32 (1.08–1.61)
12.5 g day^{-1}	132 091	167	190	1.12 (0.95–1.30)	117	132	1.02 (0.84–1.22)	50	58	1.45 (1.09–1.93)
12.5–24.9 g day^{-1}	262 064	158	158	0.93 (0.79–1.09)	113	107	0.85 (0.70–1.03)	45	50	1.22 (0.90–1.65)
25–49.9 g day^{-1}	126 763	56	162	0.95 (0.73–1.24)	44	122	0.95 (0.71–1.29)	12	39	0.95 (0.54–1.69)
≥50 g day^{-1}	57 335	35	199	1.24 (0.89–1.73)	24	129	1.06 (0.71–1.58)	11	70	1.96 (1.08–3.58)

[a]Incidence rate (1/100 000 person-years), standardized to the age distribution of person-years experienced by all study participants using 5-year age categories.
[b]RR, relative risk derived from Cox proportional hazards regression model; CI, confidence interval; adjusted for age (age at follow-up was used as time scale), body mass index [weight(kg)/height(m)^2, categorized into <20, 20–24.9, 25–29.9 and ≥30] and region of residence (northern, middle and southern Sweden).

Table 3 Relative risks of myocardial infarction for snuff users compared with nontobacco users amongst male never-smoking Swedish construction workers, stratified by age at cohort entry

	All cases		Nonfatal cases		Fatal cases	
	Cases	RR (95% CI)[a]	Cases	RR (95% CI)[a]	Cases	RR (95% CI)[a]
Age 35–54 years[b]						
Never	1463	Referent	1229	Referent	234	Referent
Ever	169	0.97 (0.86–1.09)	130	0.90 (0.79–1.04)	39	1.26 (0.98–1.63)
Former	18	0.76 (0.53–1.10)	13	0.63 (0.41–0.98)	5	1.44 (0.74–2.95)
Current	151	1.00 (0.88–1.30)	117	0.94 (0.82–1.09)	34	1.25 (0.95–1.63)
12.5 g day^{-1}	49	1.07 (0.88–1.30)	35	0.97 (0.77–1.22)	14	1.53 (1.03–2.27)
12.5–24.9 g day^{-1}	60	0.91 (0.75–1.11)	48	0.88 (0.71–1.09)	12	1.08 (0.71–1.65)
25–49.9 g day^{-1}	27	1.00 (0.75–1.33)	21	0.98 (0.71–1.35)	6	1.08 (0.56–2.10)
≥50 g day^{-1}	15	1.12 (0.76–1.64)	13	1.10 (0.72–1.68)	2	1.22 (0.50–2.96)
Age 55–65 years[b]						
Never	1423	Referent	1007	Referent	416	Referent
Ever	184	1.04 (0.90–1.20)	123	0.96 (0.80–1.15)	61	1.21 (0.95–1.55)
Former	12	0.69 (0.40–1.19)	7	0.62 (0.31–1.23)	5	0.87 (0.36–2.09)
Current	172	1.08 (0.93–1.26)	116	1.00 (0.83–1.21)	56	1.26 (0.98–1.62)
12.5 g day^{-1}	88	1.27 (1.03–1.55)	61	1.24 (0.97–1.59)	27	1.32 (0.93–1.89)
12.5–24.9 g day^{-1}	63	0.95 (0.75–1.20)	41	0.82 (0.60–1.11)	22	1.24 (0.85–1.81)
25–49.9 g day^{-1}	15	0.79 (0.49–1.27)	11	0.83 (0.47–1.47)	4	0.70 (0.29–1.69)
≥50 g day^{-1}	6	1.38 (0.74–2.57)	3	0.83 (0.31–2.22)	3	2.46 (1.09–5.55)

[a]RR, relative risk derived from Cox proportional hazards regression model; CI, confidence interval; adjusted for age (age at follow-up was used as scale), body mass index [weight(kg)/height(m)^2, categorized into <20, 20–24.9, 25–29.9 and ≥30] and region of residence (northern, middle and southern Sweden).
[b]Individuals younger than 35, or older than 65, were excluded due to few observations.

day). Sensitivity analyses excluding the first 5 years of follow-up confirmed the above results, and showed a relative risk of 1.33 (95% confidence interval 1.08–1.63) for fatal myocardial infarction amongst ever users, amongst whom heavy users had a relative risk of 1.96 (95% confidence interval 0.99–3.75). When adjusting for elevated blood pressure in the analyses, the relative risk was decreased to 1.15 (95% confidence interval 0.93–1.44) for fatal cases, amongst current snuff users.

Stratified analyses by baseline age at entry are shown in Table 3. The general risk patterns were similar amongst those who entered the cohort younger than 55 years or at age 55 or older. However, the observed excess risk for fatal myocardial infarction amongst heavy snuff users (50 g or more per day) was only evident in the older group (relative risk = 2.46, 95% confidence interval 1.09–5.55). In both age groups former snuff users tended to have a lower risk of nonfatal myocardial infarction.

Kaplan–Meier curves of mortality amongst those who experienced a nonfatal myocardial infarction during follow-up, either from all causes or cardiovascular diseases, are shown in Fig. 1 (a,b). Snuff users had a higher probability of dying from either all causes (*P*-value from log-rank test, 0.01) or cardiovascular

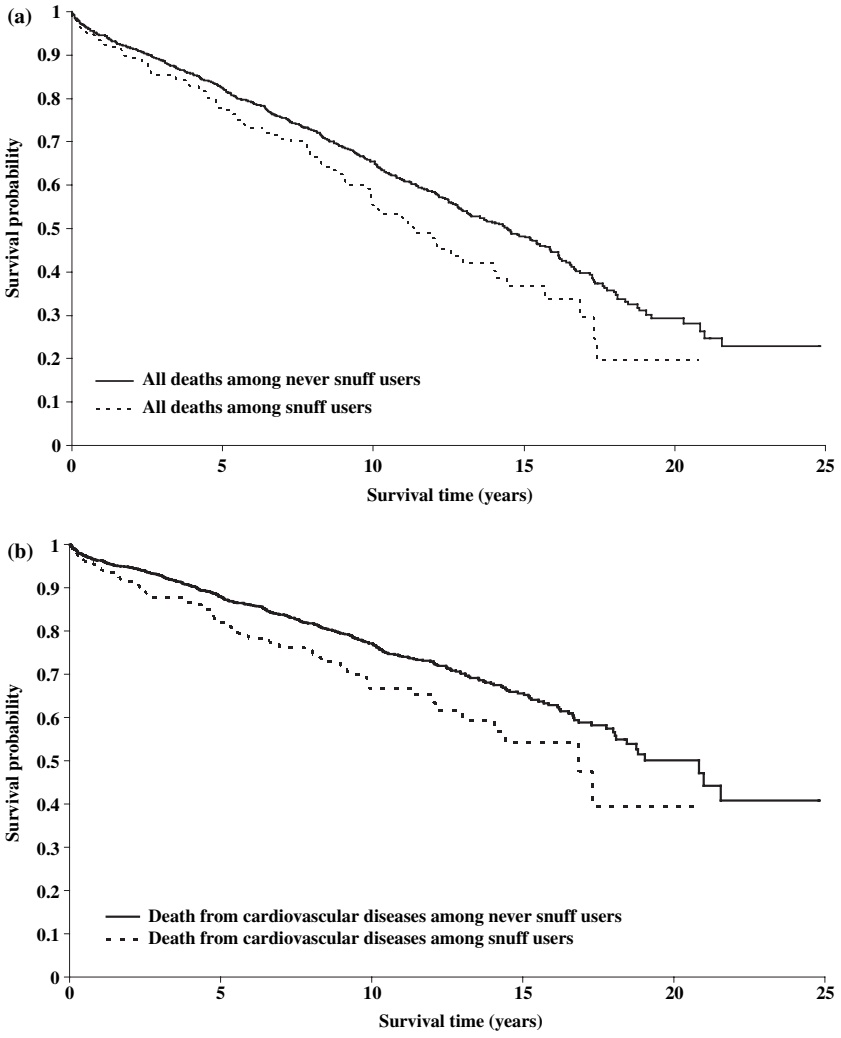

Fig. 1 Kaplan–Meier survival curves for (a) all deaths and (b) deaths from cardiovascular diseases amongst male never-smoking Swedish construction workers with prior nonfatal myocardial infarction, by snuff use at baseline.

diseases (*P*-value from log-rank test, 0.005), when compared with nonusers. Multivariable analyses showed that the relative risk for mortality from all causes was 1.38 (95% confidence interval 1.11–1.71) for ever snuff users compared with nontobacco users. The corresponding relative risk for mortality from cardiovascular diseases was 1.55 (95% confidence interval 1.19–2.01).

Discussion

Overall, we found no evidence of an elevated risk of myocardial infarction amongst snuff users. However, an increased risk was observed for fatal events amongst snuff users. Our results broadly corroborate findings in three previous Swedish case–control studies. In these studies no increased risks of myocardial infarction were observed overall, but for fatal myocardial infarction the risk estimates were elevated, albeit not statistically significant [13–15]. All of these studies, however, were based on few exposed cases, particularly for fatal myocardial infarction, which make conclusions uncertain. Results from two previous cohort studies found evidence of an increased risk of dying from cardiovascular disease amongst snuff users. The first study was based on 135 036 male Construction Workers (registered between 1971 and 1974 with follow-up until the end of 1985) and observed a relative risk of 1.4 (95% confidence interval 1.2–1.6) [11]. A recently published study was based on two US cohorts (CPS-I and CPS-II). In CPS-I (registered in 1959 and followed through 1972) the relative risk of mortality from cardiovascular diseases was 1.18 (95% confidence interval 1.11–1.26) and the relative risk of death from coronary heart disease was 1.12 (95% confidence interval 1.03–1.21) amongst users of smokeless tobacco. In CPS-II (registered in 1982 and followed through 2000) the relative risks were 1.23 (95% confidence interval 1.09–1.39) and 1.26 (95% confidence interval 1.08–1.47), for cardiovascular and coronary heart disease respectively [12]. The present study is an extension of previously mentioned cohort of construction workers [11] and included more than 200 000 new subjects and an average of 19 years of follow-up which generated a large number of cases. In this study, we also had the possibility to identify both fatal and nonfatal cases and dose-response relation across exposure categories was also explored. The present study lends further support to the hypothesis that snuff use can increase the risk of a fatal myocardial infarction.

The mechanism underlying the observed excess risk of fatal myocardial infarction is unclear. Long-term use of snuff does not appear to have a negative impact on blood lipids, fibrinolysis and other biochemical factors associated with cardiovascular disease risk. Neither has an association between snuff use and carotid or femoral atherosclerosis been found [19–21]. However, it is well known that nicotine puts additional demands on the heart by increasing the heart rate, cardiac stroke volume and coronary blood flow as well as by vasoconstriction [3,4,22]. Animal studies show that nicotine exposure can induce cardiac arrhythmias and increase the vulnerability for ventricular fibrillation following myocardial infarction [23–25]. Therefore, it is conceivable that high nicotine exposure can increase the severity of myocardial infarction amongst snuff users leading to increased risks for a fatal outcome. This hypothesis is also supported by the observed excess mortality from cardiovascular diseases amongst nonfatal myocardial infarction patients who are snuff users when compared with nonusers. When further adjusted for high blood pressure the effect of snuff on fatal cases was decreased which implies that elevated blood pressure might be in the causal pathway between snuff use and myocardial infarction. Moist snuff also includes other substances, such as sodium that could have a harmful cardiovascular effect [26]. On the other hand, it is noteworthy that moist snuff contains substances, such as fatty acids, flavonoids and nitrate that could have a protective effect for myocardial infarction [27,28]. This may contribute to explaining the null results amongst snuff users in relation to nonfatal myocardial infarction. The stronger effect of snuff use amongst the older age group might be explained by usage of older type of snuff. Former snuff users tended to have a decreased risk for nonfatal myocardial infarction. We have no obvious explanation, but negative confounding may have contributed, e.g. a healthier life style amongst those who stopped using snuff.

Our study has several strengths. The prospective design makes disease-related misclassification of exposure less likely. Furthermore, our study was limited to never smokers, minimizing the risk of confounding by smoking. Other strengths include the size of the cohort, the high exposure prevalence and the long and complete follow-up, which increases the power of the study. Recent validation of the Acute Myocardial Infarction Register, which is based on combined information from the Inpatient and Causes of Death Registers, showed that the sensitivity was 94.6% in 1987 and 95.4% in 1995, respectively, and the specificity was about 97% in both years [16]. Assuming that the misclassification of disease was the same in both exposure groups (snuff users and no-users), this would bias the observed associations toward null.

Some weaknesses of our study have to be pointed out. Although study subjects might have had up to nine repeated health check-ups, we decided to use only the baseline information, as health status (e.g. early symptoms of myocardial infarction) and exposure status (e.g. snuff use) might correlate with the likelihood of appearance in the later check-ups. Such a selection bias might influence the risk estimates. Using only baseline exposure information could, however, lead to an underestimation of the effect of snuff if users had quit their habit after start of follow-up. Further, we cannot rule out the possibility that some individuals started to smoke after enrolment which could lead to confounding from smoking, although we used all available data to exclude ever-daily smokers. Unfortunately, we lack information on a number of other potential confounders, such as alcohol intake, physical activity and diet. Several studies have shown an association between amount of alcohol consumption and the use of snuff. This association appears to be particularly pronounced amongst adolescents and young adults [8,29–31]. Moderate consumption of alcohol has been linked to a lower risk of coronary heart disease [32]. Snuff users appear to be more physically active compared with nontobacco users or users of other forms of tobacco [8,30,33], although in one case–control study a nonsignificant association between snuff use and a low level of physical activity was observed amongst the controls [15]. Furthermore, one study conducted amongst mill workers showed a nonsignificant increase of the intake of fatty foods amongst smokeless tobacco users [33]. All participants in our study were employees in the construction industry which makes this cohort relatively homogeneous in that variables, such as education and alcohol use, may not vary as much as in other, more heterogeneous populations. Taken together, it appears unlikely that confounding could fully explain the observed associations between snuff use and the risk of fatal myocardial infarction.

In conclusion, our results indicate that the use of Swedish moist snuff does not increase the overall risk of myocardial infarction, but is associated with an increased risk of fatal myocardial infarction, particularly amongst heavy users. These findings are important in a public health context considering the increasing prevalence of snuff use.

Conflict of interest

No conflict of interest was declared.

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