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The risk of myocardial infarction and sudden cardiac death amongst snuff users with or without a previous history of smoking

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Abstract. Wennberg P, Eliasson M, Hallmans G, Johansson L, Boman K, Jansson J-H (Skelleftea County Hospital, Skellefteå, University of Umeå, Umeå, and Sunderby Hospital, Luleå; Sweden). The risk of myocardial infarction and sudden cardiac death amongst snuff users with or without a previous history of smoking. *J Intern Med* 2007; **262:** 360–367.

Objectives. To investigate the risk of a first myocardial infarction (MI) and sudden cardiac death (SCD) amongst male snuff users.

Design. We used a prospective incident case-referent study design nested in the population-based Västerbotten Intervention Program and the Northern Sweden MONICA study.

Subjects. Tobacco habits and cardiovascular risk factors were assessed at baseline screening and compared in 525 male MI cases (including 93 SCD cases) and 1798 matched referents.

Results. Myocardial infarction occurred on average 4 years and 2 months after the baseline screening. No increased risk for MI was found amongst snuff users without a previous history of smoking compared with nontobacco users after adjustments for body mass index, leisure time physical activity, educational level and cholesterol level (OR 0.82; 95% CI, 0.46–1.43). For snuff users with a previous history of smoking, the adjusted OR was 1.25 (95% CI, 0.80–1.96). Significantly increased risk for MI was found in current smokers with or without current snuff use. For SCD cases with survival time <24 h, the adjusted OR for snuff users without previous history of smoking was 1.18 (95% CI, 0.38–3.70) and for cases with survival time <1 h the OR was 0.38 (95% CI, 0.08–1.89).

Conclusions. We found no increased risk for MI amongst snuff users without a previous history of smoking. Amongst snuff users with a previous history of smoking, the tendency towards an increased risk for MI may reflect the residual risk from former smoking. This study does not support the hypothesis that the risk for SCD is increased amongst snuff users.

Keywords: myocardial infarction, smokeless tobacco, snuff, sudden cardiac death.

Introduction

Smoking is a major risk factor for cardiovascular, respiratory and cancer diseases, and is considered the leading lifestyle-associated cause of death in industrialized countries. The evolving pattern of tobacco use in Sweden over the last few decades indicates a decline in smoking, especially in men, and an increasing use of snuff, a Swedish form of smokeless tobacco [1].

The effects of both smoked and smokeless tobacco use on the risk of myocardial infarction (MI) have recently been investigated in the global INTER-

HEART study [2], where smokeless tobacco was associated with increased risk. However, as the composition of the different smokeless tobacco products worldwide is very complex, general statements on cardiovascular risk may be uncertain. Five previous studies have investigated the association between the use of snuff and coronary events [3–7]. In a large Swedish cohort study which started in 1971 [4], 135 000 construction workers were followed by studying cause-specific mortality during a 12-year period. Snuff use was associated with an increased risk for dying from cardiovascular disease compared with nontobacco users. Subsequent studies have not shown an increased risk for MI amongst snuff users. However, in one study a tendency towards an increased risk of fatal MI was seen in snuff users [5], which has raised the question as to whether snuff use may initiate dysrhythmias and increase the risk of sudden cardiac death (SCD). This hypothesis is also supported by the sympathicoadrenal-activating properties of nicotine [8]. To our knowledge, there has been no previous study investigating the effects of snuff use on the risk of SCD.

The aim of this study was to investigate the risk of a first MI and the risk of SCD amongst male snuff users with or without a previous history of smoking.

Subjects and methods

Study population

We used a prospective incident case-referent study design nested in the Västerbotten Intervention Program (VIP) and the WHO MONICA study in northern Sweden. In the framework of MONICA, population-based health surveys were performed in Norrbotten and Västerbotten counties in 1986, 1990, 1994 and 1999 [9]. The participation rate in the MONICA study in northern Sweden was over 75%. In the VIP, which started in 1985, all men and women upon reaching 30, 40, 50 and 60 years of age in Västerbotten county are invited to participate in a health survey at their local primary health care centre (since 1996 at 40, 50 and 60 years of age). The participation rate in the VIP was 57%. In all, 73 880 individuals participated in the health surveys in the MONICA study in northern Sweden or the VIP from 1985 to 1999. As part of the health survey, the participants were asked to complete a questionnaire concerning cardiovascular risk factors, living conditions, medications during the last 14 days, and current and former tobacco consumption. Examinations with regard to cardiovascular risk factors such as blood pressure and lipid status were performed on all participants.

All cases of MI and SCD occurring in-hospital or out-of-hospital from the MONICA area from 1 January 1985 to 31 December 1999 were recorded in the Northern Sweden MONICA incidence registry in a standardized manner using MONICA methodology [10]. At the last follow-up on 31 December 1999, 696 cases fulfilled criteria for a first-ever MI defined by the Northern Sweden MONICA incidence registry [11] and participated in the MONICA study in northern Sweden or the VIP health surveys prior to the MI. From the population-based health surveys in VIP and MONICA, 2627 referents (≥1 per case) were randomly selected and matched for sex, age (±2 years), date of health survey (±4 months) and geographical region. Forty-five cases and 359 referents were excluded as previous MI, stroke or cancer disease could not be excluded according to questionnaire or case records. In addition, 30 referents were excluded as their corresponding cases were excluded for previous MI. Snuff use in women is rare; only 2.2% of the women in this cohort were snuff users. For that reason, 126 female cases and 440 female referents were excluded from the study. After exclusions, 525 cases and 1798 referents remained. Of these subjects, 65 cases and 210 referents were included from the MONICA study in northern Sweden and 460 cases and 1588 referents were included from the VIP study. There is an overlap of 66 of the 525 cases with previous studies using the MONICA incidence registry [3, 5]. In the present study, however, we have categorized the outcome as MI and SCD and only included first MIs. The study was approved by the Research Ethics Committee of Umeå University. Data handling procedures were approved by the National Computer Data Inspection Board. All participants gave informed consent.

Outcome variables

All cases of MI and SCD were ascertained and re-evaluated through screening of hospital discharge records, general practitioners' reports and death certificates by the Northern Sweden MONICA incidence registry in a standardized manner using MONICA methodology [10]. Thus, the diagnosis from the hospital discharge records, general practitioners' reports and death certificates were not used for classification of outcome variable. Diagnostic criteria for 'definite' MI were: unequivocal serial ECG progression (defined by the Minnesota codes), ECG progression labelled 'probable' in combination with elevated cardiac enzymes to more than twice the upper limit of normal or typical symptoms in combination with elevation of cardiac enzymes. Silent MIs found on routine examination were not included because they could not be assigned an accurate date of occurrence.

Subjects who died within 28 days from the onset of MI were recorded as fatal cases. According to the Northern Sweden MONICA incidence registry a diagnosis of fatal MI was based on necropsies and death certificates as being caused by ischaemic heart disease (ICD-9 codes 410–414, ICD-10 codes I20–I25) or cardiovascular disease, unspecified (ICD-9 code 429.2). For fatal cases we also accepted 'possible' MI [10].

For SCD cases we used two definitions: SCD with survival time <24 h and SCD with survival time <1 h. Survival time was defined as time from onset of the acute symptoms of a coronary event (or, in their absence, the fatal collapse of the person) to time of death.

Explanatory variables

Smoking was defined as daily smoking of cigarettes, cigars or tobacco pipe. Snuff consumption was defined as daily use of smokeless tobacco. Date of smoking and snuff cessation was not registered. Smoking and snuff use were categorized into eight groups: (i) never used tobacco, (ii) never smoked, current snuff user, (iii) former smoker, current snuff user, (iv) current smoker, no current snuff use, (v) current smoker, current snuff user, (vi) never smoked, former snuff user, (vii) former smoker, never used snuff, (viii) former smoker, former snuff user. Sixty-nine MI cases (including 10 SCD cases) and 130 referents could not be categorized because of missing data on either smoking or snuff use or both. Hypertension was defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg, or self-reported use of antihypertensive medication during a period of 14 days before the health survey. Statements on diabetes and the use of nitrates or other heart medicine during a period of 14 days before the health survey were obtained from the questionnaire. Body mass index (BMI) was calculated after measurements of body weight and height, as weight (kilograms) divided by height (metres squared).

As questions on leisure time physical activity differed slightly between the VIP and the MONICA questionnaire, we dichotomized this variable where individuals stating no exercise for the last 3 months (VIP) or who were never physically active during leisure time for the last year (MONICA) were categorized as low leisure time physical activity. The level of educational attainment was also obtained from the questionnaire and dichotomized. Individuals with no further education beyond compulsory school were categorized as low educational level.

Venous blood serum samples for lipid measurements were obtained after ≥4 h of fasting. Total cholesterol was measured by enzymatic methods with Reflotron bench-top analysers (Boehringer Mannheim GmbH, Mannheim, Germany) at each health survey centre at the time of the health survey. The mean interassay CV for this analysis was 2.6%.

Statistical analyses

Proportions and mean values of explanatory variables were calculated for cases and referents. In order to compare characteristics between cases and referents we used the Mann–Whitney two independent samples test for continuous variables and the chi-squared test for categorical variables. $P < 0{,}05$ (two-sided) was considered statistically significant. Conditional logistic

regression analyses were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) in univariate and multivariate models.

It is not clear whether the variables diabetes, hypertension, cholesterol and the use of nitrates or other heart medicine are mediators of an effect of snuff use on the risk or MI, or should be considered as confounders. We used the change-in-estimate method [12] to determine whether these variables should be included in the multivariate models. If inclusion of a potential confounder altered the crude OR for either of the two categories of main interest, (ii) never smoked, current snuff user and (iii) former smoker, current snuff user with 10% or more, it was considered a true confounder and included in the multivariate models.

We calculated the statistical power to detect an increased risk of MI in the two categories of main interest: (ii) never smoked, current snuff user and (iii) former smoker, current snuff user. For the category snuff users without previous history of smoking, OR >1.85 was detectable at the present exposure prevalence in referents of 15%, statistical power 80% (two-sided P <0.05). For the category snuff users with a previous history of smoking, OR >1.75 was detectable at the present exposure prevalence in referents of 18%, statistical power 80% (two-sided $P < 0.05$). Statistical analyses were performed using SPSS software package for PC version 11.5.

Missing values

The number (and proportion) of missing values per variable was: smoking 117 (8.6% in cases and 4.0% in referents), snuff use 149 (11.6% in cases and 4.9% in referents), hypertension 81 (4.4% in cases and 3.2% in referents), diabetes 73 (5.7% in cases and 2.4% in referents), BMI 73 (4.2% in cases and 2.8% in referents), cholesterol 96 (4.8% in cases and 3.9% in referents), level of educational attainment 150 (9.0% in cases and 5.7% in referents), and leisure time physical activity 316 (19.6% in cases and 11.8% in referents). The number of missing values for the use of nitrates or other heart medicine during 14 days prior to the health survey could not be estimated as only affirmative answers were registered in the questionnaire. In the conditional multivariate logistic regression tests, missing values except for smoking and snuff use were replaced by the mean value for the referent group in the continuous variables to ensure a conservative estimate. For categorical variables missing values were treated as a separate category and omitted from the tables.

Results

Myocardial infarction for the 525 cases occurred on average 4 years and 2 months after the initial participation in the health survey (with a median of 4 years and a range from 4 days to 14 years). Explanatory variables at baseline for the cases and the referents are presented in Table 1. Smoking, diabetes, hypertension and low educational level were more common in cases. Furthermore, cases had higher mean cholesterol concentrations and BMI.

Thirty per cent of the studied individuals also participated in a rescreening, with a median follow-up time of 9 years and 4 months. Analysis of tobacco habits for the individuals with participation in both health surveys showed that of 259 individuals stating no use of tobacco in the first survey, 96% stated no current tobacco use at the second survey. Of 60 individuals stating never smoked, current snuff use in the first survey,

Table 1 Baseline characteristics for 525 cases and 1798 referents at screening presented as means or proportions

	Cases	Referents	*P*-value
Age (years)	53.9	53.4	Matched
Smokers (%)	37.1	20.0	<0.001
Snuff users (%)	20.0	19.9	NS
Diabetes (%)	6.1	1.7	<0.001
Hypertension (%)	34.3	22.9	<0.001
BMI (kg m^{-2})	27.0	25.9	<0.001
Cholesterol (mmol L^{-1})	6.6	6.1	<0.001
Low leisure time physical activity (%)	41.0	36.5	NS
Low educational level (%)	59.2	50.3	0.001
Nitrates or other heart medicine (%)	3.6	2.1	0.050

BMI, body mass index; NS, not significant.

82% stated current snuff use at the second survey. Of 273 individuals stating no prior use of tobacco in the second survey, 94% stated no current tobacco use at the first survey, and 7% stated former tobacco use at the first survey.

Risk of MI

The associations with MI in univariate and multivariate conditional logistic regression are presented in Table 2. As including cholesterol level altered the crude OR for the category (ii) never smoked, current snuff user with 10%, cholesterol was included in multivariate model 3. The variables diabetes, hypertension, and the use of nitrates or other heart medicine caused only smaller alterations in crude OR in the two categories of main interest and were not included in the multivariate models. There was no increased risk for current snuff users without a previous history of smoking compared with nontobacco users. We found a weak tendency for higher risk for current snuff users who were also former smokers. Significantly increased risk was found in two categories: current smokers with no current snuff use and current smokers with current snuff use.

Risk of fatal MI and SCD

The associations with fatal MI and SCD in univariate and multivariate conditional logistic regression are presented in Table 3. BMI, leisure time physical activity, educational level and cholesterol level were considered as confounders (described above) and adjusted for. We found no increased risk of fatal MI or SCD for current snuff users without a previous history of smoking compared with nontobacco users. For current snuff users who also were former smokers, we found a weak tendency for higher risk. The only category with significantly increased risk was current smokers with no current snuff use.

Estimations of longitudinal changes in risk

In order to estimate the longitudinal changes in risk of MI for snuff users with a previous history of smoking, we dichotomized all cases according to time from baseline screening to the first MI. For snuff users with a previous history of smoking and the MI event within 4 years from baseline screening, the crude OR was 1.81 (95% CI, 1.08–3.19) compared with nontobacco users. The association was not significant after multivariate adjustments for BMI, leisure time physical activity, educational level and cholesterol, but the observed trend remained (OR 1.50, 95% CI, 0.82–2.77). For snuff users with a previous history of smoking and the MI event 4 years or longer from baseline screening, the crude OR was 1.19 (95% CI, 0.61–2.32) and the adjusted OR was 1.09 (95% CI, 0.55–2.15) compared with nontobacco users.

Table 2 Conditional logistic regression showing the risk of myocardial infarction in relation to eight categories of tobacco 'habits

	Number of referents/cases	Crude OR (95% CI)	Multivariate model 1[a] OR (95% CI)	Multivariate model 2[b] OR (95% CI)	Multivariate model 3[c] OR (95% CI)
Never used tobacco	654/130	1.00	1.00	1.00	1.00
Never smoked, current snuff user	117/21	0.90 (0.52–1.55)	0.87 (0.50–1.51)	0.90 (0.52–1.56)	0.82 (0.46–1.43)
Former smoker, current snuff user	138/37	1.50 (0.98–2.31)	1.40 (0.91–2.17)	1.38 (0.89–2.14)	1.25 (0.80–1.96)
Current smoker, no current snuff use	260/136	2.66 (1.98–3.57)	2.82 (2.09–3.82)	2.78 (2.05–3.78)	2.60 (1.91–3.54)
Current smoker, current snuff user	69/30	2.55 (1.55–4.19)	2.48 (1.50–4.11)	2.33 (1.40–3.88)	2.14 (1.28–3.60)
Never smoked, former snuff user	72/11	0.72 (0.36–1.42)	0.70 (0.35–1.41)	0.71 (0.36–1.43)	0.66 (0.32–1.34)
Former smoker, never used snuff	240/58	1.23 (0.86–1.74)	1.20 (0.84–1.71)	1.22 (0.85–1.74)	1.18 (0.82–1.70)
Former smoker, former snuff user	118/33	1.52 (0.98–2.36)	1.35 (0.86–2.12)	1.39 (0.88–2.18)	1.34 (0.84–2.12)

Referents are matched for sex and age. OR, odds ratio; CI, confidence interval. [a]Adjusted for body mass index (BMI). [b]Adjusted for BMI, leisure time physical activity and educational level. [c]Adjusted for BMI, leisure time physical activity, educational level and cholesterol level.

Table 3 Conditional logistic regression showing the risk of fatal myocardial infarction (MI) and sudden cardiac death (SCD) in relation to eight categories of tobacco habits

	Fatal MI within 28 days			SCD with survival time <24 h			SCD with survival time <1 h		
		Crude	Adjusted[a]		Crude	Adjusted[a]		Crude	Adjusted[a]
	n	OR (95% CI)	OR (95% CI)	*n*	OR (95% CI)	OR (95% CI)	*n*	OR (95% CI)	OR (95% CI)
Never used tobacco	30	1.00	1.00	24	1.00	1.00	13	1.00	1.00
Never smoked, current snuff user	7	1.02 (0.37–2.83)	1.12 (0.38–3.29)	7	1.04 (0.36–3.03)	1.18 (0.38–3.70)	4	0.53 (0.12–2.35)	0.38 (0.08–1.89)
Former smoker, current snuff user	7	1.52 (0.57–4.01)	1.24 (0.44–3.53)	6	1.78 (0.60–5.27)	1.39 (0.44–4.42)	5	2.94 (0.71–12.23)	2.67 (0.52–13.80)
Current smoker, no current snuff use	37	3.33 (1.80–6.14)	3.53 (1.83–6.84)	31	2.93 (1.52–5.62)	3.12 (1.53–6.33)	21	4.25 (1.66–10.86)	4.54 (1.55–13.25)
Current smoker, current snuff user	5	1.58 (0.52–4.84)	1.11 (0.34–3.69)	3	1.00 (0.26–3.95)	0.75 (0.17–3.28)	1	0.34 (0.04–3.16)	0.13 (0.01–2.10)
Never smoked, former snuff user	2	0.53 (0.12–2.44)	0.64 (0.13–3.18)	2	0.54 (0.11–2.52)	0.70 (0.14–3.64)	1	0.35 (0.04–3.17)	0.35 (0.03–4.56)
Former smoker, never used snuff	11	0.94 (0.44–2.01)	1.02 (0.45–2.31)	7	0.68 (0.27–1.71)	0.74 (0.28–1.97)	4	0.57 (0.16–2.08)	0.35 (0.07–1.78)
Former smoker, former snuff user	4	0.73 (0.23–2.30)	0.60 (0.18–2.02)	3	0.67 (0.18–2.47)	0.50 (0.12–2.03)	0	–	–

Referents are matched for sex and age. OR, odds ratio; CI, confidence interval. [a]Adjusted for body mass index, leisure time physical activity, educational level and cholesterol level.

Discussion

A major finding of this study was that no increased risk of MI or SCD could be detected for snuff users without a previous history of smoking. However, for snuff users who also were former smokers, we found a weak tendency towards an increased risk for both MI and SCD. The results for these two categories of tobacco habits were consistent across all outcome variables, even in cases of SCD with survival time <1 h, which is the outcome with the highest expected proportion of ventricular fibrillation.

The fall in risk for MI after smoking cessation has been estimated in a meta-analysis by Lightwood and Glantz [13]. They found a relatively rapid decline in relative risk with a reduction of 50% within 2 years, but also a small long-term excess risk approaching steady-state after 7 years. The long-term effect is probably due to the increased rate of atherosclerosis which is associated with smoking [14]. In the present study, we estimated longitudinal changes in risk of MI for snuff users with a previous history of smoking based on time from baseline screening to the MI event. Our results indicate that the tendency towards an increased risk for MI in this category may reflect the residual risk from a previous history of smoking. The fact that the duration of the smoking habits and the exact date of smoking cessation for former smokers were not registered is a limitation for estimations of longitudinal changes in risk.

One previous study has shown increased risk of MI for snuff users [4], whereas five studies including ours, have not detected any excess risk [3, 5–7]. Asplund [15] has discussed several possible explanations for this discrepancy, including the shift of high-prevalence groups of snuff users the past few decades from low- to well-educated men and the change in the composition of snuff during the last decades to a lower content of potentially toxic substances. Moreover, Asplund suggests that a dysrhythmogenic effect of snuff may enhance SCD as a third explanation for why more recent studies are inconclusive when compared with the cohort study in construction workers. Adding the results from this

study, the association between snuff use and SCD is not supported. Additionally, differences in study population may be of crucial importance as the construction worker study was performed on a defined socio-economic group whilst subsequent studies were population based.

The impact of snuff on cardiovascular determinants has been investigated in previous studies. Endothelial dysfunction has been demonstrated in one study [16], but in contrast to smoking, snuff does not increase levels of fibrinogen or high-sensitivity C-reactive protein and does not cause impairment of the fibrinolytic system [17, 18]. The adverse effects of nicotine on cholesterol metabolism have been shown in animal models [19], but snuff does not alter serum lipids in humans and does not seem to accelerate the atherosclerotic process [14, 17, 18]. Although snuff administration causes an immediate increase in blood pressure, only a few studies have shown a permanently elevated blood pressure between periods of tobacco consumption [6, 20]. A majority of the studies have not detected any adverse effects on blood pressure levels during nonexposure to tobacco, or prevalence of hypertension [7, 18, 20–22]. However, the highly addictive effect of snuffing can lead to continuous snuff use over an appreciable part of the day, which may have an impact on mean blood pressure levels as shown in a study using ambulatory 24-h blood pressure monitoring [23]. As standardized resting blood pressure measurements are performed during nonexposure to tobacco, this effect may be unappreciated during routine blood pressure measurement without ambulatory monitoring. The impact of snuff on insulin sensitivity, impaired glucose tolerance and type 2 diabetes has been studied with conflicting results [17, 18, 24–26]. Two of the studies found excess risk of type 2 diabetes [25] and metabolic syndrome [26] for heavy users, which may indicate possible dose–response relationships between snuff use and metabolic determinants. Besides, heavy use of snuff may also be a marker for a less healthy lifestyle with influence on glucose metabolism. Thus, further studies with dose stratification are needed to elucidate the shape of the cardiovascular risk curve at different doses of snuff.

Strengths and limitations

The strengths of this study include the prospective design with information on tobacco use obtained before the MI event together with the strict criteria for diagnosis of MI and SCD. Furthermore, tobacco habits were subcategorized in order to avoid potential conflict caused by the admixture of ex-smokers in the group of snuff users. A solid reference category of nontobacco users was confirmed by the second health survey, and a previous biochemical validation in the Northern Sweden MONICA study has shown a high correlation between self-reported tobacco/nontobacco use and levels of cotinine and nicotine [17]. The current study is limited by sample size, especially in analyses of SCD were type 2 statistical errors cannot be ruled out. Due to the small numbers we cannot rule out an effect of snuff use on MI and SCD, but there is nothing in our data to suggest such an effect. Another uncertainty is shifts in tobacco habits during long follow-up periods, which alters the exposition to tobacco.

Conclusions

We found no increased risk for MI amongst snuff users without a previous history of smoking. Amongst snuff users with a previous history of smoking, the tendency towards an increased risk for MI may reflect the residual risk from former smoking. In order to prevent MI, prevention and cessation of smoking are of outmost importance. However, we cannot exclude that snuff use may be associated with health hazards. This study does not support the hypothesis that the risk for SCD is increased amongst snuff users, but the SCD cases were few and the results need to be confirmed in a larger study.

Conflict of interest statement

We declare that we have no conflict of interest.

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