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CARDIOVASCULAR DISEASE

Use of snus and acute myocardial infarction: pooled analysis of eight prospective observational studies

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Abstract The use of snus (also referred to as Scandinavian or Swedish moist smokeless tobacco), which is common in Sweden and increasing elsewhere, is receiving increasing attention since considered a tobacco smoke "potential reduction exposure product". Snus delivers a high dose of nicotine with possible hemodynamic effects, but its impact on cardiovascular morbidity and mortality is uncertain. The aim of this study was to investigate whether snus use is associated with risk of and survival after acute myocardial infarction (AMI). Data from eight prospective cohort studies set in Sweden was pooled and reanalysed. The relative risk of first time AMI and 28-day case-fatality was calculated for 130,361 men who never smoked. During 2,262,333 person-years of follow-up, 3,390 incident events

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of AMI were identified. Current snus use was not associated with risk of AMI (pooled multivariable hazard ratio 1.04, 95 % confidence interval 0.93 to 1.17). The short-term case fatality rate appeared increased in snus users (odds ratio 1.28, 95 % confidence interval 0.99 to 1.68). This study does not support any association between use of snus and development of AMI. Hence, toxic components other than nicotine appear implicated in the pathophysiology of smoking related ischemic heart disease. Case fatality after AMI is seemingly increased among snus users, but this relationship may be due to confounding by socioeconomic or life style factors.

Keywords Acute myocardial infarction · Smokeless tobacco · Snus · The Swedish collaboration on health effects of snus use

Abbreviations

AMI	Acute myocardial infarction
BMI	Body mass index
CI	Confidence intervals
HR	Hazard ratio
ICD	International Classification of Diseases
IHD	Ischemic heart disease
OR	Odds ratio

Introduction

Smokeless tobacco is receiving increasing interest from the scientific community, media and the general public, in particular the product known as snus [1, 2]. Snus is finely ground tobacco with high moisture. New users are found foremost in North America and South Africa [3], but the product has a long tradition of use in Scandinavian countries, especially among Swedish men [4]. It has been suggested that the increased use of snus has contributed to the decline of smoking in Sweden [5], although the majority of Swedes who quit smoking do so without using snus [6]. A report published by the European Union's Scientific Committee on Newly Identified Health Risks concluded that the effect of snus availability on smoking prevalence is unclear [3].

Use of snus has been reported to be associated with certain cancers [7, 8] and with adverse pregnancy outcome [9–11]. Snus delivers a dose of nicotine equivalent to cigarettes [12]. Since nicotine has hemodynamic effects and is one of the components of cigarette smoke that may contribute to the pathophysiology of smoking related cardiovascular events [13], it is important to investigate the impact of snus use on risk and prognosis of cardiovascular disease. Previous studies, however, suggest that the incidence of ischemic heart disease (IHD), and more specifically acute myocardial infarction (AMI), is not increased among users of snus as compared to non-users of tobacco [14–22]. Findings for fatal IHD have, however, been conflicting. Positive associations are reported from studies based on a Swedish occupational cohort, the Construction Workers Cohort [18, 23], but not from others [15, 16, 19, 20].

The Swedish Collaboration on Health Effects of Snus Use was set up to increase the understanding of health effects of snus use. The group brought together data from eight Swedish cohort studies [18, 24–30], whereof four had never published data on snus use and cardiovascular disease before [24, 27, 28, 30]. The pooled data include users of snus from different regional areas and periods in time. Here we present results from analyses of the association between use of snus and risk of AMI among men, including case fatality and dose–response relationships, based on the largest sample to date.

Methods

Contributing studies and data collection

Epidemiological studies were eligible for inclusion if they were conducted in Sweden, of cohort design, and included information on both snus use and smoking. Nine studies met the inclusion criteria. The principal investigators of these nine studies were contacted and invited to take part in the collaboration. Principal investigators for one study [31] declined participation. Of the included studies (described in Table 1), four were population-based [24–26, 30]; two were occupational cohorts [18, 27]; one included participants in a charity-walk [28]; and one was a twin study [29]. Two studies were nationwide [18, 29], while the others were regional [24–28, 30]. Period of recruitment and duration of follow-up ranged from 1978 to 2004, and from 5 to 29 years, respectively. Since snus use was rare in women, the study was restricted to men.

Information on tobacco use was collected at baseline using self-administrated questionnaires in seven studies [18, 24–28, 30] and by structured telephone interviews in one study [29]. All studies contributed information on current use of snus, six on former use [18, 25, 27–30] while intensity and duration of use was available from six [18, 25–29] and four [18, 25, 27, 29] studies, respectively. Information on smoking was at least as detailed as that on snus, and all studies held data on current and former smoking. We also retrieved information on height and weight, which was either self-reported [24, 28–30] or measured by health professionals [18, 25–27]. Educational level was available and retrieved from all studies, except one [18]. The information collected on other covariates

Table 1 Description of the final analytical sample, according to the respective prospective cohort studies in the Swedish Collaboration of Health Effects of Snus Use

Study	Study population	Period of recruitment	Male participants (N)	Person years of follow-up (N)	Mean age at recruitment (years)	Mean age at diagnosis (years)	AMI cases (N)	Fatal AMI cases (N)	Current snus users (%)	Information available		
										Duration	Amount	Former use
Construction Workers Cohort (CWC) [18]	Employees within the construction industry, national	1978–1993	99,267	1,996,402	30	66	2,631	616	29	Yes	Yes	Yes
Malmö Diet and Cancer Study (MDCS) [26]	Population based, Malmö City	1991–1996	3,125	40,849	59	70	196	38	2	No	Yes	No
Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) [25]	Population based, Norrbotten and Västerbotten County	1986–2004	1,901	21,399	46	70	84	23	17	Yes	Yes	Yes
National March Cohort (NMC) [28]	Participants in a charity-walk for cancer	1997	6,967	65,491	49	75	101	54	6	No	Yes	Yes
Screening Across the Lifespan Twin Study (SALT) [29]	Twins born in Sweden in 1926–58	1998–2002	7,376	57,317	56	67	195	54	12	Yes	Yes	Yes
Stockholm Public Health Cohort (Sthlm_PHC) [30]	Population based, Stockholm County	2002	5,456	27,397	46	72	75	19	15	No	No	Yes
Scania Public Health Cohort (Scania_PHC) [24]	Population based Skåne County	1999–2000	2,746	21,622	45	72	99	14	14	No	No	No
Work, Lipids and Fibrinogen Study (WOLF) [27]	Employees, Väster-Norrland, Jämtland and Stockholm Counties	1992–1998	3,523	31,857	40	59	9	8	19	Yes	Yes	Yes
All studies		1978–2004	130,361	2,262,333	35	67	3,390	826	25			

varied considerably between studies, why further data was not compiled.

Outcome was assessed through record linkage using subjects' personal registration number, a unique combination of numbers assigned to all Swedish citizens, to the National Patient Register and the Cause of Death Register. The National Patient Register covers all public in-patient care in Sweden and includes information on date of admission, and primary as well as secondary diagnoses coded according to the International classification of diseases (ICD). The Cause of Death Register covers all deaths and includes ICD-codes for main and underlying causes of death. These registers reached full national coverage in 1987 and 1961, respectively.

Statistical analysis

Snus use was principally categorized into current and non-current use, but also into never, former and current use in studies where this information was available. For current users, snus use was further categorized according to duration (less than 20 years; 20 years or more), and intensity (less than four cans; four to six cans; seven or more cans per week) of use. In the Construction Workers Cohort the amount of snus consumed was reported in grams per week, and 50 grams was assumed to be equivalent to one can.

Smoking was defined as any (current or former) regular smoking of cigarettes, pipe, regular or small cigars. Body mass index (BMI) was calculated as weight in kilograms/height in meters^2, and categorized as $<$18.5; 18.5–24.9; 25–29.9; or $\geq$30 kg/m^2. Educational level was coded as $\leq$9, 10–12 and $>$12 years of education.

Participants with a history of AMI at baseline were excluded, and others contributed person-time from date of entry in the respective study until AMI diagnosis, death or end of follow-up, whichever came first. Outcome was defined as first event of AMI registered in the National Patient Register or the Cause of Death Register (ICD-10 code I21; ICD-9 code 410; ICD-8 code 410; and codes 420.10, and 420.17 in ICD 7th editions). Statistical analyses were conducted overall, stratified by period of recruitment, and excluding the Construction Workers Cohort which was larger than all other studies combined. Case fatality was defined as the odds of deaths within 28 days from diagnosis among the AMI cases occurring during follow-up.

Figure 1 illustrates the derivation of the analytical sample. In order to avoid confounding by smoking, all analyses were restricted to never smokers. We adjusted for BMI in analyses comprising all studies, and additionally for educational level in a subset of studies where this information was available.

Cox proportional hazard regression models were used to estimate study specific and pooled hazard ratios (HR) and 95 % confidence intervals (CI) of AMI, stratified by study and with attained age as time scale. Case fatality was estimated using logistic regression and presented as odds ratios (OR) and corresponding 95 % CI.

The one-year survival distribution after a first AMI was non parametrically estimated using the Kaplan–Meier technique, and the discrepancies of the cumulative mortality curves (one minus the survival) between current and non-current snus users assessed with the log-rank test. We assessed heterogeneity in results between studies with χ^2 tests. All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Ethical approval

Ethical approval was given by the Regional Ethical Review Board in Stockholm, Sweden (no. 2009/971-31/3). Study participants gave informed consent before taking part.

Results

Table 1 describes the final analytical sample according to the various cohorts included in the collaboration. In total, 130,361 men were eligible for inclusion in the analyses and these contributed 2,262,333 person-years of follow-up. During this follow-up period, 3,390 incident cases of AMI were identified, whereof 356 among the 32,560 men (25 %) who reported current snus use at baseline. Current snus users were on average younger than non-users at baseline (28 and 37 years, respectively).

Figure 2 shows the study specific and pooled HRs of AMI for current snus users as compared to non-current users. Current snus use was not associated with risk of AMI either overall (adjusted HR 1.04, 95 % CI 0.93 to 1.17) or in subgroups defined by period of recruitment (data not shown). There was no significant heterogeneity between the results from the different studies ($p = 0.23$), but some were based on small numbers. In a subset analysis, excluding the Construction Workers Cohort the HR was 1.27 (0.94 to 1.72) after adjustment for BMI and 1.20 (0.87 to 1.66) after additional adjustment for educational level.

The adjusted risk of AMI in current snus users as compared to never users of tobacco was similar (1.03, 0.92 to 1.15) to the overall finding (Fig. 2) where non-current use was the reference. Among former snus users the risk of AMI was 0.91 (0.68 to 1.21) as compared never users of tobacco. There were no clear trends in risk of AMI with either intensity (Table 2) or duration (Table 3) of current snus use.

The 1-year survival distribution for AMI in relation to snus use is illustrated in Fig. 3. Current snus users had a higher probability of dying as compared to non-users

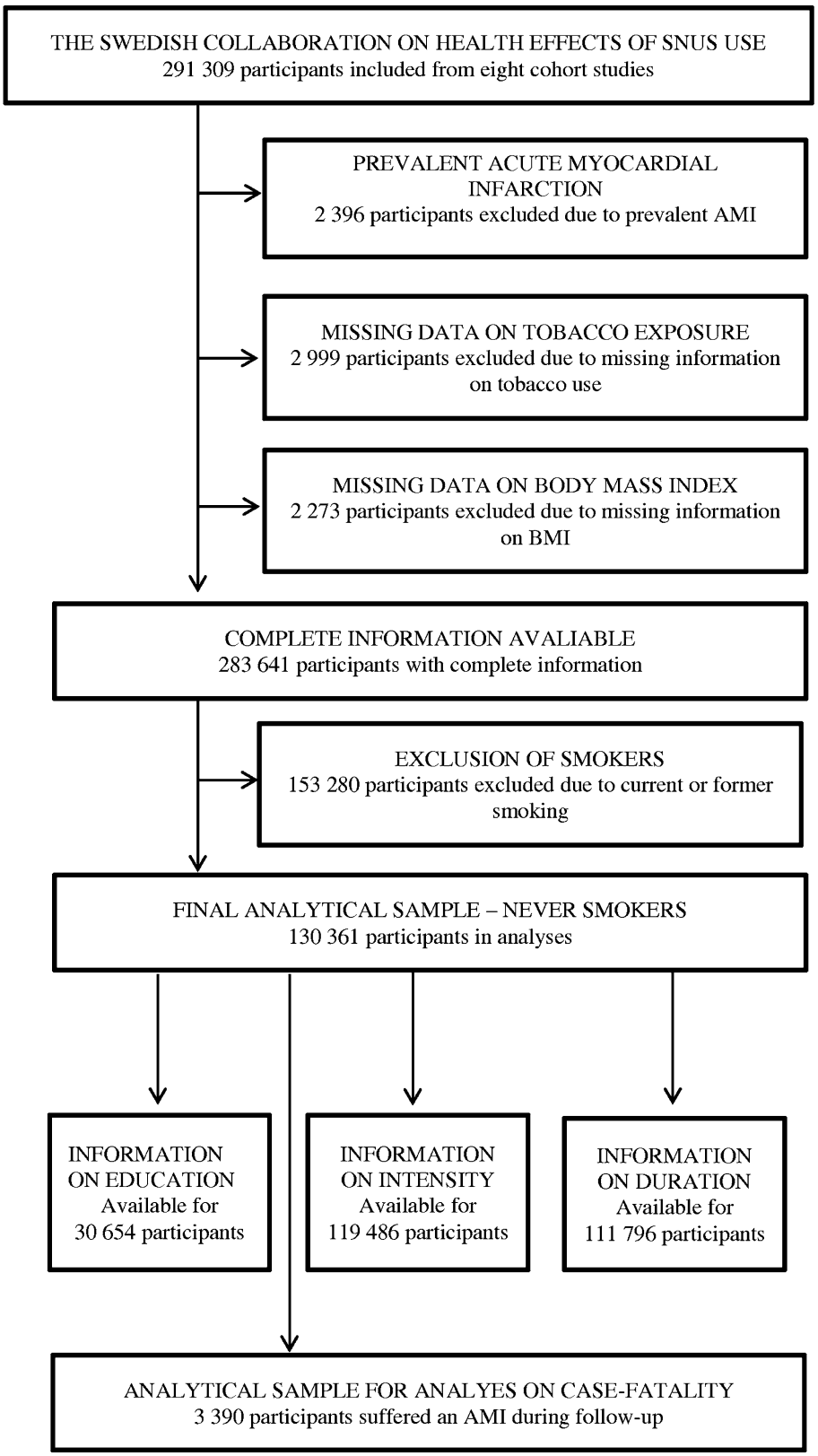

Fig. 1 Derivation of analytical sample

($p < 0.05$), and this excess fatality occurred during the first 24 h. The 28-day case fatality among snus users was 1.28 (0.99 to 1.68), adjusted for age and BMI, based on 97 exposed cases. Confounding by level of education could not be addressed, since few exposed cases in which information on education was available died ($n = 16$).

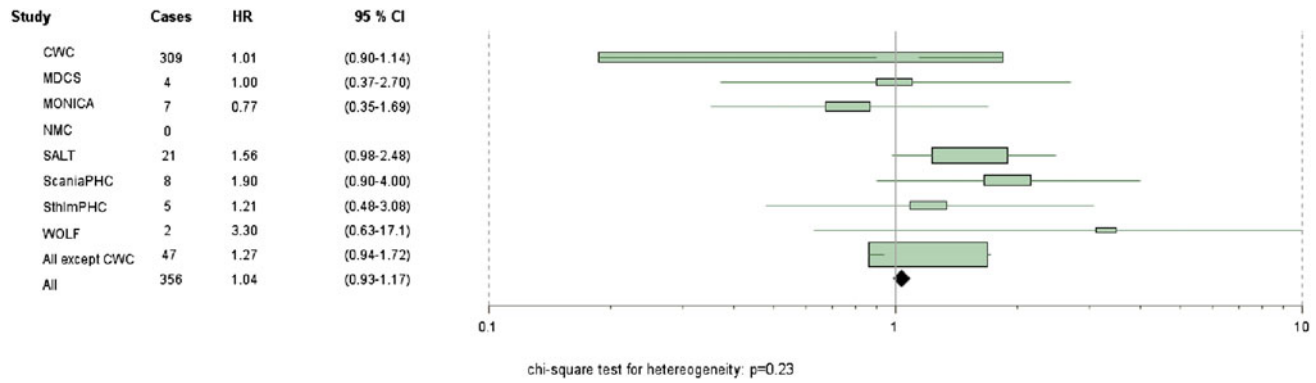

Fig. 2 Study specific and pooled estimated hazard ratio (HR) and 95 percent confidence intervals (95 % CI) of acute myocardial infarction among never smoker, according to use of snus at baseline

Table 2 Pooled estimated hazard ratios (HR) and 95 percent confidence intervals (95 % CI) of acute myocardial infarction among never smokers, according to intensity of snus use at baseline

Snus exposure	No. of cases	HR (95 % CI)[a]
Non-current use	2,873	1.00
Current use (cans/week)		
<4	270	1.02 (0.90–1.16)
4–6	27	0.94 (0.64–1.38)
≥7	26	1.17 (0.79–1.72)

Based on CWC, MDCS, MONICA, SALT, WOLF

[a] Adjusted for age and BMI

Table 3 Pooled estimated hazard ratios (HR) and 95 percent confidence intervals (95 % CI) of acute myocardial infarction among never smokers, according to duration of snus use at baseline

Snus exposure	No. of cases	HR (95 % CI)[a]
Non-current use	2,580	1.00
Duration		
<20 years	136	0.96 (0.80–1.14)
≥20 years	200	1.10 (0.95–1.27)

Based on the CWC, MONICA, SALT, WOLF

[a] Adjusted for age and BMI

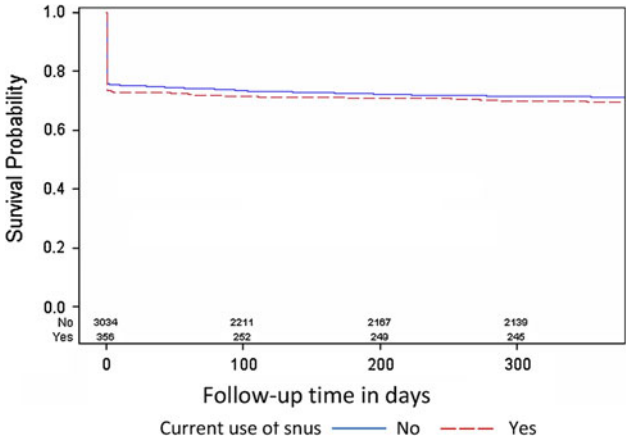

Fig. 3 Kaplan–Meier survival distribution in never smokers with acute myocardial infarction according to use of snus at baseline (log-rank test: $p < 0.05$)

Discussion

This study is the first pooled reanalysis of the impact of snus on risk of AMI, and it includes unpublished data from four studies. We did not find any association between use of snus and risk of AMI, regardless of timing, intensity, duration or period of use. Case fatality seemed modestly increased among snus users.

Our study is based on data from the majority of large cohort studies in Sweden with information on snus use. Strengths include the large sample size, the opportunity to investigate dose–response associations, and a heterogeneous study population, comprising snus users from different periods and regions. Although the cohorts were derived from different source populations they should, as a group, reflect the target population of Swedish men, age 18 and above. Even if the Construction Workers Cohort was considerably larger than the other cohorts and dominated the overall results, the risks associated with snus use did not differ substantially between analyses including and excluding this cohort.

Results from sensitivity analyses were not indicative of bias introduced by the inclusion of potential former snus users in the reference group. However, despite the large sample size, few cases among these never smoking study participants were current snus users since snus use and smoking often co-occur over the life-course. We could therefore not address whether the association between snus and AMI varied with levels of other characteristics, including gender.

Information on snus use was self-reported and only assessed at baseline. Eliasson et al. [32] have validated such self-reports by measuring serum levels of cotinine (the primary metabolite of nicotine) and found good agreement (based on data from one of the studies [25] included in this pooling project). Changes in snus use are not likely to be a source of major bias, since use tends to be stable over time. Swedish studies report continued use among 77 % of snus users after ten years [33], 80 % after 5–13 years [34] and an onset to middle age stability of 67 % [35]. Any misclassification of exposure is, however, likely to be non-differential and may hence have biased our findings towards the null. We used the pertinent ICD-codes registered in the Cause of Death Register and the National Patient Register to ascertain outcome. These registers have high reliability for the diagnosis of AMI [36].

Our results are in agreement with those from the two meta-analyses [37, 38] on snus and cardiovascular events. Boffetta and Straif [38] studied use of snus and risk of AMI and found no association with incident events, but an increased risk of fatal events. Lee [37] found no association between use of snus and incident IHD. Two cohort studies, MONICA and the Construction Workers Cohort, were included in our study as well as in the two meta-analyses. Nonetheless this pooled analysis, with access to original data at the individual level, offered opportunity to conduct more detailed analyses including those of dose–response relationships.

Although we were able to adjust estimates of associations for BMI, and to some degree also for level of education, an often used indicator of socioeconomic position [39], confounding by social or life style factors may still have biased our findings. Both incidence and, particularly, early survival after AMI follow clear socioeconomic gradients, and the noted increased in case fatality among manual workers seems to be due to an increased risk for sudden death [40]. The higher case fatality among snus users observed in this study was explained by deaths occurring during the first 24 h. We could not address whether this association was due to social disadvantage in snus users, but snus use, especially in older cohorts, is known to be more common among manual workers. Possibly, confounding by lifestyle factors may also have influenced our results. Increased consumption of alcohol as well as level of occupational physical activity (at least with manual work as a proxy) have been reported among snus users [41] and light or moderate alcohol intake as well as physical activity are protective of IHD [42]. Hence both inflating and deflating confounding may be present in these data, and perhaps the positive confounding by socioeconomic factors have outweighed any negative ditto and resulted in the seemingly increased fatality after AMI among snus. A causal association, however, cannot be ruled out. Animal studies have found that nicotine exposure can increase post infarction myocardial vulnerability to triggers of fatal cardiac arrhythmias [43–45], and hence affect the survival after AMI. Other mechanisms involving acute regulation of central blood pressure could also be hypothesized [46]. More specific information on the clinical events underlying post infarction deaths would be necessary in order to explore the plausibility of a role of tobacco toxicants in the observed excess mortality.

The unique tradition of snus use in Sweden offers opportunity to study the long-term health effects of such use. This is important in the light of the increasing prevalence of snus use as well as the interest in snus as a tobacco smoke "potential reduction exposure product". These findings, based on the largest sample to date, do not support any relationship between use of snus and development of AMI. As a corollary, nicotine is unlikely to contribute importantly to the pathophysiology of smoking related IHD. The apparent increase in case fatality noted in these data may be explained by confounding, but a small increased risk of sudden death from AMI among snus users cannot be ruled out.

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Conflict of interest The authors declare that they have no conflict of interest.

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