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Smokeless Tobacco as a Possible Risk Factor for Myocardial Infarction: A Population-Based Study in Middle-Aged Men

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OBJECTIVES To explore whether the use of snuff affects the risk of myocardial infarction (MI).

BACKGROUND Snuff and other forms of smokeless tobacco are widely used in some populations. Possible health hazards associated with the use of smokeless tobacco remain controversial.

METHODS In a population-based study within the framework of the Northern Sweden center of the World Health Organization Multinational Monitoring of Trend and Determinants in Cardiovascular Disease (WHO MONICA) Project, tobacco habits were compared in 25- to 64-year-old men with first-time fatal or nonfatal MI and referent subjects matched for age and place of living (687 cases, 687 referents).

RESULTS The unadjusted odds ratio (OR) for MI in regular cigarette smokers as compared with men who never used tobacco was 3.65 (95% confidence interval [CI] 2.67 to 4.99). When nonsmoking regular snuff dippers were compared with never-users of tobacco, the unadjusted OR was 0.96 (0.65 to 1.41). After adjustment for multiple cardiovascular risk factors, the OR was 3.53 (95% CI 2.48 to 5.03) for regular smoking and 0.58 (95% CI 0.35 to 0.94) for regular snuff dipping. Restricting the analyses to fatal cases of myocardial (including sudden death) showed a tendency towards increased risk among snuff dippers 1.50 (95% CI 0.45 to 5.03).

CONCLUSIONS The risk of MI is not increased in snuff dippers. Nicotine is probably not an important contributor to ischemic heart disease in smokers. A possible small or modest detrimental effect of snuff dipping on the risk for sudden death could not be excluded in this study due to a limited number of fatal cases. (J Am Coll Cardiol 1999;34:1784–90) © 1999 by the American College of Cardiology

The cigarette smoking epidemic is worldwide. In contrast, extensive use of snuff and other forms of smokeless tobacco is largely restricted to certain geographical areas such as North America, the Scandinavian countries (1), India, Bangladesh and Southeast Asia (2,3). In the U.S., moist snuff and cigars are now the only tobacco products with

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increasing sales (4–6). The prevalence of use of snuff and other types of smokeless tobacco is particularly high in several southern and southwestern states (5,7). Snuff is often used in certain subsets of a population, such as athletes (8,9), male adolescents and young adults (4,10,11). The Youth Risk Behavior Survey has revealed that as many as a quarter of white male students in the U.S. report regular use of smokeless tobacco (12).

Acting on a World Health Organization (WHO) recommendation to prevent snuff dipping in countries where oral tobacco use is not yet established, the European Union has prohibited the sales of snuff in its members states, Sweden exempted (13). Cardiovascular health hazards associated with the use of snuff and other types of smokeless tobacco are, however, poorly documented. During a 12-year follow-up of a cohort of Swedish construction workers, those who used snuff at baseline had a 40% higher risk of cardiovascular death compared with nontobacco users (14). On the other hand, no excess risk for myocardial infarction (MI) was noted in a Swedish study based on comparisons of tobacco status between subjects with and without MI in a population of middle-aged men (15).

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Abbreviations and Acronyms

AMI	= acute myocardial infarction
ASAT	= aspartate transaminase
CI	= confidence interval
CK	= creatine phosphokinase
MI	= myocardial infarction
MONICA	= Multinational Monitoring of Trends and Determinants in Cardiovascular Disease
OR	= odds ratio
WHO	= World Health Organization

This study was initiated to resolve some of the controversies surrounding the effects of snuff dipping on ischemic heart disease. Detailed information on tobacco habits and possible confounding factors was obtained in a population-based series of patients with fatal and nonfatal acute MI and compared with age-matched referent subjects without MI.

METHODS

This population-based study covered 25 to 64-year-old men in the two northern-most counties in Sweden (target population 139,215 in 1994), a population with a high prevalence of snuff dipping (15) in a sparsely populated area with nine acute-care hospitals. It was a substudy performed within the Northern Sweden (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) (MONICA) Center, which is one of the 38 collaborating centers in the WHO MONICA Project (16). The main objective of this prospective project is to assess how changes in the incidence of coronary heart disease and cerebrovascular disease over a 10-year period relate to changes in cardiovascular risk factors in the population (16).

All cases of acute myocardial infarction (AMI) and sudden death, fatal and nonfatal, occurring in-hospital and out-of-hospital were recorded from May 1, 1991 to December 31, 1993 in a standardized manner using the WHO definitions and the MONICA methodology (17). Cases of MI and sudden death were ascertained through screening of hospital discharge records, general practitioners' reports and death certificates with international classification of diseases (ICD) codes 410–414. This study was restricted to first-ever events of AMI. The number of subjects with confirmed or suspected MI not included in the Northern Sweden MONICA register because of refusal after information has been given averages of three per year (<0.5%).

Data collection in hospitalized patients included information on medical history, symptoms, ECG and cardiac enzymes. Patients in hospitals were visited by a MONICA team nurse to obtain additional information, including data on tobacco habits. In fatal cases, information from death certificates and necropsy reports was used as supplementary sources of information. In cases of sudden death, a family member was asked to complete a questionnaire about social conditions, risk factors, medical history and tobacco use. Detailed data collection on tobacco habits included onset, duration and amount of cigarette, cigarillo and cigar smoking and moist snuff dipping (moist snuff is the only form of smokeless tobacco used in northern Sweden). Six questions concerned use of snuff (present use, previous use, amount of snuff consumed, type of snuff preparation used, age at onset of snuff use and a question on whether or not start of snuffing was associated with quitting to smoke). The question on which most of the analyses in this study was based was, "Do you use snuff at present?" with three response alternatives (yes daily, no, occasionally). A regular cigarette smoker was defined as a person smoking one cigarette daily or more, and a regular snuff dipper took snuff at least once daily.

To validate the information on tobacco habits provided by the spouse in fatal cases, 51 spouses of surviving patients were interviewed by telephone two months after the hospitalization. There was a very good agreement between the responses by the patients and their spouses concerning use of snuff when the MI occurred (98% agreement) whereas information was somewhat less reliable on former use of snuff (92% agreement), age of onset of snuff use (82% agreement) and whether or not the snuffing habit was taken up upon quitting smoking (90% agreement).

Possible cases of AMI and sudden death were validated using the MONICA criteria (17). Methods for classification and diagnosis of MI and sudden death have been described in detail elsewhere (18). In addition to the enzymes recommended in the MONICA core study, namely creatinine phosphokinase (CK), aspartate transaminase (ASAT) and hydroxybutyric dehydrogenase (LD), LD-1 and CK-MB were included in the Northern Sweden MONICA Study.

Acute myocardial infarction cases were classified into one of the categories "definite infarction," "possible infarction or coronary death," "ischemic cardiac arrest with successful resuscitation not fulfilling criteria for definite or possible myocardial infarction," "unclassifiable infarction" or "not infarction" (17). Unclassifiable events were mostly fatal cases with a death certificate diagnosis of AMI where no information on previous history of AMI or of the clinical event was obtainable. In this article, only cases classified as "definite infarction" have been included in nonfatal events. In fatal events, "possible infarction" and "unclassifiable infarction" have also been included in accordance with the agreed convention in the core MONICA Project (17). Subjects who died within 28 days from the onset of AMI were recorded as fatal cases.

Consistency over time was ensured by regular centralized quality controls (17) and the same personnel abstracting and recording data throughout the study.

Referents (men without MI) were selected from continuously updated population registers, matching for county of residence and choosing the two individuals with the dates of birth closest to the index patient (usually the same date of birth). Informed consent was sought in a letter to the person selected first. A telephone interview was then conducted (all

Table 1. Univariate Comparisons of Tobacco Habits Between 25- to 64-Year-Old Male Patients With First MI and Age-Matched Controls

	AMI Patients	Referents	Odds Ratio (95% CI)
Never used tobacco	149 (21.7%)	217 (31.6%)	1.00
Current snuff user, no current smoking*	59 (8.6%)	90 (13.1%)	0.96 (0.65–1.41)
Current smoker, no current snuff use*	248 (36.1%)	99 (14.4%)	3.65 (2.67–4.99)
Current snuff user and smoker	20 (2.9%)	11 (1.6%)	2.66 (1.24–5.71)
Former snuff user, never smoked	11 (1.6%)	13 (1.9%)	1.23 (0.54–2.82)
Former smoker, never used snuff	129 (18.8%)	179 (26.0%)	1.05 (0.77–1.43)
Former smoker and former snuff user	37 (5.4%)	54 (7.9%)	0.99 (0.62–1.59)
Other combinations, unclassifiable	34 (4.9%)	24 (3.5%)	–
Total	687 (100%)	687 (100%)	–

*Excluding subjects who reported occasional smoking or occasional snuff dipping (less than once daily). Odds ratio for men who never used tobacco = 1.00.

interviews by the same observer) involving the same questions as those given to the patients, except that the AMI-specific items were excluded. However, a history of AMI was asked for; case-referent pairs in which the referent reported a history of AMI were excluded from the analyses. If the first control person did not respond or did not consent (≈20%), the second of the selected control men was contacted.

To achieve a uniform mode of data collection, oral interviews were not used for men who served as referents to fatal cases. Instead, they received the same questionnaire as that sent to the family members of deceased patients (cf. above).

The total number of men with a documented first AMI or sudden death was 879. In 95 case-referent pairs, neither of the two selected control persons responded or the referent had had an AMI. When information was obtained by interview, the response rate was 96% (cases and referents combined) and when it was obtained by a questionnaire the response rate was 90%. Among the respondents, information on tobacco habits was sometimes incomplete or missing. After exclusion of such case-referent pairs, 687 men with AMI or sudden death and 687 matched control men remained for analysis (78.2% of the eligible case-referent pairs). Of the 687 cases, 117 were fatal within the first 28 days.

Partial data were available in 164 patients who were not included and in 96 of the nonincluded referents. In comparison with the included patients, nonincluded patients with AMI were less often married or cohabitant (68.9% vs. 79.2%, $p = 0.007$ by Fisher's exact test) and a higher proportion had education above primary school (38.4% vs. 24.0%, $p = 0.003$). A similar proportion of nonincluded referents were married or cohabitant when compared with referents who were included (82.3% vs. 86.9%, $p = 0.21$), and a similar proportion had education above primary school (40.0% vs. 43.5%, $p = 0.39$). The mean age did not differ significantly between included and excluded subjects (55.6 years in included case-referent pairs, 55.4 years in excluded AMI patients and 57.3 years in excluded referents).

The 95% confidence intervals (CIs) were calculated according to the binomial distribution for the number of events within the age groups. Crude odds ratios (ORs) and their 95% CIs were calculated using the CIA software (BMJ Publishing Group, London, United Kingdom). Odds ratios, adjusted for various cardiovascular risk factors, were calculated by means of conditional logistic regression. The statistical package SPSS 7.5 was used for all calculations except conditional logistic regression, for which Stata was used (Stata Statistical Software: release 5.0, Stata Corporation, College Station, Texas).

The study was approved by the Ethical Committee at Umeå University and the computerized patient database by the National Computer Data Inspection Board.

RESULTS

The mean age was 55.6 years (95% CI 55.1 to 56.1 years) both in the 687 men with first AMI or sudden death and in their 687 age-matched referents. Regular smoking was much more common among men with AMI than among age-matched reference subjects (Table 1). The proportion of ex-smokers was also higher in referents than in AMI patients. As shown in Table 1, regular snuff dipping without concomitant smoking was less common in AMI patients than in referents (8.6% vs. 13.1%, $p = 0.009$). A history of previous regular use of snuff was more common in control subjects ($p = 0.009$). Among smokers, the median daily consumption of cigarettes was 20 in cases and 15 in referents. In snuff users, the median consumption was two boxes per day in both cases and referents. Information on duration of snuff use was found to be of inferior quality, in particular in fatal cases, and was not analyzed further. The median age at onset of use of snuff was as high as 31.5 years, explained by the the fact that many had started to use snuff in conjunction with quitting smoking (49% of snuffing cases and 41% of snuffing referents).

Table 2. Univariate Comparisons of Basal Characteristics Between 35 to 64-Year-Old Male Patients With AMI and Age-Matched Reference Subjects

	AMI Patients (n = 687)	Referents (n = 687)	Odds ratio (95% CI)
Not married or cohabitant	143 (20.8%)	90 (13.1%)	1.74 (1.31–2.33)
Level of education*			
Primary school	510 (74.2%)	377 (54.9%)	2.45 (1.94–3.09)†
Secondary school	97 (14.1%)	169 (24.6%)	
University	68 (9.9%)	130 (18.9%)	
First-degree family member(s)	136 (19.8%)	94 (13.7%)	1.56 (1.17–2.08)
Dying from heart disease			
Before the age of 65			
Previously diagnosed diseases			
Blood pressure elevation	290 (42.2%)	182 (26.5%)	2.03 (1.61–2.54)
High cholesterol levels	228 (33.2%)	150 (21.8%)	1.78 (1.40–2.26)
Diabetes	79 (11.5%)	28 (4.1%)	3.06 (1.96–4.77)

*Information not available in 12 cases and 11 controls; †primary school vs. secondary school or university.

When subjects without a history of regular tobacco use were used as reference, the OR for AMI associated with regular smoking (and not using snuff) was 3.65 (2.67 to 4.99), whereas the OR associated with regular snuff dipping (without smoking) was 0.96 (0.65 to 1.41).

The 117 fatal cases and their controls were analyzed separately. These included men who died from a definite (n = 52) or suspected (n = 54) MI, but also cases of sudden death without any indication of a cause other than a cardiac one (n = 11). Regular tobacco smoking was four times as common in fatal cases (53 men, 45%) compared with reference subjects (13 men, 11%). On the other hand, regular use of snuff among nonsmokers was very similar in fatal cases and in referents (15 men, 13% vs. 14 men, 12%). Former snuffing was recorded among nine AMI patients (8%) and 11 referents (9%).

Patients with AMI differed from reference persons in several aspects other than tobacco habits (Table 2). Thus, patients were less often married or cohabitant, and a lower proportion had education above primary school. Before the first AMI, the patients had more often been informed about high serum cholesterol levels and elevated blood pressure than age-matched reference men. The patients also more often had a history of diabetes, and a larger proportion had a first-degree family member who had died from an MI before the age of 65.

Conditional logistic regression models were used to analyze the predictive value of various tobacco habits, independent of confounding factors, on the risk for MI for both all events and fatal events only. Separate regression models were used for smoking and use of snuff. When all AMI patients were analyzed together and snuff dippers were excluded, smoking, hypertension, diabetes, high cholesterol, a family history of early cardiac death, low level of education and not being married or cohabitant all emerged as independent determinants of AMI (data not shown). In a corresponding model in which smokers were excluded, the same predictors except for marital status were independent predictors of MI. Snuff dipping however was not (Table 3, left column). Neither was snuff use associated with AMI if adjusted only for social variables (data not shown). After adjustment for the risk factors listed above, the OR for all

Table 3. Conditional Logistic Regression Analysis of Independent Predictors of AMI Excluding Present Smokers: 658 Valid Observations in the Analysis of Fatal and Nonfatal Events Combined and 106 Valid Observations in the Analysis of Fatal Events

	Odds Ratios (95% CIs)	
Variable	Fatal and Nonfatal AMI	Fatal AMI Only
Hypertension	1.89 (1.31–2.73)	1.47 (0.43–5.05)
Low level of education	2.01 (1.39–2.90)	1.87 (0.52–6.73)
Not married or cohabitant	1.56 (0.94–2.59)	7.60 (1.66–34.85)
Diabetes	2.41 (1.30–4.48)	1.63 (0.36–7.37)
Known high cholesterol	2.15 (1.42–3.24)	2.97 (0.91–9.67)
Heredity*	1.64 (1.01–2.66)	3.39 (0.94–12.25)
Regular use of snuff	0.58 (0.35–0.94)	1.50 (0.45–5.03)

*First degree family member who died from a myocardial infarction before the age of 65.

cardiac events associated with smoking was 3.53 (95% CI 2.48 to 5.03), whereas that associated with snuff dipping was 0.58 (95% CI 0.35 to 0.94). An unconditional logistic regression model with the matching variables included did not produce results that were qualitatively different.

When the analyses were restricted to cases with fatal outcome and their controls, the conditional logistic model, not including snuff dippers, revealed regular smoking, hypertension, heredity for AMI and marital status to be independent predictors of cardiac (or sudden) death (data not shown). In a model excluding smokers, the statistical power was low and only marital status was a significant predictor (Table 3, right column). Snuff dipping was not a significant predictor. The OR of fatal AMIs and sudden death, adjusted for multiple risk factors, associated with smoking was 8.57 (95% CI 2.48 to 30.3) and with snuff dipping 1.50 (0.45 to 5.03).

DISCUSSION

In this study, snuff dippers had no overall excess risk for MI, fatal and nonfatal events taken together. A possible small detrimental effect on the risk for sudden death could not be excluded due to a limited number of fatal cases and, thus, large CIs. In univariate and multivariate analyses, marital status, level of education, heredity for AMI and several pre-existing disorders were shown to increase the risk for MI. This closely coincides with what is known about social and biological risk factors for MI and indicates that the present study design, patient sample and selection of matched referents were valid.

Methodological aspects. Of the original set of case-control pairs, 21.8% were excluded in the analyses, often because data on tobacco habits were missing in one or both subjects. This was particularly common in pairs with a fatal case (in 60 out of 190 pairs). The proportion that was married or cohabitant was lower among excluded AMI patients than among the included patients, whereas a higher proportion of excluded patients had education above the primary school level. These differences in social background tend to counterbalance each other. When included and excluded reference men were compared, there were no important differences in marital status or level of education. In a fifth of the case-control pairs, the first selected control person did not respond and was replaced by a second control man. Since tobacco use is usually more common among nonresponders (19), this may have reduced the prevalence of tobacco consumers in the control group somewhat. If anything, it would have resulted in an even smaller likelihood for snuff being linked to an enhanced risk of AMI. Information on alcohol use was not collected in this study. Since regular intake of alcohol is associated with a decreased risk of AMI, a confounder effect may be present if the alcohol consumption pattern in snuff dippers is different from that in nonusers of tobacco.

No increased risk of AMI. The present results agree very closely with a previous smaller study performed within the framework of The Northern Sweden MONICA Project using nonmatched group comparisons (15). In that study, in which patient or control subjects did not overlap with the present matched case-referent study, we failed to show that snuff dipping was associated with an excess risk of MI in univariate as well as multivariate analyses. The results of our two studies should be compared with observations by Bolinder et al. (14) in a large cohort study involving 135,000 male construction workers who were followed for 12 years after their tobacco habits had been mapped in the early 1970s. A 40% excess risk for cardiovascular death was observed among snuff dippers. It should be emphasized that the present results, although not showing any increased risk for MI, do not exclude a possible small excess risk of cardiovascular death among snuff dippers. Nicotine has immediate effects on the heart rate (20) and the possibility that snuff is arythmogenic cannot be excluded. A change in the composition of moist snuff from the 1970s to the 1990s with a reduced content of tobacco-specific nitrosamines (21) may also have modified health hazards resulting from the use of snuff.

Smoking versus snuffing—possible mechanisms. The great difference in risk for MI between cigarette smoking and snuff dipping observed in this study provides important information in how the effects of smoking on cardiovascular risk are mediated. Some of the components of tobacco smoke are produced when tobacco is heated and burned (22). Other tobacco components are better absorbed through airways than through the buccal mucosa. However, it should be noted that tobacco-specific nitrosamines can be absorbed from snuff to a considerable extent (23,24). The first demonstration has recently been made of a single cigarette smoke component (1,3 butadiene) that accelerates atherosclerotic plaque development (25).

Other components differ only slightly between smoking and oral tobacco. The most important of these is nicotine. Even if the nicotine content is lower in Swedish than in American snuff (26), plasma levels of nicotine are as high in Swedish snuff dippers as they are in smokers (27). It appears from our data that nicotine is not an important contributor to MI (and probably not to atherothrombotic mechanisms in general). It is more likely that moieties specific to tobacco smoke mediate the excess risk. Among the about 2,500 chemical substances identified in tobacco smoke, tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons are some of the candidates as etiological agents for cardiovascular disease (24,28,29).

It is controversial whether there are any chronic hemodynamic effects of snuff dipping. In the study of Swedish construction workers performed in the 1970s, snuff dippers had a higher prevalence of elevated blood pressure levels than nontobacco users (30). Differences in resting blood pressure levels between snuff dippers and nontobacco users

have not been possible to confirm in more recent studies, including a population-based sample of 25- to 64-year-old people in Sweden (31), a study on Swedish male students (32) and an investigation among snuff-dipping baseball players in the U.S. (8).

The present results from Sweden cannot be extrapolated to other countries without caution. A major part of tobacco used in Sweden is now prepared without traditional smoke-drying and this reduces the content of polycyclic aromatic hydrocarbons markedly (33). Whereas Swedish snuff is prepared by a heating process, yielding a semisterile product (21), U.S. snuff is produced by fermentation (10,26). Although the content of tobacco-specific nitrosamines was reduced markedly in U.S. snuff during the 1980s, the concentrations were still twice as high as in Swedish snuff (26). In other countries, like Sudan, snuff may contain exceedingly high concentrations of tobacco-specific nitrosamines (23). Even within the same country, there are wide variations in the content of nicotine and carcinogenic tobacco-specific nitrosamines between different brands of moist snuff (10,26).

A complicated message. The present observations would show that, from a cardiovascular perspective, the deleterious effects of snuff dipping are much less than those of cigarette smoking. This is a complicated message. Faced with anti-smoking campaigns and restrictions on sales of cigarettes, it is tempting for the tobacco industry to turn to less controversial alternatives, i.e. various forms of smokeless tobacco. In the U.S., the Smokeless Tobacco Council contributes considerably to the total lobbying by the tobacco industry (34). The increased sales of smokeless tobacco in countries like the U.S. and Sweden during recent years is, at least partly, the result of a determined effort by the industry to promote consumption. It must be emphasized that there is often a heavy addiction to nicotine among snuff dippers, and the success rate among people who try to quit using snuff is no better than that among cigarette smokers (35). Furthermore, an excess risk of oral cancer has been observed in snuff users (3,28). From a medical point of view, the only reasonable norm is nonuse of tobacco.

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REFERENCES

1. Nordgren P, Ramström L. Moist snuff in Sweden—tradition and evolution. Br J Addict 1990;85:1107–12.
2. Bedi R, Gilthorpe MS. The prevalence of betel-quid and tobacco chewing among the Bangladesh community residents in a United Kingdom area of multiple deprivation. Prim Dent Care 1995;2:39–42.
3. Gupta PC, Murti PR, Bhonsle RB. Epidemiology of cancer by tobacco products and the significance of TSNA. Crit Rev Toxicol 1996;26:183–98.
4. Lopez LC, Hamlin PA. Use of smokeless tobacco by Mexican-American high school students. Psychol Rep 1995;77:808–10.
5. Giovino GA, Schooley MW, Zhu BP, et al. Surveillance for selected tobacco-use behaviors. MMWR CDC Surveill Summ 1994;43:1–43.
6. Anonymous. Cigars: Health Effects and Trends. Smoking and Tobacco Control Monograph No. 9. Bethesda: National Cancer Institute, 1998.
7. Winn DM, Blot WJ, Shy CM, et al. Snuff dipping and oral cancer among women in the southern United States. N Engl J Med 1981;304:745–9.
8. Siegel D, Benowitz N, Ernster VL, et al. Smokeless tobacco, cardiovascular risk factors, and nicotine and cotinine levels in professional baseball players. Am J Publ Health 1992;82:417–21.
9. Walsh MM, Hilton JF, Ernster VL, et al. Prevalence, patterns and correlates of spit tobacco use in a college athlete population. Addict Behav 1994;19:411–27.
10. Hoffmann D, Djordjevic MV, Fan J, et al. Five leading U.S. commercial brands of moist snuff in 1994: assessment of carcinogenic N-nitrosamines. J Natl Cancer Inst 1995;87:1862–9.
11. Hu FB, Hedeker D, Flay BR, et al. The patterns and predictors of smokeless tobacco onset among public school teenagers. Am J Prev Med 1996;12:22–8.
12. Anonymous. Tobacco use and usual source of cigarettes among high school students—United States, 1995. JAMA 1996;276:184–5.
13. Joosens L. EC oral snuff ban and Sweden. Lancet 1992;340:57.
14. Bolinder G, Alfredsson L, Englund A, de Faire U. Smokeless tobacco use and increased cardiovascular mortality. Am J Public Health 1994;84:399–404.
15. Huhtasaari F, Asplund K, Lundberg V, et al. Tobacco and myocardial infarction: is snuff less dangerous than cigarettes? Br Med J 1992;305:1252–6.
16. WHO MONICA Project Principle Investigators. The World Health Organization MONICA Project (Monitoring of Trends and Determinants in Cardiovascular Disease): a major international collaboration. J Clin Epidemiol 1988;41:105–14.
17. WHO MONICA Project, prepared by Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, et al. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates and case-fatality rates in 38 populations from 21 countries in four continents. Circulation 1994;90:583–612.
18. Lundberg V, Stegmayr B, Asplund K, et al. Diabetes as a risk factor for myocardial infarction: population and gender perspective. J Intern Med 1997;241:485–92.
19. Huhtasaari F, Asplund K, Lundberg V, et al. Trends in cardiovascular risk factors in the Northern Sweden MONICA Study: who are the winners? Cardiovasc Risk Factors 1993;3:215–21.
20. Benowitz NL, Porchet H, Sheiner L, Jacob P. Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. Clin Pharmacol Ther 1988;44:23–8.
21. Ahlbom A, Olsson UA, Pershagen G. Hälsorisker med snus [Health risks by snuff]. Position paper. Stockholm: Swedish National Board of Health and Welfare; 1997.
22. Nair J, Ohshima H, Nair UJ, Bartsch H. Endogenous formation of nitrosamines and oxidative DNA-damaging agents in tobacco users. Crit Rev Toxicol 1996;26:149–61.
23. Murphy SE, Carmella SG, Idris AM, Hoffmann D. Uptake and metabolism of carcinogenic levels of tobacco-specific nitrosamines by Sudanese snuff dippers. Cancer Epidemiol Biomarkers Prev 1994;3:423–8.
24. Hecht SS, Carmella SG, Foiles PG, et al. Tobacco-specific nitrosamine adducts: studies in laboratory animals and humans. Environ Health Perspect 1993;99:57–63.
25. Penn A, Snyder CA. 1,3 Butadiene, a vapor phase component of environmental tobacco smoke, accelerates arteriosclerotic plaque development. Circulation 1997;93:275–6.
26. Djordjevic MV, Brunnemann KD, Hoffmann D. The need for regulation of carcinogenic N-nitrosamines in oral snuff. Food Chem Toxicol 1993;31:497–501.
27. Holm H, Jarvis MJ, Russel MAH, Feyerabend C. Nicotine intake and dependence in Swedish snuff takers. Psychopharmacol 1992;108:507–11.
28. International Agency for Research on Cancer. Tobacco habits other

than smoking—betel quid and avoca nut chewing—and some related nitrosamines. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans (vol 37) Lyon: International Agency for Research on Cancer; 1985.
29. Benowitz NL, Goulay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. J Am Coll Cardiol 1997;29: 1422–31.
30. Bolinder GM, Ahlborg BO, Lindell JH. Use of smokeless tobacco: blood pressure elevation and other health hazards found in a large-scale population survey. J Intern Med 1992;232:327–34.
31. Eliasson M, Asplund K, Evrin PE, Lundblad D. Relationship of cigarette smoking and snuff dipping to plasma fibrinogen, fibrinolytic vaiables and serum insulin. The Northern Sweden MONICA Study. Atherosclerosis 1995;113:41–53.
32. Eliasson M, Lundblad D, Hägg E. Cardiovascular risk factors in young snuff-users and cigarette smokers. J Intern Med 1991;230:17–22.
33. Samuelsson C. Medicinska konsekvenser av polonium i snus [Medical consequences of polonium in snuff]. Läkartidningen 1989;86:2290–1.
34. Goldstein AO, Bearman NS. State tobacco lobbyists and organizations in the United States: crossed lines. Am J Publ Health 1996;86:1073–5.
35. Tillgren P, Haglund BJ, Ainetdin T, Holm LE. Who is a successful quitter? One-year follow-up of a National Quit and Win Contest in Sweden. Scand J Soc Med 1995;23:193–201.