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Review Paper

Is smokeless tobacco a risk factor for coronary heart disease? A systematic review of epidemiological studies

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Background **There is on-going debate about the wisdom of substituting smokeless tobacco products for cigarette smoking as a 'harm reduction' strategy. It is generally believed that health risks associated with smokeless tobacco use (ST) are lower than those with cigarette smoking. However, the population attributable risk of smoking is higher for cardiovascular diseases than for any cancers, and few studies or reviews have considered the cardiovascular outcomes of ST use. A systematic review was therefore carried out to highlight the gaps in the evidence base.**

Methods **Electronic databases were searched, supplemented by screening reference lists, smoking-related websites, and contacting experts. Analytical observational studies of ST use (cohorts, case–control, cross-sectional studies) were included if they reported on cardiovascular disease (CVD) outcomes, or risk factors. Data extraction covered control of confounding, selection of cases and controls, sample size, clear definitions and measurements of the health outcome and ST use. One or two independent reviewers carried out selection, extraction and quality assessments.**

Results **A narrative review was carried out. Very few studies were identified; only three from Sweden consider CVD outcomes and these are discrepant. There may be a modest association between use of Swedish snuff (snus) and cardiovascular disease (e.g., relative risk=1.4, 95% confidence interval 1.2–1.6) in one prospective cohort study. Several other studies have considered associations between ST use and intermediate outcomes (CVD risk factors).**

Conclusions **There may be an association between ST use and cardiovascular disease. However, further rigorous studies with adequate sample sizes are required.** ***Eur J Cardiovasc Prevention Rehab*** **11:101–112 © 2004 The European Society of Cardiology.**

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Keywords: cardiovascular disease, smokeless tobacco, smoking, systematic review

Introduction

Coronary heart disease (CHD) is the most common cause of death in the UK, and many developed countries [1]. It is projected to be the single leading cause of death and disability worldwide by 2020 [2]. The major risk factors for CHD are smoking, high blood pressure, high cholesterol levels, and lack of physical activity. Estimates of relative risk (RR) for smoking and CHD vary between studies, but tend to be between 1.5 and 3.0 [3,4].

The biological mechanisms through which smoking causes CHD are still debated. Smoking appears to increase CHD risk primarily through thrombosis (blood clotting) [5], but may also influence atherosclerosis [6,7]. Evidence suggests that the blood nicotine levels from smokeless tobacco (ST) use are similar to those of smoking [8]. Nicotine itself has been shown to have acute and systemic cardiovascular effects [9–12], but other aspects of tobacco smoke may be more responsible for oxidative damage [13].

Smoking 'harm reduction'

There is increased interest in the concept of 'harm reduction', persuading resistant smokers to reduce their smoking levels [14], or to switch

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to alternative less harmful products [15]. Nicotine addiction is the main hurdle to quitting smoking among those motivated, hence swapping to another less harmful form of nicotine delivery may benefit public health [16].

What is ST and how is it used?

Smokeless tobacco is tobacco consumed orally and not smoked, and includes moist oral snuff, chewing tobacco, and tobacco used with betel quid, areca nut, and other ingredients [17–19]. Its use increased in the latter half of the twentieth century in certain countries [19], particularly the US and Sweden (where 20% of young males use snuff) [20]. Forms of ST are also very commonly used in the Indian sub-continent [21].

Population attributable risks of tobacco use and cardiovascular disease

Recent Swedish studies have not found high risks of cancers associated with oral moist snuff use, but the incidence of oral cancers is very low [22]. In contrast, the incidence of cardiovascular diseases is very high [1] and increasing in many countries [2,23], and the population attributable risk of cigarette smoking is higher for cardiovascular disease than for most cancers [24–26]. Smokeless tobacco contains many of the same potentially noxious substances (nitrosamines and nicotine) as smoked tobacco. The potential cardiovascular health risks of ST use have been overlooked to date. A systematic review was therefore carried out to summarize and highlight gaps in the knowledge base. This review expands on a larger report, which considered a range of health effects associated with ST use [27].

Methods

Criteria for considering studies for this review

Study types

Analytical epidemiological studies (prospective and retrospective cohort, case–control and cross-sectional studies) were included. These must contain users of a form of ST and a group who use no tobacco products or smoke cigarettes only.

Outcome measures

Studies reporting on cardiovascular disease outcomes were included. Studies reporting on 'intermediate' outcomes (cardiovascular risk factors) such as blood pressure or lipid levels were excluded from the original review [27], but have been reported here for completeness.

Exclusions

The 'acute' effects of nicotine and tobacco on the cardiovascular system, including increases in blood pressure and heart rate, have been well-described elsewhere [13,28–35].

Search strategy for identification of primary studies

A comprehensive search strategy was developed, as part of a larger review [27]. This included electronic databases, websites, contact with experts, and checking reference lists. A few non-English language studies were identified, but not included (appendices available from author on request).

Results of searches

Each of the 2923 records identified were scanned by at least one reviewer to identify potentially relevant studies. A conservative approach was utilized i.e., all papers were retrieved unless sufficient details were available to decide the study was definitely not relevant. A second reviewer independently screened the first 1557 articles (from MEDLINE) to double-check and minimize errors. Agreement between the two reviewers was high (kappa = 0.74) (see Figure 1 for a summary of study searching, inclusion, data extraction and quality assessment). The inclusion criteria and data extraction forms were developed for the review, adapted from a form used previously [36], and pilot tested. Once initially identified, two reviewers extracted data from included studies.

Assessment of methodological quality

Unlike for randomized controlled trials, there are no generally accepted lists of appropriate quality criteria for observational studies [37] and there is little empirical research relating aspects of study quality to results [38]. Specific aspects of quality, such as control of confounding factors, selection of cases and controls, sample size, clear definitions of the CHD and ST use, evidence of a dose–response relationship were therefore detailed for each study. Table 1 describes each study in the order of reference.

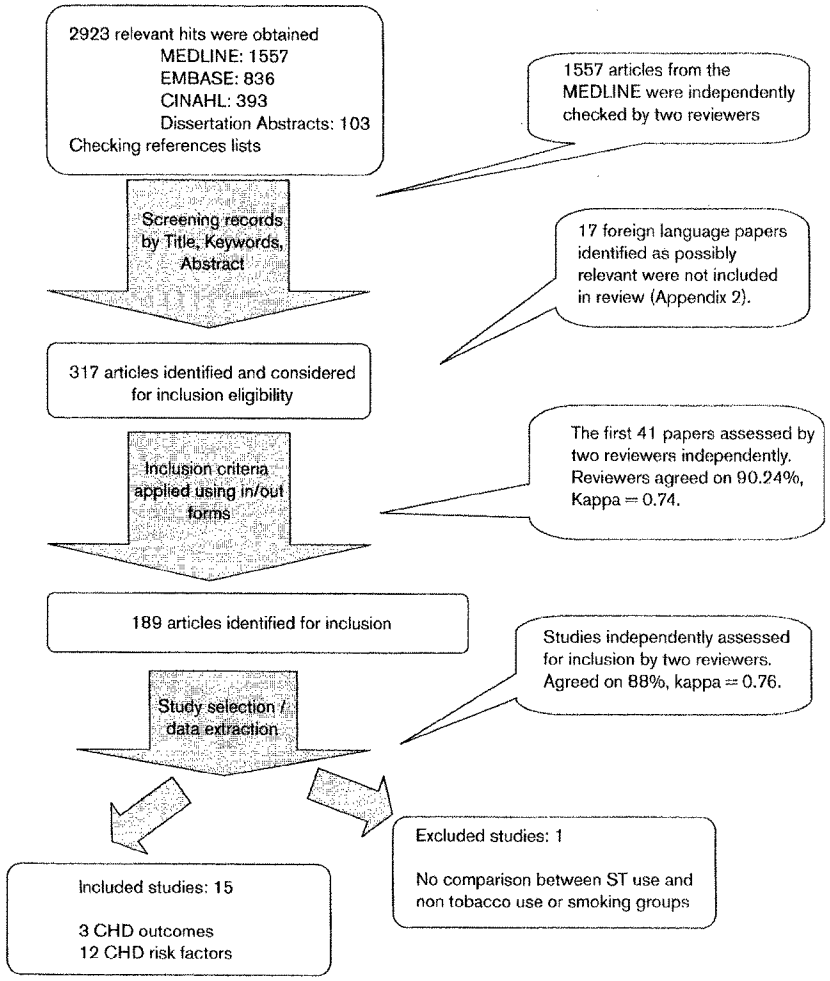
Results

Studies of cardiovascular disease outcomes

Prospective cohort study

One cohort study of ST use and cardiovascular disease was carried out in several different regions of Sweden. Bolinder *et al.* [39] followed up Swedish construction workers (135,036 men) for mortality outcomes from cardiovascular disease (CVD) and other causes for 10 years. The ST use was defined as current use of ST only and ST users were never-smokers. Also, cigarette smokers did not use any other forms of tobacco. Across all age groups, there was a 40% excess risk of both CVD death and all-cause mortality among ST users [RR = 1.4, 95% confidence interval (CI) 1.2–1.6 for all CVD; RR = 1.4, 95% confidence interval (CI) 1.3–1.8 for all cause mortality]. Among younger men aged 35–54, the age and regional origin-adjusted RR of ST use for CHD mortality was 2.0 (95% CI 1.49–2.9); for stroke, the RR was 1.9 (95% CI 0.6–5.7), and for all CVD deaths the RR was 2.1 (95% CI 1.5–2.9). There were no statistically significant associations between ST and CVD in the older

Fig. 1



Flowchart of search and selection strategy. CHD, coronary heart disease; ST, smokeless tobacco.

(55–64) age group, and the authors suggest this may be 'a healthy worker effect'. Equally, this may result from 'selective mortality' (earlier deaths among snuff users) or simply chance.

Most of the major CVD risk factors [age, body mass index (BMI), blood pressure, diabetes and history of heart symptoms or blood pressure medication at the time of entering study] were taken into account in these estimates, except cholesterol and alcohol use. Relative risks were not altered after control of these confounders (though no numerical data is shown).

We calculated the population attributable risks (PAR) for snus use and cigarette smoking using RR estimates from this study, and estimates of prevalence of cigarette smoking and snus use among men in Sweden [40]. This suggests that roughly twice as many cardiovascular disease deaths could be attributed to cigarette smoking, compared with snuff use, however 95% CIs are wide and almost overlap (Table 2).

Case–control studies

Two case–control studies of CVD were included [41,42]. Both recruited cases from the MONICA (Monitoring Outcomes in Cardiovascular Disease) Sweden Project, but the authors state that participants were different in each study. The first paper used group-matched population controls [41]. Snuff dippers had no increased risk of myocardial infarction (MI) compared to non-tobacco users (see Table 1). No dose–response relation was

Table 1 Description and quality assessment of studies

Study and type of ST	Subjects, setting and years of recruitment	Sample size and number of ST users	Measurement of exposure, outcomes and confounders	Findings or results	Comments
Cardiovascular disease outcomes: prospective cohort study					
Bolinder, 1994 [39] ORAL SNUFF USE	Swedish construction workers who had health check-ups in 1971–1974.	135 036 workers. Women workers (less than 0.05%) were excluded from the study. 1672 of those aged 35–54 years and 1734 of 55–65 years were ST users. In total, there were 6297 ST users, 14 983 smokers of <15 cigarettes per day, 13 518 smokers of >15 cigarettes per day. 6761 recent ex-smokers (quit smoking 1–5 years previously) and 9800 ex-smokers who quit more than 5 years previously. There were 32 546 non-users of tobacco.	ST use was defined as present ST usage to reduce misclassification. Non-users in this study had never used any tobacco. ST users had never smoked. Cigarette smokers did not use any other tobacco forms. Outcomes clearly defined with ICD codes. Most of CVD risk factors adjusted for ST-outcome association except cholesterol and alcohol use. Also age and regional origin adjusted.	**Age group 35–54** RR of ST use for IHD: RR=2.0, (95% CI 1.49–2.9). Stroke: RR=1.9 (95% CI 0.6–5.7). All CVD: RR=2.1 (95% CI 1.5–2.9). All cancer: RR=1.2 (95% CI 0.8–1.9). All cause RR=1.9 (95% CI 1.6–2.4). **Age group 55–65** Adjusted RR of ST use for IHD: RR=1.2 (95% CI 1.0–1.5). Stroke: RR=1.2 (95% CI 0.7–1.8). All CVD: RR=1.1 (95% CI 1.0–1.4). All cancer: RR=1.0 (95% CI 0.8–1.3). All cause RR=1.2 (95% CI 1.0–1.3). **Over all age groups** RR of ST used for all CVD: RR=1.4 (95% CI 1.2–1.6). RR smoking <15 cigarettes per day: RR=1.8 (95% CI 1.6–2.0). RR smoking ≥ 15 cigarettes per day: RR=1.9 (95% CI 1.7–2.2).	25% of the workers did not come for checkups, the reason is not clear. Statistical power of the study is high (in total 6297 users of ST were followed up and 172 IHD deaths occurred in this group). Healthy worker effect may play a role in ST CVD mortality association. When potential confounding due to age, area of domicile, BMI, blood pressure, diabetes and history of heart symptoms or blood pressure medication at the time of entering the study was analysed according to Mantel–Haenzel procedure, the RR of death from CVD remained essentially unchanged. *Reference category is male never users of tobacco.
Case–control studies Huhtasaari 1992 [41] ORAL SNUFF	First MI cases and population controls from Northern Sweden, 1989–1991.	585 cases (first MI) and 589 controls. 59 of cases and 87 of controls were regular snuff dippers. 32 cases and 31 controls were concomitant smokers and snuff users.	ST was defined clearly (at least once daily), and dose–response relation was analysed. Outcomes clearly defined (MONICA protocol). Blood pressure, cholesterol and diabetes prevalence were similar in cases and controls so they were not included in the model. Confounders adjusted for were age and smoking (by 'excluding' snuff users who also smoked). Low levels of education were also considered separately as a risk factor for MI.	Age adj. OR of snuff dipping vs. no tobacco for MI: 35–54 years: OR=0.96 (95% CI 0.56–1.67) 55–64 years: OR=1.24 (95% CI 0.67–2.30) All ages: OR=0.89 (95% 0.62–1.29) Snuff dippers had no increased risk of MI compared to non-tobacco users. Snuff ≤ 2 cans weekly OR=0.63 (95% CI 0.41–0.98). >3 more cans weekly OR=0.93 (95% CI 0.61–1.41). In a logistic regression model for MI, with smoking, snuff dipping, low level of education, and age as predictors, snuff dipping was not significant.	The study was planned within Northern Sweden MONICA project. Cases were identified according to MONICA protocol. Controls were selected from population and they were only group matched. Response rate in controls was 81.6%. A telephone survey was conducted to check non-participants smoking habits and they were found to be similar to participants. Of the original set of case-controls 21.8% were excluded because of missing smoking information. This was common amongst the fatal case pairs. To check the validity of ST information obtained from spouses of fatal MI cases, spouses of surviving cases were interviewed by telephone 2 months later. The agreement was high for snuff use (98%). Information on duration of use was not high quality. Median age of starting snuff was 31.5 years explained by the fact that many had started snuff in conjunction with quitting smoking. Proper statistical analyses were carried out.

Huhtasaari 1999 [42] ORAL SNUFF From same study pop as Huhtasaari 1992 [41] But participants differed in each study	First MI cases and population controls from Northern Sweden, 1991–1993.	687 first MI men cases and 687 matched controls from same country. The cases were MONICA Sweden project. 59 cases and 90 controls were current snuff users and -non current smokers; 20 cases and 11 controls were both smokers and snuff users. 11 of the cases and 13 of the controls were former snuff users but non-smokers.	Detailed information about ST (present use, previous use, amount, type of preparation, age of onset and whether or not snuffing was associated with quitting smoking) obtained. Median consumption of snuff was 2 boxes per week in both cases and controls. Outcomes clearly defined (MONICA protocol) Confounders adjusted for include hypertension, low level of education, not being married or cohabitant, diabetes, known high cholesterol and heredity.	OR for different combinations of snuff user for MI: Current snuff user-non smoker: 0.96 (95% CI 0.65 to 1.41) Current smoker, no current snuff use: 3.65 (2.67–4.99) Current snuff user and smoker: 2.66 (95% CI 1.24 to 5.71) Former snuff user, never smoked: 1.23 (95% CI 0.54 to 2.82) In conditional regression model, regular use of snuff was adjusted Adjusted OR of snuff use for all MI: 0.58 (95% CI 0.35 to 0.94). Adjusted OR of snuff use for all MI: 0.58 (95% CI 0.35 to 0.94). Adjusted OR of snuff use for fatal MI: 1.50 (95% CI 0.45 to 5.03).	Of the original set of case–controls 21.8% were excluded because of missing smoking information. This was common amongst the fatal case pairs. To check the validity of ST information obtained from spouses of fatal MI cases, spouses of surviving cases were interviewed by telephone 2 months later. The agreement was high for snuff use (98%). Information on duration of use was not high quality. Median age of starting snuff was 31.5 years explained by the fact that many had started snuff in conjunction with quitting smoking. Proper statistical analyses were carried out.
'Intermediate' outcomes (cardiovascular risk factors) cross-sectional studies					
Bolinder 1992 [11] ORAL SNUFF From same study as Bolinder 1994 [39]	16–65 years old Swedish construction workers, 1971–1974.	97 586 construction workers who had voluntary health checkups. 5014 of the participants were ST users who had never been regular smokers.	ST users were daily users. Confounding: persons who had mixed tobacco habits were excluded from the analyses to increase validity, also adjusted for age.	Reason for disability pension among 46–55 years old: OR of ST use vs non-users for CVD diagnosis: 1.6 (95% CI 0.7–3.5) for hypertension: 3.0 (95% CI 1.9–4.9). Among 56–65 year olds: OR of ST use vs non-users for CVD diagnosis: 1.5 (95% CI 1.1–1.9). Age adjusted RR of 'frequent sick leave' (1 day or more for four times or more per year) for all kind of diagnosis was 1.1 (95% CI 1.0–1.2) for ST users compared to non-users. Age adjusted RR 'Longer sick leave' (30 days in a year) was 1.2 (95% CI 1.1–1.2) for ST users compared to non-users.	The aim of the study was to evaluate ST effect on blood pressure and other health hazards. In this cross-sectional study, reference group was those who had never used any tobacco form. The outcomes were questionnaire reported symptoms, physical examination and disability pension due to cardiovascular and musculoskeletal diagnoses. Healthy worker effect highly possible.
Eliasson *et al.*, 1991 [44] ORAL SNUFF	Male volunteers <31 years, recruited from University students and schoolteachers.	21 snuff dippers, 18 non-tobacco users, 21 cigarette smokers	Snuff use clearly defined (at least one can 50 g per week). Measurement of outcomes clearly described. No attempt to adjust for important confounders (see comments).	Snuff users and cigarette smokers had higher serum insulin levels. Snuff users had no significant elevations of other risk factors such as serum cholesterol or triglycerides, diastolic blood pressure (BP), haemoglobin concentration, white cell count.	Sample size is very small. Considerable lifestyle differences exist between cigarette smokers and non-tobacco users e.g., physical activity levels lower, higher alcohol and coffee consumption among tobacco users then non-users (risk profile worst for smokers, intermediate for snuff dippers, best for non-tobacco users). Also substantial social class differences – non-tobacco users and snuff dippers were male volunteers, of similar social class, but 35% of smokers were blue-collar workers.

Table 1 *(Continued)*

Study and type of ST	Subjects, setting and years of recruitment	Sample size and number of ST users	Measurement of exposure, outcomes and confounders	Findings or results	Comments
Eliasson *et al.*, 1995 [45] SNUFF DIPPING (MOIST ORAL SNUFF)	Part of MONICA project – population sample of men aged 25–64 in Northern Sweden, 1990.	604 men, of whom 92 dipped snuff regularly.	ST measurements clearly defined, snuff dippers did not use other tobacco products. Blood analyses clearly described, with overnight fasting and glucose tolerance test. Also anthropometry (BMI, WHR) & BP. Multiple regressions: predictors included age, BMI, WHR, height, cholesterol, HDL cholesterol, triglycerides, and blood pressure.	There were no differences in plasma fibrinogen, fibrinolytic variables (tPA activity, PAI-1 activity), or glucose intolerance among snuff dippers compared with non-tobacco users. Men who smoked cigarettes had higher fibrinogen levels than non-tobacco users, and evidence of a dose–response relationship was found.	Snuff use clearly defined, but limited to males only (too few female snuff users). Reasonable participation rate (79.2%). Smokers were slightly older and had a longer duration of tobacco use than snuff dippers. Potentially important confounders, such as socio-economic status, educational level, and physical activity were not considered.
Siegel *et al.*, 1992 [46] ORAL SNUFF AND CHEWING TOBACCO	1061 members of seven major league baseball teams and their associated minor league teams, Phoenix and Tucson Arizona, spring 1989.	1061, of whom 473 were ST users.	ST use included type, brand, and quantity (number of cans of snuff or pouches of chewing tobacco reportedly used per week). Self-reported use biochemically validated Heart rate and pulse measured twice, sitting. Blood samples taken. Confounding: $n=41$ cigarette smokers were excluded. Other covariates adjusted by multiple logistic regression (age, race, alcohol consumption, serum caffeine).	No significant differences between ST users and non-users in systolic or diastolic BP, pulse, total or LDL cholesterol. No dose–response relationships were found (e.g., with years of use, or hours of use per day, but data not shown). ST users had lower mean white cell counts than non-users.	The aim of the study was to evaluate ST effect on blood pressure and other risk factors. Study limited to young, fit, males (77% aged between 20 and 29). Predominantly white and well educated.
Tucker, 1989 [8] ST USE (NOT DEFINED)	Adult males who were employees of over 25 companies participating in a Health Examination Programme. Time period of study not stated.	2840, of whom 93 were ST users.	ST measurements not described, no dose–response information. Physical measurements include body fat (skin-fold callipers), physical fitness (step test), blood samples (cholesterol). M–H adjustments for age, educational level, physical fitness and smoking.	The adjusted RR of hypercholesterolaemia (defined as total cholesterol >6.2 mmol/l) was 2.51 (95% CI 1.47–2.29 for ST use). This compared with RR of 1.51 (95% CI 1.14–2.0) for smoking 1–20 cigarettes daily, and 1.98 (95% CI 1.29–3.03) for smoking >20 cigarettes daily.	ST use not defined or described. ST users were younger and less educated than non-tobacco users. Limited to males only.
Khurana *et al.*, 2000 [47] CHEWING TOBACCO (NOT DEFINED)	Patients attending 'medical outdoor', SMS Medical College and Hospital, Jaipur, India, and volunteers from society. Patients with diabetes, hypertension, renal disease, hepatic impairment, endocrine disorders, alcoholics, menopausal women, and those on certain medications all excluded. No other details given.	30 current smokers, 30 current tobacco chewers (both of >10 years duration), 30 non-smokers and non-chewers.	Methods of measuring lipid profiles clearly described. No details of types of tobacco chewers. No information on confounding – states no significant difference in mean age between groups, that participants ate 'average India diet', and had body weight 'in normal range'.	Current smokers had significantly lower HDL (high density lipoprotein) than non-smokers, and significantly higher VLDL (very low density lipoprotein) and TG (triglycerides). TC (total cholesterol) and LDL (low density lipoprotein) were both also higher among smokers, but the difference was not statistically significant. Tobacco chewers also had significantly lower HDL, and significantly higher VLDL and TG. For example, HDL was 39.80 ± 5.62 in smokers, 37.55 ± 5.81 in chewers, and 44.38 ± 3.86 in non-tobacco users. Similarly, TG was 154.44 ± 43.98 in smokers, 160.33 ± 47.76 in chewers, 96.49 ± 25.78 in non-tobacco users. There were no statistically significant differences between smokers and tobacco chewers.	Sample size small (30 in each of three groups), unclear precisely how patients and volunteers were selected. Very little information provided on these participants (no information on sex, very limited information on age, and other potential confounders). Validity of results is therefore questionable.

Bolinder *et al.*, 1997 [48] SNUFF USE	Male firemen aged 35–60 years.	143, of whom 28 were long-term ST users, 40 never-users of tobacco, and 29 smokers.	ST user clearly defined (daily use for more than 6 months). Outcome: ultrasonographic examination of carotid artery clearly described and carried out blind to tobacco use status. Annual compulsory fitness test, BP, blood analyses. Confounders considered included biochemical risk factors, age, BMI, blood pressure.	Snuff users did not differ significantly from those who had never used tobacco, in terms of intima medial wall measurements or lumen diameters of common carotid or bulb area. Significant increases in wall thickness were found for smokers. Plaques were found in two ST users and no never-users, but this difference was not significant.	Small sample size–biochemical risk factors (serum cholesterol, LDL cholesterol, triglycerides, fibrinogen) all tended to be slightly higher (and HDL cholesterol lower) among ST users compared with never-users, but differences not statistically significant.
Bolinder *et al.*, 1997 [51] ORAL SNUFF	Male firemen aged 35–60, Stockholm City.	144, of whom 50 were ST users, 68 non-tobacco users, and 33 smokers.	ST use clearly defined, as above. Graded exercise test on a bicycle ergometer, until exhaustion. Continuous recording of HR, ECG respiratory rate, O_2 uptake and CO_2 production, and respiratory rates. Fasting blood sample. Test results adjusted for differences in age, BMI, WHR, alcohol, physical training, occupational physical activity.	No significant differences in maximal work or oxygen uptake for ST users compared with non-tobacco users. Smokers performed significantly worse in terms of maximal workloads and oxygen uptake. For example VO_2 max (mL/min/kg) for non-users was 3.51 ± 0.51, 3.48 ± 0.49 for ST users, and 2.88 ± 0.49 for cigarette smokers. No dose–response relationships observed with quantity of tobacco used for ST users, but in smokers a statistically significant negative correlation between maximal workload and number of cigarettes smoked per day was observed.	Study population may overlap with the study above, Bolinder *et al.*, 1997 [55]. 'Healthy worker' effect is possible: it may be harder to investigate potentially deleterious effects of ST use among healthy and physically fit males.
Schroeder and Chen, 1985 [52] TYPES OF ST NOT DESCRIBED	Volunteers, not specified.	1663 volunteers over 18, 710 males, 923 females. 69 males were ST users, but blood pressure reported for only 19 males aged 18–25.	Not described	Mean BP of 19 current male ST users was 143.7/80.7 mmHg, 23 male cigarette smokers 127.7/70.0 mmHg, non-users of tobacco 131.6/72.8 mmHg. This was statistically significant for tobacco users combined versus non-users (7.9 mmHg, $P<0.01$), but no significance test was carried out for ST users versus non-tobacco users.	Letter only–very limited details. Unclear why analyses limited to those aged 18–25, which much reduces the sample size available.
Westman and Guthrie, 1990 [53] CHEWING LEAF TOBACCO AND SNUFF	Men attending rural county fairs in Kentucky, US.	32 leaf tobacco users (25 light users, less than 1 pouch/day, seven heavy users), 15 snuff users, 27 non-ST users.	Exposure measured by questionnaire and clearly described. Outcome measurements not described. Confounders not mentioned.	Mean systolic BP of heavy tobacco chewers was 15.1 mmHg higher than that of non-users ($P=0.007$). Systolic BP: 139.3 ± 25.1 in heavy users, 122.9 ± 10.9 in light users, 124.2 ± 13.5 in non-users and 125 ± 9.8 in snuff users. Diastolic BP: 31.3 ± 16.9 in heavy users, 79.3 ± 9.0 in light users, 74.0 ± 13.6 in non-users and 74.3 ± 6.8 in snuff users. Plasma renin concentrations, and excretion of sodium and potassium tended to be higher in heavy users.	Letter only, ST use clearly described but few other details. Most notably selection is not described; heavy tobacco chewers were substantially older than non-chewers (37.3 ± 14.9 vs. 27.5 ± 8.9 for non-users, 30.3 ± 9.9 for light users, and 26.1 ± 9.32 for snuff users). It is also unclear whether non-ST users used other forms of tobacco. Clearly, apart from age, other lifestyle differences between the groups could account for the differences in blood pressure.

Table 1 ***(Continued)***

Study and type of ST	Subjects, setting and years of recruitment	Sample size and number of ST users	Measurement of exposure, outcomes and confounders	Findings or results	Comments
Stegmayr *et al.*, 1995 [54] ORAL SNUFF	Part of MONICA project, Northern Sweden, 1990. Men aged 40–49.	17 snuff dippers, 26 cigarette smokers, 54 non-tobacco users.	Snuff use clearly defined. Measurements of outcomes described in detail. Men with 'mixed' tobacco habits were excluded, but no other attempts to adjust for confounders.	Levels of plasma vitamins were similar in snuff-dippers and non-tobacco users. Regular smokers had significantly lower plasma levels of ascorbate ($P<0.001$), lipid-standardized α-tocopherol ($P=0.032$), α-carotene ($P<0.001$) and ascorbate, lipid-standardized α-tocopherol, α-carotene and β-carotene than non-tobacco users e.g. β-carotene 0.37 μmol/l (95% CI 0.32–0.42) in non-tobacco users, 0.31 (95% CI 0.22–0.40) in snuff users, and 0.26 (95% CI 0.2–0.32) in smokers.	Small sample size, limited to males only. Response rates reasonable (77.3%). Intake of fruit and vegetables tended to be lower for smokers than for snuff users and non-tobacco users.
Persson *et al.*, 2000 [55] ORAL SNUFF	Stockholm–men born during 1938–1957 (aged 35–56 years), 50% had strong family history of diabetes.	3162 men 376 former snuff users, 492 current users	Snuff use clearly defined and some attempt to measure quantity used per week. Outcome–glucose intolerance and type II diabetes clearly defined. Confounders considered include age, alcohol consumption, BMI, family history of diabetes, physical activity, cigarette smoking.	No statistically significantly raised OR for glucose intolerance associated with oral snuff use or cigarette smoking. The OR of type II diabetes was raised, but not statistically significant for both current cigarette smokers and current snuff users (OR=1.5, 95% CI 0.8–3.0 for current snuff users, OR=1.3, 95% CI 0.6–2.7 for current smokers). However, statistically significant OR were found among those who consumed the most cigarettes or snuff. (OR=2.7, 95% CI 1.3–5.5 for snuff users consuming three or more boxes per week, OR=2.6 95% CI 1.1–5.8 for smokers consuming 25 or more cigarettes per day).	Well-designed cross-sectional study with large sample size. Most important confounders were considered. Exposure and outcomes clearly described. Representativeness of sample may be an issue; 79% responded to initial 'screening' questionnaire, but then a further 27.4% were excluded due to incomplete answers, and only 70% of those selected to take part agreed to do so.

ST, smokeless tobacco; RR, relative risk; CI, confidence interval; IHD, ischaemic heart disease; BMI, body mass index; CVD, cardiovascular disease; MI, myocardial infarction; BP, blood pressure; WHR, waist-to-hip ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HR, heart rate; ECG, electrocardiogram; M–H, Mantel–Haenzel; tPA, tissue plasminogen activator; PAI, plasminogen activator inhibitor.

Table 2 **Cardiovascular disease (CVD) deaths attributed to smokeless tobacco (ST) use and smoking in men aged 35 and over, in Sweden 1999**

	Cardiovascular disease mortality PAR % (95% CI)	Number of CVD deaths attributed (95% CI)
Smokeless tobacco use	7% (4–11%)	1597 (829–2309)
Smoking		
<15 cigarettes a day	7% (6–9%)	1597 (1220–1960)
>15 cigarettes a day	8% (7–11%)	1780 (1410–2309)
Total cigarette smoking	15% (13–20%)	3376 (2630–4269)

Approximately 21 555 deaths from CVD among men over 35 in Sweden in 1999 [40]. Estimated Swedish prevalence of ST use and cigarette smoking both about 20% in men [40]. Approximately half of these are light smokers (<15 cigarette per day, and half heavy smokers ≥ 15 cigarettes per day) [Sylwan Lisen. Swedish Cancer Society, 2003. (Personal Communication)]. PAR, population attributable risks; CI, confidence interval.

shown between snuff use and MI. In a logistic regression model for MI (including smoking, low levels of education, and age), snuff use was not a significant risk factor for MI. Blood pressure, cholesterol, and diabetes prevalence were similar in cases and controls so not included in the multivariate model.

In the second paper by Huhtasaari *et al.* [42], (Table 1) more detailed information about ST (present use, previous use, amount, type of preparation, age of onset and whether or not snuffing was associated with quitting smoking) was obtained from MI patients, or if cases had died, from next of kin. Median consumption of snuff was two boxes per week in both cases and controls. Median age of starting snuff use was 31.5 years, which may be explained by the fact that many had started snuff in conjunction with quitting smoking. Regular use of snuff was adjusted to control for confounding by hypertension, low levels of education, not being married or cohabiting, diabetes, known high cholesterol and heredity in conditional logistic regression. Odds ratios (OR) for all and fatal MI remained statistically insignificant after this adjustment.

Explanations for the differences between the prospective cohort and case–control studies

It is difficult to assess why these studies should have obtained such discrepant results. Bolinder's study [39] was carried out 10 years earlier, and it is possible that types of snuff in use may have changed during this time period [20]. All three studies have some non-response bias—in Bolinder's around 25% of employees did not attend the baseline assessment, and in Huhtassari's around 20% of the case-series did not take part. Bolinder's study is prospective, large, and well designed, and its 40% excess mortality risk should not be dismissed. Misclassification of tobacco users is possible, as smoking was not re-measured after baseline in this survey. However, at a population level a higher proportion of cigarette smokers have quit to use snuff than vice versa [43]. This could result in an underestimate of the risk associated with cigarette use, making it appear more similar to that of snuff use, but should not greatly affect the risk associated with snuff use. Adjustment for confounders in each study might have played a role. Unlike Bolinder's cohort, Huhtasaari's studies [41,42] adjusted for low levels of education and marital status along with other factors. However, this is not likely to explain all the association as the cohort was relatively uniform socio-economically (construction workers), and Swedish surveys during the 1980s show little differences in snus use by socio-economic status [40]. Huhtasaari's studies are well designed, but are not prospective, and may dilute risk estimates slightly because of inclusion of occasional and former smokers in the reference group, or recall biases.

Studies considering 'intermediate outcomes' (CHD risk factors)

Studies of multiple risk factors

A number of cross-sectional studies have evaluated the relationship between ST use and CVD risk factors. These studies can be hard to interpret, as the time relationship between ST use and CHD risk factors is uncertain (previous exposure to ST use may be more relevant than exposure at the time of the study).

Bolinder's large study of mortality among construction workers also considered receipt of disability pensions, and symptoms among exclusive snuff users compared with non-tobacco users at baseline [11]. Among 46–55 year olds, snuff users were more likely to have a CHD diagnosis or hypertension (OR = 1.6, 95% CI 0.7–3.5 and OR 3.0, 95% CI 1.9–4.9, respectively).

One Swedish study reassuringly found little evidence of increased risk factors among young male ST users, except for elevated serum insulin and higher fibrinogen levels [44]. However, this study was very small ($n = 60$), used 'convenience' volunteer samples, and was limited to young men under the age of 30. Evidence was found of differences in other CHD risk factors (such as increases in alcohol and coffee consumption and lower exercise levels compared with non-tobacco users), and there were differences in educational levels between cigarette smokers, snus users, and non-tobacco users. As no multivariate analyses were performed, it is difficult to attribute any differences observed to snuff use or other lifestyle factors. It is also possible that further changes in risk factors may occur with longer-term snuff use among older men.

A further North Swedish study, (part of MONICA) found no associations between ST use, plasma fibrinogen, serum insulin and fibrinolytic variables [45], despite high plasma nicotine, and higher plasma cotinine levels among snuff users compared with cigarette smokers. Cigarette smokers, however, had significantly raised plasma fibrinogen.

These findings were supported by a further large cross-sectional study ($n = 1061$) of young male baseball players in the USA [46]. All participants were well educated and there were no significant differences between users and non-users. After adjustments, no associations were found between ST use with systolic or diastolic blood pressure, pulse, and total or high-density lipoprotein cholesterol. Again, these are relatively young men, and also light, often seasonal users of ST [46]. Whether risk factor profiles would be altered among older men or women, with higher use remains unexplored.

Hypercholesterolaemia

Two studies considered the relationship between ST use and cholesterol levels. One large cross-sectional study ($n = 2840$) from the USA found a 2.5-fold increased risk of hypercholesterolaemia among ST users compared with non-tobacco users (RR = 2.51, 95% CI 1.47–4.29) [8]. The risk among cigarette smokers was also raised, (RR = 1.51, 95% CI 1.14–2.0). Possible confounding with dietary factors, however, was not considered. Smokeless tobacco use was more common in younger and less educated subjects. The types of ST used were not stated or described.

One further small study from Jaipur, India, compared lipid levels among 30 smokers, tobacco chewers, and non-tobacco users [47]. It is not very clear how the participants were selected, and the type of tobacco used is not stated. It is also unlikely that major confounders (such as diet) were considered; the sex distribution of the participants is not even given. However, statistically significantly higher levels of low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and triglycerides, and lower levels of high-density lipoprotein cholesterol were found among both the smokers and chewers compared with non-smokers. No statistically significant differences were found between the smokers and chewers.

Atherosclerosis and other risk factors

One Swedish study of carotid artery ultrasonography among 143 middle-aged firemen found no evidence of increased wall thickness of the artery or carotid bulb among ST users (significant increases among cigarette smokers were observed) [48]. No statistically significant increases were found in atherosclerotic plaques, or other cardiovascular risk factors (lipid fractions, blood pressure) among ST users though these tended to be slightly higher than among those who had never used tobacco. Exposure to nicotine, however, was 37% higher among the ST users than cigarette smokers.

Physical capacity

Low levels of fitness are independently predictive of cardiovascular mortality [49,50]. A further study of physical performance from the same population of firemen [48,52] found that long-term use of ST did not significantly influence exercise capacity (no significant differences in maximal work performed or oxygen uptake between snuff dippers and non-tobacco users, cigarette smokers however, performed significantly worse) [52].

Hypertension

A number of studies have considered the effects of ST use on blood pressure, although the majority of these have considered the 'acute' effects rather than possible chronic influences. Bolinder's study (described above) found associations between ST use and blood pressure [11]. In a cross-sectional study from the 1980s, Schroeder and Chen [52] found a relationship between ST use and higher blood pressure among 710 young men volunteers aged 18–25. The mean blood pressure of 19 ST users was 143.7/80.7 mmHg compared with 131.6/72.8 among non-tobacco users. This report was in the form of a letter, and no other details of the participants, selection, and possible confounding factors were provided.

A further cross-sectional study of ST use and hypertension in the USA reported that mean systolic blood pressure was significantly higher among 'heavy' tobacco chewers compared with non-tobacco users (139.3 ± 25.1 versus 124.2 ± 13.5). Diastolic blood pressure was also slightly but not significantly raised [53]. Snuff use was not associated with higher blood pressure. The authors attribute this to the high liquorice content of chewing tobacco, but not of snuff. However, the study was reported as a letter, sample size was small, and selection unclear, and other potential lifestyle factors (such as physical activity or BMI) were not controlled for. Indeed, 'heavy tobacco chewers' were 10 years older than non-chewers, and this alone could account for much of the increase in blood pressure (snuff users were slightly younger than non-tobacco users).

Anti-oxidant nutrients

A further study from the MONICA project in Northern Sweden considered the effects of ST use on plasma levels of anti-oxidant vitamins in a small sample of 40–49 year old males (ascorbate, tocopherols, carotenoids) [54]. Regular smokers had significantly lower levels of ascorbate, lipid-standardized α-tocopherol, α-carotene and β-carotene than non-tobacco users. Levels among snuff users were generally similar to non-tobacco users, except that slightly lower α- and β-carotene were observed. However, consumption of fruit and vegetables tended to be lower for smokers than the other two groups, though these differences were not statistically significant. The authors suggest that high turnover of these vitamins in cigarette smokers may therefore be caused by components of tobacco smoke other than nicotine, though the sample size is small ($n = 97$).

Glucose intolerance and diabetes

One Swedish study has examined the relationship between use of oral moist snuff, cigarette smoking, and glucose intolerance in men [55]. This was a large, well-designed cross-sectional study. A raised but not statistically significant relationship between both current snuff use and cigarette smoking was found with type II diabetes (OR 1.5, 95% CI 0.8–3.0 for current snuff use, OR = 1.3, 95% CI 0.6–2.7 for current cigarette smoking), but not with glucose intolerance or insulin resistance. A dose–response relationship was also found; both snuff users and cigarette smokers consuming the most tobacco had the highest odds ratio for diabetes (OR = 2.7, 95% CI 1.3–5.5 for snuff users consuming three or more boxes per week, OR = 2.6, 95% CI 1.1–5.8 for smoking 25 or more cigarettes per day).

Discussion

Numerous studies have explored the possible influence of ST use on cancers, especially oral cancers. Most of these cancers are relatively rare. For example, in the UK the incidence of oral cancers (ICD 9, 140–149) was 9.3 per 100 000 in men, 5.0 in women in 1994 [22]. Conversely, estimates of the MI (ICD 9, 410–414) incidence in men are 100-fold greater, at 950 per 100 000 in the UK [56]. Estimates for women vary from 94–265 per 100 000. Studies investigating oral and other cancer outcomes must have had sufficient power to report on much more common cardiovascular outcomes; however, these results are generally not reported in the published literature. The potential cardiovascular effects of ST use have thus been largely overlooked.

The evidence for an effect of cigarette smoking on CVD risk is clear-cut, but an area of contention is how exactly these effects are mediated. Most studies have found very low cardiovascular risks associated with medicinal nicotine products (nicotine replacement therapies such as patches and gum) [57–59]. In conjunction with several studies showing little increased CVD risk factors or risk of CHD associated with ST, this suggests that nicotine *per se* may not be a major factor promoting atherosclerosis or thrombolysis, and other components of smoked tobacco may be responsible [45].

One well-designed and very large prospective cohort study found an increased risk of CHD deaths in Sweden [39]. Based on this study, it seems possible that there is a modest risk of cardiovascular disease associated with snus use in Sweden. Calculation of PARs for snus use and cigarette smoking from the estimates of RR in this study, and estimates of prevalence of cigarette smoking and snus use among men in Sweden, suggest that roughly half the number of CHD deaths could be attributed to snus use compared with cigarette smoking. Several other, smaller, cross-sectional studies have suggested possible increased risks [8,55]. Many of the studies reviewed are relatively poor in determining causality; they are cross-sectional in design, sometimes small, use convenience samples and do not necessarily adjust for important confounders. In particular, socio-economic status is not always measured and controlled for [44,47,52,53]. Most of the studies come from Sweden, and it cannot be assumed that the results would be generalizable to the types of ST used elsewhere. Most ST products are probably considerably lower risk than cigarette smoking (taking all the potential health effects, particularly cancers, into account). Switching to ST may reduce risks of major death and illness for *some* nicotine-addicted cigarette smokers. However, any 'tobacco harm reduction' strategy will need to acknowledge the lack of evidence and uncertainties (particularly for cardiovascular disease) and determine how best to communicate these reservations to the general public [60].

As with any review, it is possible that some published or unpublished studies may have been overlooked. Studies considering acute effects of cardiovascular disease were also excluded. However, the search strategy was comprehensive, involving extensive database searching carried out by two researchers independently, as well as contact with a number of experts in the field. It is therefore unlikely that important studies have been missed. Further, large, well-designed epidemiological studies of ST use and cardiovascular diseases and mortality are required in a variety of regions to clarify the potential risks.

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