Systematic review of the health effects of modified smokeless tobacco products

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EXECUTIVE SUMMARY

Objective

To systematically identify and appraise international epidemiological evidence for reduced harm relating to the major health effects of using modified smokeless tobacco products compared with conventional combustible tobacco products. The safety of using modified smokeless tobacco products compared with not using any form of tobacco is also considered. A broader overview of issues relating to the applicability of the current evidence base to other settings, and the population impact of reduced harm products, is also presented.

Data sources

The literature was searched using the following bibliographic databases: Cinahl, CochraneCentral Register of Controlled Trials, Current Contents, Embase, Medline, PsychInfo, PubMed, Science Citation Index, Social Science Citation Index. Other electronic and library catalogue sources searched included: ACP Journal Club, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database, and the Health Technology Assessment Database. Several Internet websites were also searched to access publications from major tobacco research sites as well as commercial and news sites providing product and marketing information. Relevant publications referenced in material obtained in the course of research on the topic were also identified. The author also identified publications through the membership of Globalink, the listserver of the International Tobacco control community.

Database searches were performed from inception to 21 June 2006 and then updated on 17 October 2006, and again on 13 November 2006. Publications identified from Globalink updates were considered between September 12 2006 and November 30 2006 inclusive.

Selection criteria

Studies were included if they:

- were published in the English language;
- evaluated smokeless tobacco products which have been modified to reduce toxicants (eg tobacco-specific nitrosamines) compared with conventional tobacco products (smokeless and combustible), and/or which have been marketed to consumers as being less harmful alternatives to conventional tobacco products;
- compared risks for users of modified smokeless tobacco products with non tobacco users, and/or users of conventional combustible tobacco products (ie cigarettes);
- were analytical epidemiological studies including prospective cohort studies, retrospective cohort studies, and case-control studies, or were systematic reviews or meta-analyses including at least one study which met the current review's selection criteria;
- were studies with samples of at least 100 people;
- were studies which controlled for critical confounders including age, sex, and use of other tobacco products;
- were studies which analysed for the incidence and mortality outcomes from illnesses and conditions related to tobacco products.

Excluded studies were those which:

- were narrative reviews, 'correspondence', conference proceedings, or abstracts;
- were articles not published in the English language;
- had samples of fewer than 100 participants;
- were pre-clinical research studies including animal studies or *in vitro* testing;
- evaluated products used in conjunction with medicinal nicotine or used for short-term smoking cessation therapy;
- reported on intermediate, relatively minor or temporary health outcomes;
- did not provide separate analyses for eligible forms of modified smokeless tobacco;
- and/or did not clearly describe their methods and results, or which had significant discrepancies.

Of 217 articles identified by the search strategy, 71 articles were retrieved as full text, from which a final group of 16 primary data papers and two systematic reviews were identified as eligible for appraisal and inclusion in the review. An additional 150 papers were considered as background material for preparing the report.

Data extraction and synthesis

A systematic method of literature searching, selection and appraisal was employed in the preparation of this report. Explicit inclusion and exclusion criteria were applied in a two-stage process to selecting papers for retrieval, and then for inclusion in the review. A quality checklist developed by Critchley and Unal for their systematic review of smokeless tobacco (2003) was adapted and simplified, with permission, for use in appraising primary studies. Studies were also ranked in terms of study design quality according to the National Health and Medical Research Council's interim levels of evidence criteria for aetiological studies (2005). Systematic reviews were described and critiqued in terms of whether the review asked a focused question, if the eligibility criteria for included studies were explicit, what search strategies were used, how the validity of included studies was assessed, and whether results of included studies were similar. Summaries of appraisal results were presented in tabular form in Evidence Tables.

Key findings and conclusions

Key results and conclusions made from the systematic review are listed below.

Eighteen papers were eligible for inclusion in this review: 16 primary studies (all conducted in Sweden), and two systematic reviews. All evaluated snus, a form of oral moist Swedish snuff which is a prominent modified low-nitrosamine product. This number of epidemiological studies is relatively slight compared to the wealth of literature published relating to smoking. Meta-analyses for outcomes were not possible due to study and outcome heterogeneity.

1. Six case-control studies were appraised that compared snus use with smoking across a range of head, neck and gastro-intestinal cancers. These suggest that compared with smoking, snus use has much lower health risks. Larger studies are required to increase the precision of risk estimates, however studies also indicate that compared with non tobacco use, snus did not lead to an increased risk for these cancers. Meta-analyses for outcomes were not possible due to study and outcome heterogeneity, and no pattern of findings was observed with respect to different cancer sites.

2. Five of six studies investigating risks for fatal and/or non-fatal cardiovascular disease (CVD) outcomes in men, including three case-control studies, a nested case-control study, and a cohort study, found no significantly increased prevalence of CVD for snus users compared with no tobacco use. However, a large cohort study of construction workers recruited in the early 1970s found a 40 per cent increased risk of death from cerebrovascular and cardiovascular disease in snus users compared with no tobacco use. These risks were greater in men aged 35-54 years than for those aged 55 years and over. This finding of increased CVD mortality is in contrast to the five studies of more recently observed cohorts which did not have the statistical power to detect small increases in mortality. The excess risks found in the construction worker study may be associated with population and exposure characteristics specific to the cohort, and findings may be less applicable to snus products currently on the market. Nevertheless, an increased risk for death from cerebrovascular and cardiovascular disease in (at least, middle aged) snus users cannot be excluded, and this risk does not appear to be linked to increased risk for developing CVD. Additional, high quality research with better controlling of confounders and measurement of tobacco exposure over time is required to further understand the potential association between snus use and CVD mortality. Notably, all six studies consistently demonstrated strong positive associations between smoking and major CVD events, accompanied by evidence of dose-response associations.

3. Other outcomes were investigated in five separate studies including inflammatory bowel disease, pregnancy outcomes, diabetes, and malignant lymphomas. The large cohort study of construction workers found no increased mortality from all cancers in snus users, but did

find a 40 per cent increased risk for all-cause mortality. No association was found between snus use and inflammatory bowel disease, diabetes, and malignant lymphomas. With respect to pregnancy outcomes, compared with non-tobacco use, snus use was associated with reduced infant birth weight, and increased risks for both pre-term delivery and, in contrast to smoking, pre-eclampsia. The study was limited by its measurement of tobacco exposure, possible reporting biases, and lack of controlling for potential confounders. Nevertheless, the study suggests that there are adverse effects in pregnancy from the use of snus and that snus use should not be encouraged as a safe alternative to smoking among pregnant women. High quality, prospective research is needed to corroborate these findings and explore possible dose-response effects.

4. Limitations of the evidence base included the following:

    - an emphasis on oropharyngeal cancers and cardiovascular disease health outcomes with investigation of other health outcomes limited to single studies;
    - reliance on retrospective, unvalidated self-report of tobacco exposure at study entry;
    - potential confounders such as alcohol abuse, illicit drug use, diet, physical exercise, body mass index (BMI), and family history of disease often not suitably controlled or adjusted;
    - health risks associated with snus use in ex-smokers, or with dual (smoking and snus) users were rarely measured;
    - risk estimates tended to be imprecise and studies underpowered to rule out small to moderate excess health risks associated with snus use;
    - in five of the 18 papers appraised in the review, the research, or in one case a researcher, received some financial support from the tobacco industry. This may have introduced subtle biases into the design, conduct and interpretation of the research, although no evidence of systematic differences were observed as a function of funding source.

5. The evidence from this review suggests that the harm of using snus relative to non-tobacco use is significantly less than found for smoking with respect to cancers of the head, neck and gastro-intestinal region, and cardiovascular disease events. While studies were underpowered to detect small increases in mortality risk compared to no tobacco use, results suggested that the product does not lead to significant risks for these outcomes. One older cohort study provided some evidence for a 40 per cent increased risk of death from all causes and a 40 per cent increased risk of death from cerebrovascular and cardiovascular disease in snus users compared with no tobacco users. However, there was no increased risk for all-cancer mortality. Further research is needed to investigate CVD risks in other populations using low-nitrosamine snus products and to investigate what diseases contributed to the increased risk for all-cause mortality, apart from CVD mortality. Single investigations of limited quality did not indicate increased risks in snus users for diabetes, inflammatory bowel disease or malignant lymphoma, and suggested increased adverse effects for snus use in pregnancy. Other known risks associated with snus but not included in studies appraised here are the dependence potential of nicotine and oral effects including snus-induced lesions, oral mucosal changes that are apparently reversible upon cessation and gingival recessions.

6. The review included a discussion of the applicability of the Swedish experience of snus evident in appraised primary research studies conducted in Sweden into other settings. Factors discussed included variations in product, eg manufacture, storage and toxicity; variations in acceptability and use of smokeless tobacco, including ethnic, demographic, social and cultural factors; and the risks of dual use and variations in accessibility and regulatory controls, including warning labelling, reporting of constituents, restrictions on marketing and sales, setting maximum toxicity levels, and taxation/price regimes.

7. Finally, issues relating to how the availability or promotion of snus as a harm reduction product may impact on the population's tobacco use and health were explored. Regulatory, commercial and ethical challenges to the role of modified smokeless tobacco in harm reduction, and alternative approaches, were also discussed.

Medical Subject (MeSH) Headings:
tobacco, smokeless
nitrosamines
scandinavia
clinical trials
epidemiologic studies

Additional keywords
snus
snuff
modified tobacco
low nitrosamine
harm minimisation
harm reduction

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LIST OF ABBREVIATIONS AND ACRONYMS

χ^2	—	chi squared test
95% CI	—	95% confidence interval
AC	—	adenocarcinoma
ASH	—	Action on Smoking and Health
AMI	—	acute myocardial infarction
BAT	—	British American Tobacco
BMI	—	body mass index
CDC	—	Centers for Disease Control
CI	—	confidence interval
CINAHL	—	Cumulative Index to Nursing and Allied Health Literature
CVD	—	cardiovascular disease
CHD	—	coronary heart disease
CLL	—	chronic lymphocytic leukaemia
CVD	—	cardiovascular disease
ETS	—	environmental tobacco smoke
g	—	grams
HD	—	Hodgkin's disease
HPV	—	human papilloma virus
HR	—	hazard ratio
IBD	—	inflammatory bowel disease
ICD-7	—	International Classification of Diseases – Seventh edition
IHD	—	ischemic heart disease

IRR — incidence rate ratios

kDM — known diabetes mellitus

kg — kilograms

MeSH — Medical Subject Headings

MI — myocardial infarction

MONICA — Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases

NHMRC — National Health and Medical Research Council

NHL — non-Hodgkin's lymphoma

NIH — National Institute of Health

NAB — *N'*-nitrosoanabasine

NAT — *N'*-nitrosoanatabine

NNAL — 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanol and its glucuronide

NNK — 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone

NNN — *N'*-nitrosonornicotine

NZHTA — New Zealand Health Technology Assessment

OGTT — oral glucose tolerance test

OR — odds ratio

OOSCC — oropharyngeal squamous cell carcinoma

PGT — pathological glucose tolerance

ppm — parts per million (unless otherwise specified, based on dry weight)

PREP — potential reduced-exposure product

RR — relative risk

SCC	—	squamous cell carcinoma (SCC)
SD	—	standard deviation
SES	—	socio-economic status
SIL	—	snus-induced lesion
ST	—	smokeless tobacco
THR	—	tobacco harm reduction
TSNA	—	tobacco specific N-nitrosamines
UICC	—	International Union Against Cancer (Union Internationale Contre le Cancer)
UK	—	United Kingdom
US	—	United States of America
VIP	—	Västerbotten Intervention Project
WHO	—	World Health Organisation

GLOSSARY

bias   Deviation of results or inferences from the truth, or processes leading to such deviation. Any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth.

blinded study   A study in which observers and/or subjects are kept ignorant of the group to which they are assigned. When both observers and subjects are kept ignorant, the study is referred to as double blind.

case-control study   An epidemiological study involving the observation of *cases* (persons with the disease, such as oral cancer) and a suitable *control* (comparison, reference) group of persons without the disease. The relationship of an attribute or exposure, such as the use of tobacco products, to the disease is examined by comparing retrospectively the past history of the people in the two groups with regard to how frequently the attribute is present. See also *nested case control*.

case fatality rate   The proportion of cases of a specified condition which are fatal within a specified time.

case series   A descriptive study of a subset of a defined population, ie a single patient or group of patients, which aims to describe the association between factors or attributes which patients in the sample are exposed to, and the probability of occurrence of a given disease or other outcome. Case series are collections of individual case reports which may occur within a fairly short period of time.

chewing tobacco   Tobacco product placed in the gingivo-buccal area of the oral cavity, including loose-leaf (scrap), plug (press), twist (roll), and fine-cut tobacco.

cohort study   The analytic method of epidemiologic study in which subsets of a defined population can be identified in terms of who are, have been, or in the future may be exposed or not exposed to a factor or factors such as tobacco use, hypothesised to influence the probability of occurrence of a given disease or other outcome, such as myocardial infarction. Studies usually involve the observation of a large population and/or for a prolonged period, ie years.

confidence interval (CI)   The computed interval with a given probability, eg 95 per cent, that the true value of a variable such as a mean, proportion, or rate is contained within the interval. The 95 per cent CI is the range of values in which it is 95 per cent certain that the true value lies for the whole population.

confounder   A third variable that indirectly distorts the relationship between two other variables, because it is independently associated with each of the variables, eg cigarette smoking in relationships between snus use and cancer.

confounding   A situation in which the measure of the effect of an exposure on risk, such as snus use on risk for developing cancer, is distorted because of the association of exposure with other factor(s), such as cigarette smoking, that influence the outcome under study.

cotonine   A biomarker of nicotine exposure to verify tobacco use.

cross-sectional study   A study that examines the relationship between diseases or other health related characteristics and other variables of interest as they exist in a defined population at one particular time.

descriptive study   A study concerned with, and designed only to describe the existing distribution of variables, without regard to causal or other hypotheses.

dual use   In the context of this review, dual use refers to having a smokeless tobacco habit concurrently with a smoking habit, usually of cigarettes. Sometimes referred to as combined, concurrent, or mixed use.

evidence based   Based on valid empirical information.

generalisability   Applicability of the results beyond the study setting and the particular people studied to another group or population.

harm-reducing product   For this report, a product is harm reducing if it lowers tobacco-related mortality and morbidity, even though its use may involve exposure to tobacco and related toxicants.

hazard ratio (HR)   When time to the outcome of interest is known, this is the ratio of the hazards in the treatment and control groups where the hazard is the probability of having the outcome at time t, given that the outcome has not occurred up to time t.

incidence   The number of new events (cases, eg of disease) occurring during a certain period, in a specified population.

level of evidence   Study designs are often grouped into a hierarchy according to their validity, or the degree to which they are not susceptible to bias. The hierarchy indicates which studies should be given most weight in an evaluation.

matching   The process of making a study group and a comparison group comparable with respect to extraneous factors, eg controls could matched in age to cases by selecting those born in the same year.

mean   Calculated by adding all the individual values in the group and dividing by the number of values in the group.

median   The value that divides the probability distribution of a variable in half. For a finite population or sample the median is the middle value of an odd number of values, arranged in ascending order, or any value between the two middle values of an even number of values.

meta-analysis   The process of using statistical methods to combine the results of different studies. The systematic and organised evaluation of a problem, using information from a number of independent studies of the problem.

misclassification   The erroneous classification of an individual, a value, or an attribute into a category other than that to which it should be assigned.

morbidity   The number of people with a specified illness or injury that are diagnosed or reported during a defined period of time in a given population, especially in relation to the burden caused.

modified smokeless tobacco products   Non-combustible tobacco-containing products which have reduced toxicants, eg nitrosamines, compared with conventional tobacco products, and/or have been marketed as being less harmful alternatives to conventional tobacco alternatives.

MONICA study   A very large multinational study of cardiovascular diseases and their risk factors.

mortality   The number of deaths from a specified disease that are diagnosed or reported during a defined period of time in a given population.

multiple regression   An analysis of data that takes into account a number of variables simultaneously.

Nested case-control study   A case-control study in which cases and controls are drawn from the population in a cohort study. That is, the case-control study is 'nested' within the cohort study design so that the effects of some potential confounding variables are reduced or eliminated. A case-control study can also be nested into a cohort study. See also *case-control study*, *cohort* study, and *case-series* study.

odds ratio (OR)   A measure of the degree or strength of an association. In a case control or a cross-sectional study, it is measured as the ratio of the odds of exposure (or disease) among the cases to that among the controls.

oral leukoplakia   With respect to snus users, these are characteristic lesions in the mucosa corresponding to the site where a quid of snuff is regularly placed. Also described as snuff dipper's lesion, snuff-induced oral leukoplakia, and snus-induced lesion (SIL).

power   The ability of a study to demonstrate an association if one exists.

precision   Statistical precision indicating how close the estimate is to the true value. It is defined as the inverse of the variance of a measurement or estimate.

prevalence   The number of events in a given population at a designated time (point prevalence) or during a specified period (period prevalence).

P-**value**   The probability, obtained from a statistical test, that the null hypothesis, eg, that there is no treatment effect, is incorrectly rejected. That is, the probability of claiming that there is an effect when in fact there is no real effect.

quality of evidence   Degree to which bias has been prevented through the design and conduct of research from which evidence can be derived.

random sample   A sample that is arrived at by selecting sample units such that each possible unit has a fixed and determinate probability of selection.

randomised controlled trial   An epidemiologic experiment in which subjects in a population are randomly allocated into groups to receive or not receive an experimental preventive or therapeutic procedure, manoeuvre, or intervention. Randomised controlled trials are generally regarded as the most scientifically rigorous method of hypothesis testing available in epidemiology.

recall bias   Systematic bias due to differences in accuracy or completeness of recall or memory of past events or experiences, such as exposure to tobacco.

relative risk (RR)   The ratio of the risk of disease or death among those exposed to the risk compared to among the unexposed. It is a measure of the strength or degree of association applicable to cohort studies and randomised controlled trials.

relative risk reduction (RRR)   The proportional reduction in rates of undesirable events between experimental and control participants in a trial. If there was an increase in the rate of undesirable events, the term would then be relative risk increase.

reliability   The degree of stability that exists when a measurement is repeatedly made under different conditions or by different observers, and the thing being measured is assumed not to have changed.

risk factor   An exposure or aspect of personal behaviour or lifestyle which, on the basis of epidemiologic evidence, is associated with a health-related condition.

selection bias   Error due to systematic differences in characteristics between those who are selected for inclusion in a study and those who are not, or between those compared within a study and those who are not.

snus   A form of oral moist Swedish snuff, a prominent modified low-nitrosamine product.

snus-induced lesions (SILs)   Mucosal changes that are regularly seen in users of moist snuff (snus). Also referred to as snuff dipper's lesion or snuff-induced oral leukoplakia.

systematic review   Literature review reporting a systematic method to locate, appraise and synthesise a number of independent scientific studies to obtain a reliable overview.

tobacco-specific *N*-nitrosamines (TSNA)   Cancer-causing compounds found in smokeless tobacco and cigarette smoke. Includes potent carcinogens NNK and NNN.

variance A measure of the variation shown by a set of observations. Defined by the sum of the squares of deviation from the mean, divided by the number of degrees of freedom in the set of observations.

Chapter 1: Background

THE TOBACCO PROBLEM

Tobacco use is the prime environmental cause of death and disease, with smoked tobacco being the most prevalent and harmful tobacco product. Smoked tobacco causes a range of cancers, chronic obstructive pulmonary, cardiovascular, and oral diseases, and adverse pregnancy outcomes (Stratton et al. 2001). The global health consequences of smoking are shocking. Half of all regular smokers die as a consequence of their smoking (Britton 2003; Peto et al. 1996), accounting for nearly 5 million deaths worldwide in 2000 (Ezzati and Lopez 2003). Tobacco control initiatives have had measured success in deterring smoking. Policy interventions have included increasing taxes, restricting access, banning advertising, strengthening warning labels, undertaking litigation, promoting smokefree environments, and offering education and media campaigns aimed at encouraging smoking prevention and cessation (Anderson and Hughes 2000; Gilpin and Pierce 2002; Hatsukami et al. 2002; Shiffman et al. 2002). While the rate of smoking cigarettes has decreased markedly in the last 40 years, the decline appears to have levelled off in the last decade with annual decline in prevalence estimated to be less than 1 per cent in the US and UK (Stead et al. 2006). Consistent with these data, 28 per cent of New Zealanders aged 15 years or older smoked cigarettes in 1990, dropping to 25.5 per cent in 1999 and 23.5 per cent in 2005. The downward trend in smoking prevalence has been even less evident for Maori and Pacific people over this period (Ministry of Health 2006).

Quitting smoking is notoriously difficult. Tobacco contains nicotine which is both pleasurable and highly addictive. While 70 per cent of smokers report wanting to quit, only about a third of smokers attempt to quit each year and only 10 per cent of these are tobacco-free one year after quitting (Stratton et al. 2001). Smokers seem to have unrealistic expectations about quitting, at the same time overestimating the likelihood of stopping in the future and greatly underestimating how long it is likely to take (Jarvis et al. 2002). As many smokers will not or cannot quit, and as experimentation with tobacco remains common among adolescents, it has been argued that there will remain, at minimum, a resistant group of 10-15 per cent of adults who will continue to smoke despite effective prevention and cessation programmes (Stratton et al. 2001). Such resistant smokers include underprivileged and undereducated people, psychiatric patients, and highly nicotine-dependent smokers (Martinet et al. 2006). For inveterate smokers, some have advocated the development of 'harm reduction' products that attempt to reduce the harm associated with conventional tobacco use. In an extensive investigation of the topic, the Institute of Medicine's *Clearing the Smoke* report referred to such products as potential reduced-exposure products or PREPs (Stratton et al. 2001). Exposure to tobacco and nicotine use can be reduced to some extent through modifying the design, blending, and ingredients of tobacco products, and their production methods. New products are being developed to capture a niche market for smokers concerned for their health (Royal College of Physicians of London 2002) and, in the case of smokeless tobacco products, for smokers responding to smoking bans in their workplace or public spaces. Many of these products are being developed and test-marketed with explicit or implicit claims of harm reduction, and the implications of their introduction are being hotly debated in the tobacco control field.

TOBACCO HARM-REDUCTION PRODUCTS

There are many and varied approaches to tobacco harm reduction (THR). Broadly, these can be categorised into two groups: (I) non-tobacco interventions aimed at decreasing tobacco consumption, and (II) alternative tobacco products.

(I) Non-tobacco interventions aimed at decreasing tobacco consumption

Interventions aimed at decreasing consumption of tobacco products include:

i.   Non-tobacco agents. These include nicotine replacement therapies that offer 'medicinal nicotine' in gum, patches, nasal spray, inhaler/inhalator, and other forms. Other pharmaceutical agents including antidepressants such as bupropion, nortriptyline and clonidine have been used, and other non-nicotine agents under investigation include glucose, rimonabant, and selegiline (Foulds et al. 2006),

with varenicline recently gazetted as a prescription medicine for smoking cessation in New Zealand. *Smokey Mountain* is a tobacco-free and nicotine-free herbal product designed as a snuff substitute. While many of these pharmaceutical agents have been developed and are now standard practice for smoking cessation, they are not currently licensed for long-term use as alternatives to smoking (McNeill 2004).

ii.   Behavioural interventions. These include therapies and strategies designed to aid cessation or reduce intake of cigarettes. Several strategies associated with reduced smoking include increasing the interval between cigarettes, smoking less than half a cigarette, setting daily limits, reducing the number of cigarettes smoked, smoking on only certain days, and not inhaling deeply (Okuyemi et al. 2002). However, the benefits of reduced smoking are not clear-cut. For example, there is evidence of significant risks associated with smoking one to four cigarettes per day (Bjartveit and Tverdal 2005; Kendrick et al. 1995).

iii.   Chemoprevention. These are treatments to reduce the probability of manifesting a smoking related disease (Hatsukami et al. 2002), taken by continuing users or ex-users.

(II) Alternative tobacco products

The second group of approaches to tobacco harm reduction involves alternative tobacco products that are designed to reduce tobacco toxin exposure compared with conventional tobacco products. These include products, and others in the process of being developed, in the following categories:

i.   Modified cigarettes. Historically, the tobacco industry has promoted two product modifications to cigarettes in an attempt to allay fears of tobacco harm in consumers and to address decline in smoking rates (Warner and Warner 2002). These include the introduction of filter tips in the 1950s and lower tar and nicotine content products in the late 1960s and 1970s (Warner and Warner 2002). The marketing of such 'low-yield' products as 'light' and 'ultralight' has been perceived by smokers as claims that these products are less of a risk to their health and therefore have deterred them from quitting (Gilpin et al. 2002). However, yields, as measured by Federal Trade Commission/ISO smoking-machines, do not necessarily reflect smokers' tar and nicotine intake as they do not reflect smoking behaviour (Shields 2002). Most of the reduction is due to filter venting, ie holes in the paper surrounding the filter, which are not occluded by test machines, but often are by smokers. The holes mean that the puff taken by machines is diluted by air and thus has lower concentrations of the target chemicals. Smokers are able to regulate their intake of nicotine, through compensation, by smoking more cigarettes per day, inhaling more deeply, puffing more frequently, smoking further down the butt or occluding filter holes by fingers or mouth to reduce smoke dilution (Shields 2002; Stratton et al. 2001; Warner and Warner 2002). The result is that smokers end up taking in similar amounts of toxins regardless of the notional tar yield. There is a substantial increase in toxicants in the smoke of low-yield cigarettes and such products have not led to health risk reduction (Shields 2002). Moreover, there has been a trend toward increasing occurrence of adenocarcinomas of the lung attributed to increased smoking intensity with low-nicotine cigarettes. The history of 'light' cigarettes has been presented as a cautionary tale of unintended consequences in tobacco harm reduction initiatives (Shiffman et al. 2002; Warner and Warner 2002).

More recently, attempts to modify tobacco products to reduce harm have led to cigarettes that are cured, blended, processed, modified, or sprayed with chemicals to selectively reduce certain tobacco-specific carcinogens. The product *Omni* claims to reduce catechols and polyaromatic hydrocarbons, although it also introduces other toxins such as palladium. Other products, such as *Quest,* have been genetically engineered to offer little or no nicotine, while also offering low tobacco-specific nitrosamines. The concept is that smokers would reduce or eliminate their nicotine dependence and subsequently stop or reduce smoking. However, it has been suggested that smokers may compensate behaviourally to the removal of nicotine, as occurred with low yield cigarettes discussed above, thus increasing their tobacco exposure (Shiffman et al. 2002).

ii.   Cigarette-like tobacco products. These are 'high-tech', pseudo-cigarette devices that produce less burning compared with traditional cigarettes, eg *Premier, Eclipse*, *Accord,* and thus change the composition of the smoke that the user inhales, potentially reducing some toxicants. However, their toxicology is uncertain (Shiffman et al. 2002). Research into *Eclipse* has suggested that some toxicants, such as carbon monoxide, can be increased and new risks can be introduced, such as inhaling fibreglass

particles into the lungs (Stratton et al. 2001). There has been extremely low uptake of these products by consumers, and they have not been commercial successes (Chapman 2007).

iii. Conventional smokeless tobacco products. Traditional smokeless tobacco comes in many different forms, including *toombak* in Sudan, snuff in South Africa, *maras* powder in Turkey, homemade *iqmik* in Alaska. In Central, South and Southest Asia the various forms include *betel-nut quid, pan masala, shammah, alqat, nass, naswar, khaini, mishri, zarda, mawa, ghutka, bajjar, and gudakh* (Gupta et al. 1996). Products mix tobacco with other substances including slaked lime, areca nut, spices, catechu, menthol, ash, molasses, oils, and various colourings and perfumes (Gupta et al. 1996; International Agency for Research on Cancer 1985). In Western countries, traditional smokeless tobacco tends to be used in the form of chewing tobacco, ie plug, roll or twist, and snuff dipping, either moist with 40-60 per cent water content, or dry with less than 10 per cent water content. Smokeless tobacco is often used in subsets of the population, with prevalence being highest in the US in athletes, young white males, and in the South (Asplund 2003). In that country, the popularity of loose-leaf chewing tobacco has waned, declining by 35 per cent in 15 years, as has the use of dry snuff, declining almost 60 per cent over the same period. However at the same time the sale of oral moist snuff has increased by 77 per cent, after renewed and aggressive advertising (Ebbert et al. 2004; Rodu and Jansson 2004).

Traditional non-combusted products have not been developed as low-toxin alternatives to smoking. Indeed, several major reports released in the mid-1980s (International Agency for Research on Cancer 1985; US Department of Health and Human Services 1986; World Health Organisation 1988) emphasised the health risks of smokeless tobacco, with an emphasis on oral cancer. It appears well established that smokeless tobacco is a major risk factor for oral and pharyngeal cancer in Asia (Critchley and Unal 2003). Based on such concerns, many governments have banned the sale of oral snuff, including the EU in 1992.

iv. Modified smokeless tobacco products. In recent years, there has been attention given to the relatively less harmful health consequences of smokeless tobacco compared with combustible tobacco, given that smokeless products reduce the inhalation of products of tobacco pyrolysis. The Royal College of Physicians of London's report, *Protecting smokers, saving lives* (2002) concluded that, as a way of using nicotine, smokeless tobacco is 10-1,000 times less hazardous than smoking, depending on the product. Modified smokeless tobacco products are those which have reduced toxicants compared with conventional tobacco products (Shiffman et al. 2002) and/or which have been marketed to consumers as being less harmful alternatives to conventional combustible tobacco products. In particular, efforts have been made to reduce tobacco specific *N*-nitrosamines (TSNA) which have been suggested as leading sources of harm in smokeless tobacco and implicated in cancer as well as in cardiovascular disease and other conditions.

Considerable attention has been given to a form of oral moist Swedish snuff known locally as snus. This prominent modified low-nitrosamine product is manufactured for oral use from moist ground tobacco of Dark Kentucky or Virginia species mixed with an aqueous solution of water and blending ingredients to produce various brands (Idris et al. 1998). Since 1984, snus has been available as portion-packed pouches, like tea-bags, of moist snuff (World Health Organisation 1988). The most common way of using snus is by placing a 1-2 gram pinch of loose snuff or a 0.5-1 gram portion bag in the vestibule of the upper lip (Idris et al. 1998). In production, snus is heated in order to eradicate micro-organisms and lower nitrate and subsequent nitrosamine formation. Possibly due to this, snus has lower levels of toxins than most commonly used conventional tobacco products marketed in the United States (Hatsukami et al. 2004; Nilsson 1998; Ramstrom 2000). The Institute of Medicine's *Clearing the Smoke* report (Stratton et al. 2001) noted that 'Swedish snus (lower TSNA and nicotine levels than American brands) should be evaluated as a possible harm reduction product since two recent epidemiological studies have suggested that it does not increase the risk of oral cancer and has favourable cardiovascular outcomes' (p 301).

With the public more aware of health risks and prominent private lawsuits, the tobacco industry has incentives to create a safer product; making such a product is also likely to provide a significant market advantage over competitors (Fox and Cohen 2002). Notably, Swedish Match, the producer of almost all snus in Sweden, sold its cigarette business to an Austrian company in 2000; therefore increasing snus use at the expense of smoking would be to its commercial gain (Vainio and Weiderpass 2003). More recently, other modified smokeless tobacco products have been developed and test marketed in the US.

Revel and *Exalt* are 'spit-free' low-nitrosamine tobacco packets available for oral use in paper sachet form. *Ariva* and *Stonewall* are lozenges or tablets of compressed low-nitrosamine tobacco which are allowed to dissolve slowly in the mouth. These have been marketed as smokeless alternatives for situations where an adult smoker cannot or chooses not to smoke (Shiffman et al. 2002).

A panel of experienced tobacco epidemiologists estimated that compared with cigarette smoking, long-term use of low nitrosamine smokeless tobacco, such as snus or *Ariva*, could lead to relative risk reductions in total mortality in the range of 90-95 per cent (Levy et al. 2004). In addition to offering potentially reduced harm to individuals from lower toxicities, the absence of sidestream smoke from smokeless products also reduces health risks from environmental tobacco smoke (ETS) and fire risks (Bates et al, 2003).

The focus of this review is on the health effects of using modified smokeless tobacco products. As snus has been popular in Sweden for many decades it is one of the few modified smokeless tobacco products that have been evaluated through epidemiological studies at the population level and for which evidence relating to disease outcomes and mortality is available. More novel modified products such as *Ariva* are relatively new and there hasn't been sufficient time or extent of use to permit epidemiological studies evaluating longer-term health outcomes. Snus has also been the subject of vigorous and divisive debate in the public health field, and many issues relevant to the opportunities and threats of snus in harm reduction are common to existing and future potential reduced exposure products.

SNUS AS A POTENTIAL REDUCED-EXPOSURE PRODUCT

The 'Swedish experience'

Introduced in 1637, snus (Swedish for snuff) has been a traditional and well-established habit in Sweden. Following a large drop in snus consumption between 1920 and 1968, snus use has steadily increased from about 10 per cent of the male adult population in 1976 to about 23 per cent in 2002. This resurgence in use has been spurred by a determined effort by the industry to promote consumption, particularly among young people (Asplund 2001; World Health Organisation 1988). There has been a marked shift in the age distribution of users, from elderly poorly-educated men to educated, young and middle-aged men (Asplund 2001; Foulds et al. 2003). The country now has the highest per capita consumption of snuff in the world (Idris et al. 1998). Its use was restricted almost exclusively to males, but is becoming more popular with women whose use of snus increased by 137 per cent between 1996 and 2002 (Osterdahl et al. 2004). In 2005, 22 per cent of Swedish men used snus daily compared with 4 per cent of Swedish women[1]. Use is more prevalent in the northern counties of Sweden (World Health Organisation 1988). Prevalence data from this area in 2004 indicated that 27 per cent of adult men use snus exclusively, ie they do not smoke, while the prevalence for men aged 25-34 years is 34 per cent. Snus use in adult women in Northern Sweden has grown from 0.5 per cent in 1986 to 8.9 per cent in 2004 (Stegmayr et al. 2005).

As mentioned above, oral snuff including snus was banned throughout the European Union (EU) in 1992, but the Swedish Government intervened to obtain an exemption in Sweden upon entry to the EU in 1995 because of its widespread traditional use among men (McNeill et al. 2006)[2]. Despite 23 per cent of adult male Swedes using snus, Sweden boasts declining lung cancer and smoking-related mortality rates in males (Foulds et al. 2003). Rates of myocardial infarction have also declined for men at twice the rate of women aged 30-64 years (Rosen et al. 2000). Sweden has one of the lowest incidences of cancers of the lip and oral cavity in the Western world (Nilsson 2006b; Osterdahl et al. 2004), and is significantly lower than in countries where oral tobacco use is prevalent, such as the US, Sudan and India (Chapman 2007). The prevalence of oral cancer among snus users in Sweden is no higher than among non-tobacco users, in contrast to the US where rates of oral cancer are higher for smokeless tobacco users than non-tobacco users (Hatsukami et al. 2004). The lack of strong associations between snus use and squamous cell oral cavity and oesophageal cancers in two Swedish case-control studies (Lewin et al. 1998; Schildt et al. 1998) contributed to the EU's decision to remove the requirement for warning labels regarding oral cancer on snus in 2001 (Rodu and Jansson 2004). Oral moist snuff, including snus remains banned in all other EU member states, despite the continued

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1 Institute for Tobacco Studies and Research Group for Information and Societal Studies (ITS/FSI) 2005.

http://www.swedishmatch.com/Eng/TobaccoUseInSweden.asp accessed December 18 2006.

2 To date, various legal challenges to this ban by snus manufacturer Swedish Match have been unsuccessful.

availability of chewing tobacco and nasal snuff, including highly toxic forms from South Asia (Bates et al. 2003; Sweanor 2003).

While snus use by men has demonstrated a steady increase since the 1970s, smoking rates have decreased. The extent of this decrease is gender-related. Between 1976 and 2000, the prevalence of daily smoking has decreased by 25 percentage points in Swedish males and by 13 percentage points in Swedish females aged 18-70 (Ramstrom 2003). This has led to a reversal of the gender effect usually noted for smoking and in Sweden, more women now smoke (19 per cent) than men (14 per cent) (Rosenquist et al. 2005). In Northern Sweden, where snus use is most prevalent, only 9 per cent of adult men smoke and only 2 per cent of those aged 25-34 years (Stegmayr et al. 2005).

From such ecological data, it has been argued that the popularity of snus in Sweden has contributed to unusually low rates of smoking among Swedish men compared with other European countries (Foulds et al. 2003). That is, that tobacco users substitute snus for cigarettes, either by initially taking up snus instead of smoking, or using snus after quitting, or reducing, smoking, arguably as a cessation tool. The co-occurrence of high snus use, low smoking rates, and relatively low tobacco-related harm has been presented as a real world uncontrolled experiment in tobacco harm reduction (Sweanor 2003) and is sometimes referred to as the 'Swedish experience'. Sweden's use of snus has also been described as an example of widespread use a non-medical form of nicotine replacement therapy (NRT) (Furberg et al. 2005). However, its role in harm reduction in Sweden, and as an example of a potential harm reduction product in other countries, remains highly contentious. Key concerns relate to the interplay between snus use and smoking.

Snus and smoking cessation/reduction

The relationship between snus use and smoking cessation is extremely complex and the role of snus use in Sweden's low smoking rates remains controversial (Henningfield and Fagerstrom 2001). There have been many recent reports from Sweden and the US (where moist oral snuff is experiencing a resurgence in popularity) exploring the extent to which snuff leads to smoking cessation or reduction, with varying conclusions (Foulds et al. 2003; Furberg et al. 2005; Furberg et al. 2006; Gilljam et al. 2003; Lindstrom and Isacsson 2002; Rodu et al. 2002; Rodu et al. 2003; Tomar 2003a). While it is beyond the scope of this review to consider these studies in depth, some key issues will be outlined.

A common argument used to demonstrate the impact of snus on smoking rates is that smoking has reduced more dramatically for men than women, and men use snus to a much higher degree than women (Foulds et al. 2003). Countering this view is the observation that smoking in Sweden has also decreased significantly among females without snus use. Indeed, prevalence of female smoking is much lower in Sweden than in neighbouring countries of Norway (32 per cent) and Denmark (29 per cent) (Fagerstrom and Schildt 2003; Henningfield et al. 2003). It has been countered that the reduction in smoking prevalence in men, facilitated by the use of snus, has assisted in 'denormalising' the culture of smoking and led to a concomitant reduction of smoking in women (Bates et al. 2003). It has also been suggested that other factors, such as Sweden's tobacco control efforts, have played a role in lowering smoking rates, These have included information about health risks of smoking, increased taxation on tobacco products, restrictions on their marketing, and increased treatment availability (Tomar et al. 2003; Vainio and Weiderpass 2003). Non-prescription nicotine gum was available in Sweden in the 1980s, earlier than in most countries, and the level of medicinal nicotine use in Sweden, though still low, greatly exceeds other nations (Henningfield and Fagerstrom 2001).

In Sweden, half of middle-aged men are ex-smokers (Asplund 2003; Huhtasaari et al. 1999). Recent Swedish research suggests that a minority of men (26-29 per cent) have used snus as a quitting method (Gilljam et al. 2003; Ramstrom and Foulds 2006). Nevertheless, this extent of snus use in quitting could be considered impressive given that snus has not been promoted as a cessation tool by the manufacturers, health providers or the public health community. Moreover, some suggest that people who use snus have been more successful in quitting smoking (66 per cent) than those who have used other aids, such as nicotine gum (47 per cent) or the nicotine patch (32 per cent) (Ramstrom and Foulds 2006). In a retrospective Swedish survey, Gilljam and Galanti (2003) found that the use of snus at the latest quit attempt increased the probability of being abstinent from cigarettes by about 50 per cent. It has also been argued that snus has been just as helpful to highly dependent smokers as less dependent smokers (Fagerstrom and Schildt 2003), and may have an advantage for such smokers over medicinal nicotine (Fagerstrom and Ramstrom 1998). Advantages include that snus can offer nicotine more

efficiently and at higher levels than most available nicotine patches and gum (Benowitz et al. 1988). Snus may also be attractive to inveterate smokers who consider their tobacco use a recreational habit that they wish to maintain, in a more benign form, rather than a problem to be medically treated.

While some have balked at the notion that snus be seriously investigated as a cessation tool (Jorenby et al. 1998), in recent years there has been some interest in conducting randomised, controlled trials to explicitly test the efficacy of snus use as a smoking cessation or reduction aid, and to compare it with other therapies (Furberg et al. 2006; Hatsukami et al. 2004; Ramstrom and Foulds 2006). One pilot study has been performed (Tilashalski et al. 1998), although it suffered methodological flaws including a small sample size, a protracted recruitment period that suggested snus may have not been an acceptable alternative to some smokers, lack of a control group, and lack of randomisation (Fagerstrom and Ramstrom 1998; Jorenby et al. 1998).

Snus and nicotine dependence

Snus contains nicotine and is therefore still dependence forming, which contributes to difficulty in quitting. It also has the potential to sustain a dependence on tobacco, including more dangerous forms. Smokeless tobacco produces dependence and withdrawal symptoms following cessation, with high relapse rates (Foulds et al. 2003). However, while the blood levels of nicotine are quite similar to those reached by cigarette smokers, the speeds of absorption differ. The overall nicotine level in the blood reaches its peak three to four times more rapidly during smoking than during use of oral moist snuff (Ramstrom 2000). In addition to the more gradual absorption of nicotine from smokeless tobacco, peak concentrations of nicotine are sustained over a longer period (Savitz et al. 2006). This may expose users to a greater amount of nicotine overall (see Stratton et al, 2001). It has been suggested that it is this addictive nicotine content which makes snus a viable substitute for cigarettes. For some smokers, it is also a potentially more acceptable alternative than some forms of medicinal nicotine which provide nicotine at lower levels than snus (Bates et al. 2003; Foulds et al. 2003).

Reviewing research in this area, Hatsukami et al (2004) concluded that smokeless tobacco appears to have slightly lower abuse liability, with possibly lower severity of addiction or dependence compared with smoking and greater ease of cessation. However, it has a higher abuse potential than medicinal nicotine. They also concluded that it may be possible that switching from cigarettes to smokeless tobacco would increase the potential for cessation from all tobacco products. Nevertheless, continued snus use appears to be more common than cessation (Furberg et al. 2006), which may relate more to a lack of motivation to quit using a product perceived to be safer than smoking.

Snus and smoking initiation – the 'gateway' issue

An issue related to the possible role of snus in smoking cessation is whether snus use leads to smoking initiation. Specifically, there have been fears that modified low-nitrosamine products such as snus may have particular appeal to teenagers and act as 'gateways to smoking', in contrast to being gateways from smoking, and (Benowitz 1999; Shiffman et al. 2002). There have been conflicting results and conclusions about the extent to which snus use precedes, and causes, smoking. In recent years, there has been a flood of data from US and Swedish studies which have offered conflicting conclusions. Some data appear to suggest that snus is a significant gateway to smoking (Haddock et al. 2001; Tomar 2003a) while other data appear to demonstrate that most snus use is not (Furberg et al. 2005; Kozlowski et al. 2003a; O'Connor et al. 2003; O'Connor et al. 2005; Ramstrom and Foulds 2006; Rodu et al. 2005). Interpretations of findings have been hotly debated and data re-analysed, with attempts made to take into account confounding factors of smoking initiation (Bates et al. 2003; Foulds et al. 2003; Henningfield et al. 2002; Kozlowski et al. 2004; O'Connor et al. 2003; Tomar 2003b; Tomar et al. 2003; Tomar and Loree 2004).

From largely cross-sectional and follow-up data, researchers have erroneously drawn causal inferences from individual transitions between snus use and smoking. However, in the absence of randomised controlled trials, what cannot be proven is what smokeless tobacco users would have done in the absence of snus; that is, whether they would have moved on to smoking or not (Bates et al. 2003). Other reasons for observed associations have been suggested, such as linked experimentation and risk taking (Foulds et al. 2003; O'Connor et al. 2005), given that smoking and smokeless tobacco use share many risk factors (Kozlowski et al. 2004).

The gateway issue and the potential net public health impact of snus use is discussed in greater depth in the Discussion chapter.

The toxicity profile of snus

In considering the harm of smokeless tobacco products, the recent focus has been on the potent carcinogens, tobacco-specific *N*-nitrosamines (TSNA) such as NNN, NNK, NAT, and NAB (see Glossary). These form by the nitrosation of nicotine and other tobacco alkaloids. Of greatest interest are NNN and NNK, which are thought to be important carcinogens in humans based on animal studies and strong mechanistic evidence in exposed humans (International Agency for Research on Cancer 1985)[3]. A recent analysis of a wide range of traditional and modified smokeless tobacco products found that TSNA levels varied 130-fold (McNeill et al. 2006).

Assessments of TSNA have tended to focus on moist snuff available in Sweden and the US and suggest that moist snuff of Swedish origin has consistently had significantly lower levels of TSNA than moist snuff sold in the US. In Sweden, TSNA levels in moist snuff have decreased 85 per cent since the 1980s; a survey of Swedish snus in 2002 indicated a mean level of the total TSNA content of 1.0 microg/g (*n* = 27 samples) (Osterdahl et al. 2004). Large reductions in TSNA have also been observed for some brands of moist snuff sold in the US, with levels approaching those for Swedish snuff (Stratton et al. 2001). However, the decrease in toxicity of US snuff has not been universal. In recent tests, some US snuff samples still exhibited relatively high concentrations of TSNA (Brunnemann et al. 2002; Osterdahl et al. 2004; Rodu and Jansson 2004). A study by Hoffman et al (1995) showed TSNA levels were not consistent within US brands when purchased at the same time. The lower TSNA yields of Swedish snus compared with US moist snuff appear to translate to reduced carcinogen uptake in the bloodstream. A recent small human trial demonstrated that total urinary levels of NNAL (metabolites of NNK) were reduced by almost 50 per cent when users of high nitrosamine products ie US smokeless tobacco, switched to low nitrosamine products, ie snus for a four-week period (Hatsukami et al. 2004).

The lower nitrosamine profile of Swedish snus compared to traditional American moist snuff may relate to differences in manufacturing and storage. TSNA is formed from tobacco alkaloids during the curing, fermentation and aging of tobacco leaves (Hatsukami et al. 2004). Lower TSNA levels in Sweden may have been achieved through improving the quality of the raw tobacco used, but manufacturing procedures are also likely to have contributed. Swedish Match, the manufacturer of more than 99 per cent of all snus in Sweden (Österdahl et al, 2004), switched to a strictly non-fermentation method in 1981 (Ramstrom 2000). Since around 1982-83, mainly air-cured and some sun-cured ground tobacco (Foulds et al. 2003) is subjected to a heat treatment process that renders the product practically free of microorganisms and lowers the risk of formation of nitrates and TSNA (Ramstrom 2000; Rosenquist et al. 2005). It is claimed that snuff is virtually free of bacteria, and as a sterile product is therefore unlikely to change during storage. The Swedish practice of refrigerating snuff at the outlet until sale also is said to help maintain lower levels of TSNA over time (Ramstrom 2000). The Swedish production methods compare to the American procedure where there is a microbiological fermentation of mainly fire-cured tobacco. Fire-curing is associated with the development of carcinogenic polycyclic aromatic hydrocarbons such as benzopyrene (Savitz et al. 2006). Fermentation permits continued formation of TSNA, especially if the finished product is then stored unrefrigerated for an appreciable time (Ramstrom 2000). Variation in storage practices and periods may contribute to the lack of consistency in TSNA levels that have been observed within US brands (Hoffmann et al. 1995).

It is unclear precisely why Swedish snus appears to have lower TSNA levels than snuff sold in the US. However, Swedish Match's use of a voluntary GothiaTek standard establishes maximum permissible limits for 'undesirable substances', setting the total TSNA limit at 10 ppm (dry weight). Other limits apply to toxicants including nitrates, benzpyrene, cadmium, lead, arsenic, nickel and chromium (Rodu and Jansson 2004). It is not clear whether all Swedish Match products produced in Sweden and abroad adhere to the GothiaTek standard (Foulds et al. 2003).

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3 NAB is a weak carcinogen whereas NAT was inactive in one rat study (see Österdahl et al, 2004).

Adverse health effects

As mentioned above, smokeless tobacco contains nicotine, which contributes to tobacco addiction and helps sustain tobacco use. There are other associated adverse health consequences of nicotine intake. It can increase the heart rate, blood pressure, cardiac stroke volume and output, and coronary blood flow (World Health Organisation, 1988). It has also been suggested that nicotine may play a role in decreasing fetal growth through increasing vaso-constriction and decreasing perfusion through the placenta (Verma et al. 1983). A preventive or treatment role of nicotine has also been proposed for ulcerative colitis, Alzheimer's disease, Tourette's syndrome, and some mental health disorders (Benowitz 1999). Nicotine is unlikely to be a cancer-causing agent in humans (Stratton et al. 2001), however the risks of long-term nicotine supplementation are unknown (Chapman 2007).

From clinical and histological data, habitual users of snus commonly develop characteristic lesions in the mucosa that take the form of local tissue reactions with thickening or whitening. These correspond to the site where a quid of snuff is regularly placed (Axell 1993). The change has been variously described as snuff dipper's lesion, snuff-induced oral leukoplakia, and snus-induced lesion (SIL). A selective dose-response relationship has been observed. In one study, the daily amount of snuff used and hours of daily use seem to have a greater impact on the risk for developing changes of a higher clinical degree than the number of years of the habit or age of the snus user (Axell 1993). However, oral mucosal changes appear to be reversible following cessation of the snus habit (Larsson et al. 1991). In a study of Swedish adolescents, the use of snus was strongly associated with gingival recessions, but not with other forms of periodontal disease including gingivitis and clinical attachment loss (Monten et al. 2006). The use of portion-bags seems to be associated with less pronounced oral mucosal changes and less prevalent gingival recessions than the use of loose moist snuff (Andersson et al. 1990; Axell 1993).

Some snus-induced lesions exhibit histological features similar to dysplasia, a condition that precedes and often indicates a developing carcinoma. However, the true nature of these changes is uncertain and some researchers consider them to be reactions to local irritation (Axell 1993; Roosaar et al. 2006). The probability that snus-induced characteristic lesions will develop into carcinomas appears to be small (Ramstrom 2000; Roosaar et al. 2006). Supporting this, the incidence of oral cancer among Swedish men and women who take snuff is relatively low compared with snuff users elsewhere (Osterdahl et al. 2004).

Snus use internationally

As well as being sold in Sweden, Swedish snus is also sold in Norway, which is not a member of the EU. While only 5 per cent of Norwegian adults use snus daily (Chapman 2007), 18 per cent of men aged 16-24 years are occasional users (Vainio and Weiderpass 2003). Snus use is relatively low in countries such as Denmark and Finland since the EU ban was applied in 1992 (Asplund 2003). However, snus can easily be purchased 'under the counter' in Finland, or can be imported from tax-free sales on the ferries (Vainio and Weiderpass 2003). Estimates suggest that, despite the ban, 5 per cent of male adolescent boys use oral snuff daily in Finland (Haukkala et al. 2006). Most recently, Swedish Match has attempted launches of snus into India after developing a cardamom flavoured snus for that market, and Russia.

Snus has been marketed strongly and is gaining popularity in the United States, where forms of smokeless tobacco have a long history of traditional use. Swedish Match's product *Exalt* is available in the US, although locally available forms may differ from products of Swedish origin (Tomar et al. 2003). Other major cigarette companies have been moving into the snus market. British American Tobacco (BAT) has test-marketed its version of *Lucky Strike* snus in South Africa (Gray 2005). In 2006, Philip Morris test-marketed *Taboka*, a form of pasteurised low-nitrosamine tobacco pouches manufactured in the US, in Indianapolis. In the same year, RJ Reynolds Co began test-marketing *Camel snus*, which is named after Swedish snus, in Austin, Texas and Portland, Oregon. *Camel snus* is a smokeless, spitless pouch product manufactured in Sweden[4]. It is not clear to what degree these products vary from Swedish snus although, like snus, production does not involve fermentation.

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4 http://www.tobaccoretailer.com/uploads/Features/2006/0610_snuff_smokeless.asp, accessed on 27 November 2006.

Apart from the EU (excluding Sweden), smokeless tobacco products including oral moist snuff are banned in New Zealand, Australia, Hong Kong, Japan, Switzerland and Israel (Chapman 2007). New Zealand was one of the first countries to ban smokeless tobacco, in January 1987 (Regulation 46A, Toxic Substances Regulations, amended December 1986)[5].

Focus on Swedish snus

Despite growing markets for snus outside of Scandinavia, studies of snus have tended to take place in Sweden and these have several advantages over studies of smokeless tobacco use that have been performed in the US. First, Swedish-origin snus has consistently lower TSNA levels than those tested in US-sourced samples of smokeless tobacco. Although the precise reasons for this remain unclear, it is possibly due to differences in production and storage practices in the two countries (Osterdahl et al. 2004),. Second, the low toxicity profile is supported by the application of the GothiaTek standard by Swedish Match, although it is not known whether it is adhered to for all of its products (Foulds et al. 2003). Third, snus is virtually the only form of smokeless tobacco used in Sweden (Nilsson 1998; Rodu and Jansson 2004), and therefore studies measuring smokeless tobacco use can more readily attribute effects to use of snus. In the US by comparison, several forms of smokeless tobacco are used including traditional forms of chewing tobacco and many brand varieties of moist and dry snuff with widely ranging TSNA levels. As US-based studies do not permit analysis of outcomes as a function of brand or often, even type of smokeless tobacco, isolating results for low-nitrosamine forms, including the sale of Swedish snus, is not possible.

An advantage of considering Swedish research is that the country has excellent population-based statistical information available facilitating effective sampling and collection of disease incidence and mortality data (Critchley and Unal 2003). As cancers of the oral cavity and pharynx are relatively rare tumours, the large proportion of male Swedes using snus also increases the power of detecting any snus-related oral cancer risk in Sweden compared to others (Nilsson 1998). Finally, it is useful to examine epidemiologically the evidence of health effects of snus in a country where ecological claims based on the 'Swedish experience' have been used to promote snus as a harm-reduction tool.

It should be noted that, while this review focuses on snus, many of the broader issues discussed here relate to PREPs more generally.

REVIEW OBJECTIVES

To systematically identify and appraise international epidemiological evidence relating to the major health effects, for reduced harm, of using modified smokeless tobacco products compared with conventional combustible tobacco products; the safety of using modified smokeless tobacco products compared with not using any form of tobacco is also considered.

STRUCTURE OF REPORT

This report is divided into sections. Following this Background chapter, Chapter 2 presents the Review Methodology and includes the search strategy, inclusion and exclusion criteria, outcomes considered, appraisal methodology, and review limitations. In Chapter 3 are the Results, beginning with appraisal of relevant systematic reviews (secondary research), and then primary research grouped according to major health outcomes. Results are summarised in the text as well as in detailed Evidence Tables. which present the key characteristics of each included study and reviewer's comments on the study's strengths and limitations. Chapter 4, the Discussion section, includes a summary and discussion of the review results, considers methodological limitations of the field and gaps in research and summarises key issues relating to the applicability of results beyond Sweden and the impact of reduce harm products on the wider population. Finally, key Conclusions of the review are presented.

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5 The current legislation which prohibits the sale and distribution of oral tobacco, is set out in sections 29 and 2 of the Smoke-free Environments Act 1990.

The product can be imported for personal use (John Stribling, New Zealand Ministry of Health, *personal correspondence*, 14 November 2006).

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Chapter 2: Review methodology

SELECTION CRITERIA

Study inclusion criteria

Publication type

Studies published in the English language, including primary (original) research published as full original reports and secondary research (systematic reviews and meta-analyses) appearing in the published literature.

Exposure/s of interest

Smokeless tobacco products that have been modified to reduce toxicants , eg tobacco-specific nitrosamines, compared with conventional tobacco products (smokeless and combustible), and/or which have been marketed to consumers as being less harmful alternatives to conventional tobacco products. By modified, we mean that the product, through its content, manufacture (curing, processing, packaging), storage, or other means, intentional or not, has reduced toxicants compared with conventional tobacco products. It was beyond the scope of the review to investigate the relationship between specific toxicants and health outcomes. Impact of use of products as a whole rather than aspects of their modified characteristics on health outcomes in eligible studies was assessed.

Specific eligible products considered in the search strategy included the following:

- low-nitrosamine moist oral Swedish snuff (known as snus) (eg *General*, *Exalt*),
- low-nitrosamine tobacco in paper sachets (eg *Revel)*, and
- low-nitrosamine compressed tobacco lozenges (hard pellets or 'cigaletts') (eg *Ariva, Stonewall*).

Comparators

- users of conventional combustible tobacco products (ie cigarettes)
- non tobacco users

Study design

Eligible study designs were limited to those that provide at least level III-3 level of evidence according to the National Health and Medical Research Council's (2005) revised interim hierarchy of evidence for aetiological studies (see **Table 1** below). This represents analytical epidemiological studies including prospective cohort studies, retrospective cohort studies and case-control studies. Nested case-control studies were also considered and designated as Level III-3.

Table 1   Designations of levels of evidence for aetiological studies

Level of evidence	Study design
I	A systematic review of level II studies
II	A prospective cohort study
III-1	All or none. All or none of the people with the exposure/risk factor experience the outcome.
III-2	A retrospective cohort study
III-3	A case-control study
IV	Cross-sectional study

(National Health and Medical Research Council, Australia 2005)

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Systematic reviews and meta-analyses with an explicit search strategy and selection criteria were also eligible for appraisal where they identified at least one study that met the current review's selection criteria. This criterion was employed to exclude outdated reviews of poorer quality evidence or reviews reporting on studies considering ineligible exposures (eg conventional smokeless tobacco).

Sample size

Studies with samples of at least 100 people

Management of confounders

Studies that controlled for critical confounders including age, sex, and use of other tobacco products, eg through matched controls or in multivariate analyses).

Outcomes

Studies that included measures of, and analyses for, at least one of the following morbidity and mortality outcomes:

- All-cause mortality

- incidence and mortality outcomes from illnesses and conditions related to tobacco products (Stratton et al. 2001). These include the following:
  - oropharyngeal cancer, arising in the oral cavity, tongue, pharynx, and larynx;
  - other cancers , eg gastric, pancreatic, malignant lymphomas;
  - cardiovascular disease, including coronary heart disease and extracardiac vascular disease;
  - non neoplastic respiratory diseases, including chronic obstructive pulmonary disease, asthma, respiratory infections;
  - reproductive and developmental effects, ie pregnancy outcomes;
  - other clinically diagnosed health conditions or diseases, including peptic ulcer disease, wound healing, inflammatory bowel disease, rheumatoid arthritis, oral disease, dementia, osteoporosis, ocular disease, diabetes, dermatological disease, schizophrenia, and depression.

Note that the review did not systematically consider the impact of eligible modified smokeless tobacco products on initiation or cessation of smoking. However, data on the potential impact of eligible products on initiation of smoking or intention to quit using tobacco was included in evidence tables where reported alongside relevant health outcomes in eligible studies. Furthermore, issues relating to the possible impact of modified smokeless tobacco products on smoking rates are discussed in the Introduction and Discussion chapters.

Study exclusion criteria

Research papers were excluded if they:

- were narrative reviews;
- were 'correspondence', conference proceedings, abstracts;
- were not published in the English language;
- had samples of fewer than 100 participants;
- were pre-clinical research studies including animal studies or *in vitro* testing;
- evaluated the following tobacco products as the exposure: cigars, pipes, products used in conjunction with medicinal nicotine, products used for short-term smoking cessation therapy, and unmodified (to reduce toxicants), conventional smokeless tobacco;
- reported on intermediate outcomes, such as blood pressure, heart rate, lipid levels, weight gain, oral (non-cancerous) snus-induced lesions or dysplasia;
- reported on relatively minor or temporary health outcomes;
- did not state the form of smokeless tobacco considered in analyses or provide separate analyses for eligible forms of modified smokeless tobacco;
- did not clearly describe their methods and results, or had significant discrepancies.

SEARCH STRATEGY

A systematic method of literature searching and selection was employed in the preparation of this review. The search was not restricted by language or publication date.

Principal sources of information

The following databases were searched using the full search strategy outlined in **Appendix 1**:

Bibliographic databases
- Cinahl
- CochraneCentral Register of Controlled Trials
- Current Contents
- Embase
- Medline
- PsychInfo
- PubMed (last 60 days)
- Science Citation Index
- Social Science Citation Index

Review databases
- ACP Journal Club
- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effects (DARE)
- NHS Economic Evaluation Database
- Health Technology Assessment Database

Websites and other sources
- Minnesota Transdisciplinary Tobacco Use Research Center http://www.ttur.umn.edu
- World Health Organization (WHO) publications http://www.who.int
- US National Cancer Institute – Tobacco Control Research http://cancercontrol.cancer.gov
- Other website sources located in the course of the extended search including commercial sites providing product and marketing information;
- Documents supplied by the New Zealand Ministry of Health as background material to the topic;
- Hand searching of journals was not done, although tables of contents for special issues on the topic area, including *Nicotine and Tobacco Research* 2002, 4(Suppl 2), were scanned to identify papers of interest.

Extensive retrieval of background material also was conducted including narrative reviews, commentaries, editorials and correspondence. Reference lists of retrieved papers were carefully scanned and cross-checked to identify additional articles that were potentially eligible for appraisal and inclusion in the review. The author joined Globalink, the listserver of the international tobacco control community, which provided regular communications concerning recent publications, news and a listserv discussion group relating to harm reduction. Manufacturers and researchers were not contacted to obtain unpublished research.[6]

The search was completed on 21 June 2006 and updated on 17 October 2006 and again on 13 November 2006. Publications identified from Globalink updates were considered between September 12 and November 30 2006 inclusive.

In addition, an initial 'scoping search' was conducted in May 2006 considering smokeless tobacco generally. This identified 422 articles, many of which were retrieved as background material for the review and assisted in the development of the review protocol.

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6 Several researchers were contacted with specific queries relating to their work, as noted where applicable in the report.

Search terms used

A comprehensive literature search was undertaken for references that referred to snus or smokeless tobacco linked with terms that indicate Scandinavian origin, *or* low nitrosamine, *or* modified tobacco or moist snuff.

- MeSH terms: tobacco- smokeless, Scandinavia, nitrosamines, Sweden, Norway, Finland, Iceland, Denmark;
- Additional keywords (not standard index terms) were used in all databases: snus, low nitrosamine$, (modified adj3 tobacco), revel, exalt, ariva, stonewall, (lozenge and tobacco), (snuff and moist), Swedish, Norwegian, Finnish, Icelandic, Danish;
- The above index terms were used as keywords in databases where they were not available and in those databases without controlled vocabulary.

STUDY SELECTION

Studies were selected for appraisal using a two-stage process. Initially, the titles and abstracts where available identified from the search strategy were scanned and excluded as appropriate. The full-text articles were retrieved for the remaining studies and these were appraised if they fulfilled the study selection criteria outlined above.

There were 217 references identified by the bibliographic search strategy. Seventy-one full-text articles were obtained after excluding studies from the search titles and abstracts. Fifty-three of these 71 articles did not fulfil inclusion criteria and were excluded. These excluded papers are listed in **Appendix 2**, appended by reason for exclusion. Eighteen articles were eligible for inclusion, listed in **Appendix 3**, and were fully critically appraised (see **Chapter 3**). In addition to retrieval processes for identifying eligible studies for the systematic review, extensive retrieval of, approximately 150 articles, was undertaken to identify background information used in writing the report. These publications were identified in the initial scoping search, the official search strategy, internet searching, reference checking, contact with experts in the course of the review, and the Globalink listserv. Cited publications are presented in the **References**.

APPRAISAL OF STUDIES

The evaluation initially ranked studies in terms of study design quality according to the National Health and Medical Research Council's interim levels of evidence criteria for aetiological studies (2005), which are currently being piloted (see **Table 1** above). These evidence levels are only a broad indicator of the quality of the research, as the levels describe groups of research which are broadly associated with particular methodological limitations. However, these levels are only a general guide to quality because each study may be designed and/or conducted with particular strengths and weaknesses.

Appraisal of secondary studies

Only systematic reviews reporting on data from at least one study relevant to a particular eligible outcome were included. These reviews, while being appraised and included in Evidence Tables, were considered principally as background. Systematic reviews were described and critiqued in terms of whether the review asked a focused question, if the eligibility criteria for included studies were explicit, what search strategy were used, how the validity of included studies was assessed, and whether results of included studies were similar. A summary of these criteria is presented in **Table 2**.

Table 2.   Validity criteria for appraisal of secondary studies

Is there a focused research question?
ie PICO elements: patient, intervention of interest, outcomes, causation?
Were appropriate inclusion and exclusion criteria for selected studies stated?
Is there an explicit and comprehensive search strategy?
Is it unlikely that important articles (bibliographic databases, reference lists, contact experts) were missed?
Are the included trials appraised for validity?
Were assessments of studies reproducible?
Were results similar from study to study?
What were the overall results of the review?

Adapted from Evidence Based Medicine Toolkit, University of Alberta (http://www.med.ualberta.ca/ebm/ebm.htm) accessed May 23 2006.

Summaries of appraisal results for systematic reviews are presented in tabular form in **Evidence Tables** and include:

- source (authors, publication date);
- review aims;
- source of funding (noting whether financial support from tobacco industry was received);
- search strategy (including time period, search sources, key search terms);
- selection criteria for review;
- results, emphasising those papers eligible for the current review;
- reported conclusions from the authors;
- comments on the review's quality and relevance to the current review.

Appraisal of primary studies

A quality checklist developed by Critchley and Unal for their systematic review of smokeless tobacco (2003) was adapted and simplified, with permission, for use in this review (Dr Julia Critchley, personal correspondence, 11 August 2006). The revised checklist is presented in Appendix 4. Key aspects of internal validity (West et al. 2002) considered include:

- sample size;
- study base and case ascertainment;
- demographic characteristics of cases and controls, and their comparability;
- definition and measurement of exposure, frequency and extent of use, whether validated, recall biases;
- definition and measurement of outcome, and whether variation between cases and controls;
- controlling or adjustment for potential confounders, eg age, sex, other tobacco use, socio-economic status, and other risk factors associated with the outcomes of interest such as alcohol consumption, diet, body mass index, physical exercise, etc;
- statistical analyses and investigation of dose-response relationships, including indices of precision and statistical significance;
- and source of funding.

Primary studies were grouped relevant to specified health outcome groups and, as for systematic reviews, summaries of appraisal results presented in **Evidence Tables**. These included:

- reference, ie authors, publication date;
- country where study was principally conducted;
- study aims;
- funding source;
- study design, eg prospective cohort, case-control, and evidence level, applying NHMRC criteria (2005);
- study base and sample details for exposure for smokeless tobacco users and comparator groups of non-tobacco users and smokers;
- inclusion and exclusion criteria;
- observation time, ie dates, mean length of time;
- description of exposure and comparator definitions including minimum amount of tobacco used and regularity of use, and, any efforts to validate exposure;
- eligible outcome measures used, definitions, and follow-up interval/s;

- potential confounders, and whether adjusted for/controlled in analyses;
- results of analyses comparing exposure and comparator groups on eligible outcomes, eg OR, RR, rates, survival analyses including survival curves, log-rank test, hazard ratios;
- investigation of dose-response relationships;
- authors' conclusions;
- reviewer's comments relating to study quality;
- whether funding included support from industry, that is, companies with a commercial interest in tobacco products.

Strength of evidence

Studies were narratively synthesised to determine the strength of evidence supporting exposure to modified smokeless tobacco being a risk factor *for each* health outcome of interest. Strength of evidence is determined by three domains (West et al. 2002):

- **quality** (of the individual studies predicated on the extent to which bias was minimised);
- **quantity** (magnitude of effect, numbers of studies, and sample size or power); and
- **consistency** (the extent to which similar findings are reported using similar and different study designs).

The generalisability of the evidence beyond the study settings, and to countries such as New Zealand, is considered in the Discussion.

LIMITATIONS OF THE REVIEW

This study has used a structured approach to review the literature included for appraisal. However, there were some inherent limitations with this approach. Namely, systematic reviews are limited by the quality of the studies included in the review as well as the review's methodology.

This review has been limited by the restriction to English language studies in study selection and appraisal. Restriction by language may result in study bias. However, language restrictions were not applied on the search and abstracts were commonly presented in English. From these it was apparent that no study appeared to be eligible for inclusion that was not available in the English language, although abstracts were not always available to ascertain this. One systematic review written in Norwegian[7] was opportunistically identified from a poster presentation at the Adelaide HTAi Conference in July 2006. The report was prepared by the Norwegian Knowledge Centre for Health Services and the author, Ida-Kristen Elvsaas, was contacted. A brief English summary was obtained but details in English were insufficient to permit full appraisal. However, a list of included papers was scanned to identify studies that may have been eligible for inclusion in the current review.

In addition, the review was limited to the published academic literature and has not appraised unpublished work. Restriction to the published literature may lead to publication bias such that small-sampled studies are more likely to be published if they report 'positive' findings whereas larger studies are published regardless of findings. To address this, and as a minimum quality criterion, small-sampled epidemiological studies ($n<100$) were excluded.

The studies were initially selected by examining the abstracts of these articles. Therefore, it is possible that some studies were inappropriately excluded prior to examination of the full-text article. To minimise this possibility, where detail was lacking or ambiguous, papers were retrieved as full text. In addition, cross-checking of references of retrieved papers, including those of a large number of papers retrieved as background, was employed to identify additional potentially eligible articles.

The scope of the review required that studies reported on analyses relating to use of modified smokeless tobacco alone. This focus, for reasons outlined in Chapter 1, meant that the review focused on studies set in Scandinavian countries evaluating Swedish snus. This was primarily due to methodological reasons associated with distinguishing low-nitrosamine smokeless products from other smokeless tobacco of variable TSNA levels, particularly those in the US. Findings from this review may not be transferable to the use of modified low nitrosamine tobacco (LNT) products when used

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7 'Rapport fra Kunnskapssenteret Nr 6-2005', http://www.kunnskapssenteret.no/index.php?back=2&artikkelid=213, accessed July 2006.

outside Sweden due to variations in LNT products, user characteristics, user behaviour, acceptability, cost and regulatory controls. Such factors affecting applicability of this review's results to other countries are discussed in Chapter 4.

This systematic review was related to an examination of evidence for the major tobacco-related health effects of modified smokeless tobacco. However, the Background and Discussion Chapters also include an overview of broader issues relating to harm reduction. This provides a context for the evidence appraised, its application beyond the study settings and potential impact of reduced harm products on the wider population. Such issues were based on a non-systematic, narrative review of extensive background material retrieved from a range of sources in the course of the review. As such, the overview of these broader issues was less robust.

The review did not systematically consider evidence for the acceptability of, or ethical, economic or legal considerations associated with these products, although some of these issues were discussed in Background and Discussion. Interventions were not assessed in terms of their impact on general quality of life. Relatively minor or reversible effects of use of modified smokeless tobacco products, and risk factors for disease, were not considered as eligible outcomes. The justification for this is that the review was framed around a consideration of relevant products for reduced harm compared with use of conventional tobacco. Therefore the outcomes of interest were major illnesses and conditions, including mortality, known to be associated with tobacco use.

Data extraction, critical appraisal and report preparation was performed by a single reviewer over a limited timeframe (May, 2006 to February, 2007). For a detailed description of tobacco products, methodology, measurement and analyses in the studies appraised, the reader is referred to the original papers cited.

This review has benefited from comments provided by the consultant peer reviewer and internal peer reviewer. However, it has not been exposed to wider peer review. The review scope was developed with the assistance of Ministry of Health staff. The information was sought to assist in developing policy advice around a range of tobacco harm reduction approaches.

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Chapter 3: Results

Approximately 217 references were identified by the search strategy. Of these, 71 articles were identified as potentially eligible for inclusion and retrieved as full text. A final group of 18 papers was selected for appraisal, including two systematic reviews and 16 primary studies. Summary and appraisal of these studies is reported below, first the systematic reviews (secondary research), and then primary research grouped according to the following health outcomes considered: head, neck and gastro-intestinal cancers, cardiovascular disease outcomes (including cardiovascular mortality), and a mixed group of a range of health outcomes, including all-cause mortality.

SECONDARY RESEARCH

The search strategy identified two relevant systematic reviews (Critchley and Unal 2003; Roth et al. 2005). The review appraisals are summarised in evidence tables (**Table 3**; **pages 21-22)**. Other major reports which considered smokeless tobacco (International Agency for Research on Cancer 1985; Ranney et al. 2006; Royal College of Physicians of London 2002; Stratton et al. 2001; US Department of Health and Human Services 1986) but which did not meet inclusion criteria as systematic reviews, or did not include any studies eligible for review here, were not formally appraised.

Critchley and Unal (2003)

The most comprehensive systematic review of smokeless tobacco (ST) published to date was undertaken by Julia Critchley and Belgin Unal (2003). The review, funded by the UK's Health Development Agency, considered epidemiological studies reporting on health risks associated with smokeless tobacco use in any part of the world. A comprehensive search strategy was employed including extensive use of websites and databases, cross-checking of references and contacting experts. Studies were independently rated by two reviewers as being either flawed or of adequate quality, where flawed was defined as having one of the following limitations: having fewer than 10 cases among ST users, did not control for age, sex or tobacco use, and did not report analyses by ST type. Studies discussed in the paper were those that were of adequate quality, had a sample size of least 500 and were published since 1980. Of these, eight were from Scandinavia, reporting on oral/pharyngeal cancers (*n*=2 papers), other cancers (*n*=2), all-cause mortality (*n*=3), cardiovascular diseases (*n*=3), and dental outcomes (*n*=1). As some of these were cross-sectional studies, not all are included in the current review, but seven were (Bolinder et al. 1994; Huhtasaari et al. 1992; Huhtasaari et al. 1999; Lagergren et al. 2000; Lewin et al. 1998; Schildt et al. 1998; Ye et al. 1999). While crude estimates of population-attributable risk in Sweden were determined for oral cancer and ischemic heart disease, the 95 per cent CI and estimate ranges were wide, and reflected inconsistency between studies of variable quality. Heterogeneity in findings between ST types and regions was noted. The reviewers concluded that while chewing betel quid and tobacco was associated with a substantial risk of oral cancers in India, most recent studies from the US and Scandinavia were not statistically significant. However, moderate positive associations cannot be ruled out due to lack of power. Other limitations of the literature included that many studies were not designed to evaluate ST; few considered non-cancer outcomes and many had imprecise measurement, particularly to determine dose-response relationships; and poor control for cigarette smoking and other important confounders. The authors recommended that future studies improve validation, provide trend information and consider individual brands. It was noted that as ST toxicities have changed over time, the health impacts of newer types would take some years to establish.

A subsequent publication from the same review focused on studies concerning coronary heart disease (Critchley and Unal 2004) and was expanded to include studies reporting on intermediate outcomes such as risk factors for cardiovascular disease (CVD). It provided useful extended discussion of the Scandinavian papers and hypotheses for their discrepant results. However, as the paper did not identify additional studies of relevance to the current review, it was not included for appraisal here.

Roth, Roth and Liu (2005)

Roth, Roth and Liu's (2005) systematic review, funded by manufacturers of snus, aimed to identify all analytic epidemiological studies that provided quantitative risk estimates associated with Swedish snus and cigarette smoking in a single population, using a common reference group. The search strategy considered 32 databases from various disciplinary areas and cross-checking of references, although the paper did not identify the actual bibliographic databases employed. Selection criteria were explicit and considered specific outcomes. While the paper reported that it omitted 'probably few of the potential health effects of snus', outcomes considered *a priori* did not include pregnancy outcomes, dental diseases, or diabetes. Appraisal checklists were not used and there was only limited narrative critique of seven included studies reporting on cardiovascular disease (*n*=4 papers), oral cancer (*n*=1), gastrointestinal diseases (*n*=2), lung cancer (*n*=1); and all-cause mortality (*n*=1); Bolinder et al. 1994 reported on more than one outcome. It is noted that all of these papers were also included in the current review (Asplund et al. 2003; Bolinder et al. 1994; Hergens et al. 2005; Huhtasaari et al. 1992; Schildt et al. 1998; Persson et al. 1993; Ye et al. 1999). Results focused on data relevant to the health risks of exclusive snus use compared with exclusive smoking. The review did not consider the risks of dual use, or the safety of snus compared with not using any form of tobacco. The reviewers concluded that 'these seven studies do provide quantitative evidence that, for certain health outcomes, the health risks associated with snus are lower than those associated with smoking'. However, there appeared to be some selectiveness in discussion of results. For example, the divergent findings of Bolinder et al (1994) on risks for CVD-related mortality for snus users discounted as 'an anomaly', without further critique. Other studies were described as being of 'reasonable quality' and said to have adjusted for 'one or more' of a list of important confounders, but there was no discussion of where confounders were not adjusted. In general, there was sparse mention of methodological limitations of the field, as discussed in Critchley and Unal's (2003) systematic review appraised above or in references to that review.

Table 3.   Systematic reviews appraised relevant to health effects of modified smokeless tobacco use

Source, aims, funding source	Search strategy	Criteria for inclusion/exclusion	Results and reported conclusions	Reviewer comments
(Critchley and Unal 2003) **Aims:** To summarise health risks associated with smokeless tobacco (ST) use. Explicitly the aims were to identify and describe epidemiological studies, to provide narrative and tabular summaries of results, and interpret results including impact on the population **Funding source**: Health Development Agency, UK	**Design:** Systematic review **Level of Evidence:** Considered levels II – IV evidence (cohort, case-control, and cross-sectional studies) **Search strategy:** Databases searched (from inception): Medline, Embase, CINAHL, dissertation abstracts. Websites searched: WHO, ASH UK, ASH US, NIH, CDC, using the key term 'smokeless tobacco'. Cross-checked reference lists of articles. Contacted experts in the field and tobacco industry to identify further references. Search terms (keywords and MeSH headings) for databases included smokeless tobacco or synonyms and epidemiological studies and synonyms.	**Inclusion criteria:** Analytical epidemiological studies (cohort, case-control, cross-sectional) comparing ST users with non tobacco-users or with cigarette (only) tobacco users. Sample size ≥500. Detailed tables provided in an appendix available from the journal website. The paper described those papers which were (i) published after 1980, and (ii) adequately met minimum quality criteria. Studies rated as 'flawed' which were not described in the paper were those which contained <10 cases among ST users, which did not control for confounders of age, sex, and use of other tobacco products, or did not state form of ST or provide separate analyses for each type of ST. **Outcomes reported:** One or more of the following: oral/pharyngeal cancers, other cancers, all - cause mortality, cardiovascular diseases, dental health, complications of pregnancy, and surgery. **Appraisal/synthesis:** Quality assessed independently by two reviewers (agreed on 88%, kappa=0.76). Results were narratively summarised, organised by region, study type, and health outcome. Provided estimates of the number of deaths attributable to ST use (with 95% CI) for oral cancer, and for ischemic heart disease, based on prevalence of ST use and OR data of appraised studies, including from Sweden.	**Results:** Included studies (rated as being of 'adequate quality') described in the review reported on: oral/pharyngeal cancers (n=46 studies), other cancers (n=34), cardiovascular diseases (n=2), dental diseases (n=9), and pregnancy outcomes (n=1). Of these studies, eight were from Scandinavia, reporting on oral/pharyngeal cancers (n=2 papers), other cancers (n=2), all-cause mortality (n=3), cardiovascular diseases (n=3), and dental outcomes (n=1). Seven of these were also appraised in the current review. Authors provided estimates of population-attributable risk which were 'extremely crude' due to the following limitations: the range of estimates was wide, the studies of variable quality, the estimates may not have been fully adjusted for interactions with cigarette smoking, and many studies did not agree. The reviewers commented that the field has focused on cancer outcomes and highlights the uncertainty in the area. **Authors' conclusions:** 'Chewing betel quid and tobacco is associated with a substantial risk of oral cancers in India. Most recent studies from the US and Scandinavia are not statistically significant, but moderate positive associations cannot be ruled out due to lack of power. Further rigorous studies with adequate sample sizes are required, especially for cardiovascular disease.' (from abstract)	**Strengths and limitations of review:** - Used a focused research question. - Presented clear eligibility criteria for the review and only described more recent and less flawed studies - Employed a systematic and comprehensive search strategy. - Date search conducted not given. - Included/reported on studies rated as being of adequate quality by two reviewers based on broad explicit criteria. Some inconsistency noted however: cited one study rated as 'flawed' (Hansson et al. 1994) in the paper, and did not mention a study rated 'adequate' (Ye et al. 1999) in the appendicised tables available on the Journal website. - Appraisal used a standard checklist developed and piloted for the review. - Appraisal presented narratively and in separate tables (in appendices). - Discussed lack of homogeneity between studies and between regions. - Summary of main findings provided. - Strengths and limitations of the field briefly discussed. In summary, a high quality, comprehensive and carefully conducted systematic review providing an important assessment of studies of ST use across the world. Sub-sections on Scandinavian research relating to snus of relevance to the current review.

Key: ASH = Action on Smoking and Health, CDC = Centers for Disease Control, CINAHL =   Cumulative Index to Nursing & Allied Health, MeSH = Medical Subject Headings, NIH = National Institute of Health, ST = Smokeless Tobacco, WHO = World Health Organisation

Table 3.   Systematic reviews appraised relevant to health effects of modified smokeless tobacco use (continued)

Source and aims	Search method	Criteria for inclusion/exclusion	Results and reported conclusions	Reviewer comments
(Roth et al. 2005) **Aims:** To identify all analytic epidemiological studies that provided quantitative risk estimates associated with Swedish snus and cigarette smoking in a single population, using a common reference group. **Funding source**: Swedish Match North Europe Division (industry).	**Design:** Systematic review **Level of Evidence:** Considers levels II-III evidence (cohort and case-control) **Search strategy:** Databases searched 'through a Dialog search of 32 scientific databases relevant to health topics, medicine, chemistry, toxicology, food, and agriculture'. The search string included 'variations of the term snus, Swedish snuff, and oral snuff'. 'Tree-searched' reference lists of articles.	**Inclusion criteria:** Analytical epidemiological studies that provided risk estimates associated with Swedish snus and cigarette smoking within a single population. **Outcomes reported:** One or more of the following: head and neck cancers, cardiovascular diseases, lung cancer, gastrointestinal cancer and total mortality. **Appraisal/synthesis:** Data on risk estimates extracted from papers. Where possible, multivariate results were selected. Meta-analysis was not possible due to study heterogeneity. Included studies were described in Tables and narratively described.	**Results:** Identified 11 studies which provided risk estimates for snus use compared with smoking in a single population, but only reported on seven studies which used common reference groups. Excluded identified studies were (Hansson et al. 1994); (Huhtasaari et al. 1999); (Lagergren et al. 2000); and (Lewin et al. 1998) The seven included studies reported on the following outcomes (some on more than one): cardiovascular disease (Asplund et al. 2003; Bolinder et al. 1994; Hergens et al. 2005; Huhtasaari et al. 1992); oral cancer (Schildt et al. 1998); gastrointestinal diseases (Persson et al. 1993; Ye et al. 1999); lung cancer (Bolinder et al. 1994); and all-cause mortality (Bolinder et al. 1994). All of these studies were included in the current review. **Authors' conclusions:** 'These seven studies provide quantitative evidence that, for certain health outcomes, the health risks associated with snus are lower than those associated with smoking.' 'This review has likely omitted many of the adverse effects of cigarettes, but probably few of the potential health effects of snus.' (selected from abstract)	**Strengths and limitations of review:** - Used a focused research question. - Search scope considered limited health outcomes (eg did not include pregnancy outcomes or diabetes). - Presented clear eligibility criteria for the review to identify studies with comparable design types and comparators. - Appears to have employed a wide search strategy with many databases searched and cross-checking of references performed. However, databases were not explicitly identified and therefore the search is not replicable. - Date search conducted not given, though latest paper identified was published in January 2005. - Appraisal checklists were not mentioned, however listed key aspects of design quality considered. - Detailed tables presented key design, outcomes and reviewers' conclusions for each included study. - Narrative summary of main findings provided. - Possible selectiveness in reporting of findings in Discussion. - Little critique of study limitations and no mention of how adjustment of confounders was managed, or of lack of power in risk estimates. Did not consider the risks of dual use, or the safety of snus compared with not using any form of tobacco. - Funded by manufacturers of snus. In summary, the review lacked details on its search strategy and appraisal, and provided a selective review relevant to risk for some health outcomes of snus use compared with smoking.

ORAL, NECK AND GASTRO-INTESTINAL CANCERS

The search identified six eligible primary research studies which considered oral, neck and gastro-intestinal cancers. Some studies reported on oral and oropharyngeal cancer outcomes, some on gastric cancers, and some studies from both groups also reported on oesophageal cancers. Due to these overlapping outcomes, all studies are considered together here. Summaries of the appraisal results for each study, presented in chronological order, are below, followed by the evidence table for all six papers (**Table 4, pages 29-35**).

Hansson et al (1994)

Hansson et al's (1994) population-based case-control study (**Table 4, page 29**) considered risks for all forms of gastric cancer as a function of tobacco use and alcohol, with a minor focus on snuff[8] use. The study base was individuals aged 40-79 years living in five counties of Sweden from February 1989 through January 1992. Cases (*n*=338) were diagnosed with histologically confirmed gastric cancer identified from regional hospital departments and national cancer registries. Controls (*n*=679) were drawn by random sampling from population registers, stratified by age and gender.

Face-to-face interviews ascertained tobacco exposure and adjustments were made for selected potential confounders including SES and vegetable intake. No details were given of snus use in the study population. While participation rates were moderately high, they were slightly higher for controls at 77 per cent than for cases at 74 per cent.

In multivariate analysis adjusting for age, gender, SES, vegetable intake, and other tobacco use, compared with 'never tobacco-users', 'snus-users' had no increased risk of gastric cancer (OR = 0.70 95% CI, 0.47-1.06). In contrast, compared with never tobacco-users, there was an increased risk for 'current smokers' (adjusted OR = 1.72 95% CI, 1.16-2.54). Funding from industry provided partial support for this study.

Conclusions

This study was well conducted but focused on smoking and alcohol as risk factors. Results do not indicate any increased risk for gastric cancer for snus users, in contrast to an increased risk for smokers when compared with never tobacco-users. However, as snus use was not defined and the number of snus users not described, the precision of these results is difficult to determine.

Lewin et al (1998)

The population-based case-control study by Lewin et al (1998) investigated snus use, smoking and alcohol intake as potential risk factors for oesophageal and oral cancer. Specific outcomes were squamous cell cancers of the oral cavity, oro- and hypopharynx larynx, and the oesophagus (**Table 4, page 30**). The study population were males aged 40-79 years living in two geographical regions of Sweden (Stockholm and Southern Healthcare) during the years 1988-1990. Cases (*n*=605) were identified from diagnoses though confirmation was not described, occurring in relevant hospital departments and registrations at the regional cancer registries. Referent controls (*n*=756) were drawn by random sampling from population registrations every six months during the study period, stratified by region and age.

Tobacco exposure was measured by self-report in face-to-face structured interviews with nurses who were not blind to case/control status. Cases were interviewed in hospital within a month of diagnosis, while controls were usually interviewed at home. Response rates were uniformly high between cases and controls and very detailed information was gathered on tobacco use including total consumption, duration, and mean intensity (dose per day) of exposure. Tobacco exposure was based on use one year prior to diagnosis, given that symptomatic cases could reduce, or increase, their exposure. 'Ever snus-users' were defined as (ever) regularly using 1 packet (50 grams) per week, and 'ever smokers' were those who reported (ever) regularly smoking 7 grams of tobacco (cigarettes or other smoking forms) per week (about

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8 The words snus and snuff are used interchangeably in relation to Swedish primary research to indicate Swedish snus (snus being Swedish for snuff).

7 cigarettes). Tobacco exposure was not validated and recall bias is a possibility, particularly given the different sites for interview for cases and controls.

Compared with 'never tobacco-users', relative risk (RR) for squamous cell head and neck cancer for 'current snus-users' was 3.3 (95% CI, 0.8-12.0), and the RR for 'ex-snus-users' was unexpectedly higher at 10.5 (95% CI, 1.4-117.8), suggesting a possible selection bias (Critchley and Unal 2003). However, these analyses using the referent category of never tobacco-users had low precision as there were very few people (nine cases, 10 controls) who had used snuff exclusively, ie never smoked. When using 'never snus-users' as the referent category and adjusting for alcohol and smoking in multivariate analysis, RRs for squamous cell head and neck cancer were close to 1.0 for current snus-users (RR=1.0, 95% CI 0.6-1.6), and for ex-snus-users (RR=1.2, 95% CI, 0.7-1.9). However, the reference group of never snus-users for these analyses included smokers, which may have lead to an underestimate of risk for snus use.

Higher intensity of snus use (>50g per week) was associated with moderately, but not significantly, higher risk for oral cavity cancer (RR=1.7, 95% CI, 0.8-3.9), and for oesophageal cancer (RR=1.9, 95% CI, 0.8-3.9). However, it was not clear whether these risk estimates were adjusted for smoking as they were only reported as an aside in the Discussion, with no other details.

As a check for residual confounding, adjustments were also made for age at starting, years of smoking, total amount used in a lifetime, oral hygiene, and a range of dietary factors, with reportedly little or no impact on results. Other results relating to the affect of smoking and alcohol use on cancer risk were reported, and suggested highly increased risks for head and neck cancers for ever-smokers, and an almost multiplicative effect for tobacco smoking and alcohol intake on risk. The research was supported by a mix of cancer society and industry sources.

Conclusions

This well conducted population-based case-control study suggests that, compared with the associations of tobacco smoking with squamous cell head and neck cancer, there was not evidence of strong associations between snus use and oral cavity and oesophageal cancers. While tobacco use was generally adjusted for, some residual confounding may be possible, particularly for comparisons using a reference group of never snus-users. Analyses comparing exclusive snus users with never-tobacco users lacked precision due to the low number of snus-users who had never smoked.

Schildt et al (1998)

Another population-based case-control study (Schildt et al. 1998) also focussed on snus use, smoking and alcohol intake as potential risk factors for squamous cell oral cancer (see **Table 4, page 31**). The study population were from the four most northern counties in Sweden, where snus use is most prevalent (International Agency for Research on Cancer 1985). Cases were 354 people (117 females, 237 males, mean age 70 years) diagnosed with squamous cell oral cancer between 1980 and 1989 (histopathologically verified and reported to the Cancer Registry). Of cases, 211 (60 per cent) were deceased. Controls were drawn from the National Population Registry, matched for age, sex, county of residence and vital status while those matched with deceased cases were drawn from the National Registry for Causes of Death.

Tobacco exposure information was measured through retrospective self-report in mailed questionnaires, with supplementary telephone interviews where clarification was required. Attempts were made to conceal study hypotheses in the questionnaire, and interviewers and data coders were blind to case/control status. Response rates were uniformly high between cases and controls. In 60 per cent of the sample, this information was sought from the next-of-kin of deceased subjects with matching of vital status standardised recall conditions for relatives of cases with relatives of controls. Details on daily consumption and time period of use permitted estimates of lifetime exposure to snus, although it was not clear whether changes in use over time were measured or incorporated into this outcome. It was also not clear whether a minimum use, whether quantity or frequency of snus was required to permit classification as a user.

Compared with never-users of tobacco, univariate ORs were not increased for 'exclusive snuff users', ie who had never smoked (OR = 0.7, 95% CI, 0.4-1.2). However, there was an increased risk for oral cancer indicated for 'exclusive smokers', ie smokers who had never used snuff (OR = 1.7 95% CI, 1.1-2.6). Multivariate analyses controlling for alcohol and smoking did not differ substantially from univariate

findings. There was a suggestion of heightened risk of lip cancer among 'ex snuff users' (OR = 1.8, 95% CI 0.9-3.7), but this risk was non-significant, and was not observed for 'current snuff users'. Higher levels of consumption of snus and brand of snus used were not associated with risk. There remained no evidence of altered risk for oral cancer from snus use regardless of level of liquor intake, which was the largest independent risk factor for oral cancer in the study.

The large proportion of deceased subjects in the study is a limitation. Tobacco exposure and alcohol use are related to earlier death generally, and recall is likely to be less accurate from relatives than from live respondents. Statistics were not reported but the authors reported that analyses repeated for live cases and controls alone revealed similar ORs to those from the whole sample. Like all studies relying on unvalidated retrospective recall of lifetime exposure to snus, results are open to recall biases. Affected cases may be more likely to remember or report exposure to potentially hazardous exposures. A bias in this direction would mean that any effect was exaggerated, which would not alter the finding here of no significant risk.

The number of oral snuff users was not large, with 93 people classified as 'active snuff users'. Some potential confounders to these findings were not investigated, including socio-economic status, nutrition, and illicit drug use. However other exposures including oral infections, dental status, anaemias, and occupations were measured (reported elsewhere). The study received funding from a mix of industry and non-industry sources.

Conclusions

While limited by possible biases in reporting from relatives on tobacco exposure for a significant group of deceased cases, there was no consistent evidence of associations between exclusive snus use and squamous cell oral cancers. This contrasted with the increased risk observed for squamous cell oral cancers in people who exclusively smoked.

Ye et al (1999)

This population-based case-control study by Ye et al (1999) (**Table 4, page 32**) appears to have employed the same study base as Hansson et al (1994), above, and is co-authored by Hansson. In both papers, the population was recruited from individuals aged 40-79 years, born in Sweden, and living in five counties of central and northern Sweden from February 1989. In Ye et al's 1999 report, the recruitment period extended to January 1995. Case ascertainment was comprehensive and considered newly diagnosed, histologically confirmed gastric cancer, with analyses restricted to cardia cancer and distal stomach cancer, both intestinal type and diffuse type. Cases (*n*=514) diagnosed with gastric cancer were identified from regional hospital departments, supplemented by national cancer registries. Controls (*n*=1,164) were drawn by random sampling, of approximately two controls per case, from population registers with frequency matched by age and gender.

Face-to-face interviews using structured questionnaires measured tobacco exposure, including age at start, duration and daily frequency, as well as alcohol intake, dietary habits and socio-economic status. Interviewers were not blind to case/control status but were blind to study hypotheses. It was not reported whether coding was blinded. Snuff use was defined as using Swedish snuff at least once a week for six months or more. Current smokers were those who were smoking at least two years before the interview.

No females used snuff. The numbers of 'ever snus-users' in the study sample of males was 275. A history of snus-use and smoking was common; 83 per cent of ever snus-users had ever smoked, and 62 per cent of snus users were ex-smokers. Considering males only, multivariate analysis were adjusted for age, residence area, BMI, and SES, and excluded the 22 people who had ever chewed tobacco. Compared with 'never tobacco-users', there was no evidence of increased risk of gastric and cardia cancer for male snus users who had never smoked (OR = 0.5 95% CI, 0.2-1.2), based on 47 snuff users. In contrast, compared with never tobacco-users, there was an increased risk of gastric and cardia cancer for current smokers who had never used snuff (OR = 2.0 95% CI, 1.3-2.9), based on 236 smokers. Analyses adjusted for smoking also investigated subtypes, ie cardia, intestinal and distal, and dose-response relationships within sub-types, and found no excesses of risk in any strata and no clear trends. However, cell sample sizes were small and results lacked precision.

Participation rates were higher for controls, at 76 per cent, than for cases, at 62 per cent. About 3 per cent (28) of cases and 16 per cent (245) controls refused to participate. This may have introduced bias of unknown direction. Thirty per cent, a significant number of cases, died or rapidly became too ill to be interviewed. If tobacco use and alcohol exposure were related to prognosis, the deficit in cases who had used tobacco and alcohol would bias results towards null. Despite this possibility, there was a significant two-fold increased risk found for never snuff users who were current smokers. Recall bias for retrospective accounts of snus exposure is possible. However, differential recall such that cases may recall increased exposures to potentially hazardous substances, including snus, would inflate estimates of risk, which would not alter the negative findings here for snus.

Conclusions

This population-based case-control study was well conducted. Results suggest that, for a sample of males, there was no evidence of increased risk for gastric and cardia cancer associated with exclusive snus use. However, these analyses lacked precision due to the low number of snus-users who had never smoked. In contrast, there was a two-fold increased risk for gastric cancer in exclusive current smokers.

Lagergren et al (2000)

More recently, Lagergren et al (2000) conducted a population-based case-control study of three forms of gastric cancer (**Table 4, pages 33-34).** There are some similarities with the study designs of two case-control studies appraised above reporting on gastric cancer risk with overlapping authorship (Hansson et al. 1994; Ye et al. 1999). However, the study period for Lagergren et al (2000) does not overlap with the earlier papers and considers the whole of Sweden in its study base.

The study base comprised residents of Sweden from 1995-1997, aged under 80 years. Cases (*n*=618) were all newly diagnosed with gastric cardia adenocarcinoma (AC) (*n*=262), oesophageal AC (*n*=189), and half the cases of oesophageal squamous cell carcinoma (SCC) (*n*=262) born on even dates and identified from Swedish hospital departments and supplemented by national cancer registries. Histologically defined diagnoses were confirmed by biopsies and/or surgical specimens by a pathologist. Controls (*n*=1,164) were drawn by random sampling of population registers, stratified by age and gender, by frequency matching.

Face-to-face interviews were conducted, blind to study hypotheses but not to case/control status, using structured questionnaires. Current tobacco users were those who were snuff dipping/smoking at least two years prior to the interview. Snuff use was defined as regular use of a quid of oral moist Swedish snuff at least once a week, for six months or more.

In total, 123 cases and 126 controls had ever regularly used snuff. Analyses involved very thorough investigation of potential confounders, with adjustment for age, gender, other tobacco smoking, alcohol use, educational level, body mass index, reflux symptoms, intake of fruit and vegetables, energy intake, and physical activity. Compared with 'never snus users', 'ever snuff users' were not significantly at risk for oesophageal AC (OR = 1.2 95% CI 0.7-2.0). Similarly, compared with never snus users, ever snuff users were not significantly at risk for gastric cardia AC (OR = 1.2 95% CI 0.8-1.8). However, compared with never snus users, ever snuff users were at slightly, but not significantly, higher risk of oesophageal SCC (OR = 1.4 95% CI 0.9-2.3). Some point estimates of borderline significance were observed in single categories. Specifically, compared with 'non snus-users', for those with a moderate intensity of use (of 15-35 quids per week), there was a two-fold risk for oesophageal ACC (OR = 2.0 95% CI 1.0-4.3) and for oesophageal SCC (OR = 2.1 95% CI 1.0-4.4). However, the ORs were close to 1.0 for use <15 quids per week, and use >35 quids per week. No dose-response relationships or trends were evident in terms of duration of use (in years), or intensity (quids per week). These borderline findings for point estimates should be interpreted with caution. Given the number of statistical tests performed, some positive findings, particularly in the absence of dose-response trends, could be the result of type I error and be chance findings. Note also that the reference group of never snus users for these analyses included smokers, which may have lead to an underestimate of risk for snus use.

Multivariate analyses were performed for smoking, also adjusted for other tobacco use. Compared with 'never tobacco users', there were significant increased risks and dose-response effects associated with current smoking and gastric cardia AC (OR = 4.5 95% CI, 2.9-7.1), and oesophageal SCC (OR = 9.3 95%

CI 5.1-17.0). However, there was only a borderline association found compared with never tobacco users, for smoking and oesophageal AC (OR 1.6 95% CI 0.9-2.7), without any dose response relationships observed. As the reference group for these analyses (never tobacco users) differed from that used in estimating risk for snus use (never snus users), the risk estimates for smoking and snus use are not directly comparable.

This study was well conducted and designed, employing the entire country's population as the study base with comprehensive and rapid case ascertainment and verification. Participation rates were relatively high, and consideration of confounders thorough. Nevertheless, as with all case-control studies, there were some possibilities of bias to be considered. Participation was somewhat higher for cases at 73-83 per cent than for controls at 73 per cent. There were particularly higher refusal rates for controls at 19 per cent compared with 3 per cent for cases. Allaying concerns of participation biases somewhat, the authors state that an analysis of 24 controls who had initially refused to participate suggested that their smoking and alcohol habits were strikingly similar to those of participants (data not reported). The generalisability of these findings to consistent refusers is unknown. Despite interviewing most cases shortly after their diagnosis, some 116 or 15 per cent of cases had died or become too ill to be interviewed, which is not unexpected given the poor prognosis of oesophageal cancer. If tobacco use is associated with poor survival, a deficit of tobacco users among participating cases may result in a spuriously weak association. Nevertheless, high associations were noted for smoking and squamous cell carcinoma, which had higher losses to interview than the other cancer sub-types. The authors argue that this result, consistent with other research, is evidence for good study validity and sensitivity. Finally, the possibility of recall bias exists for retrospective accounts of snus exposure. Overestimation of exposure by cases to potential hazards such as snus would lead to an overestimate of risk, which would not alter the findings of no association for this study.

Conclusions

Taking the strengths and limitations of this study into account, the results suggest that, compared with the strong associations of smoking with gastric cardia AC and oesophageal SCC, there was no evidence of strong associations between snus use and oesophageal and gastric cancers. However, a small risk cannot be ruled out. While tobacco use was adjusted for in analyses, some residual confounding may be possible, and risks for snus use may have been underestimated. Analyses comparing exclusive snus users with never tobacco users would have provided clearer results, and been more comparable to the analyses estimating risks for smokers.

Rosenquist et al (2005)

The recently published population-based case-control study by Rosenquist et al (2005) (see **Table 4, page 35**) considered risk for oropharyngeal squamous cell carcinoma (OOSCC) in people living in the Southern Healthcare regions of Sweden, one of the two regions included in Lewin et al's study reported above. There were 132 cases (41 females, 91 males) diagnosed in two regional hospitals where almost all patients with cancer are treated. The 320 controls (105 females, 215 males) were drawn by stratified random sampling of three controls per case from the Swedish Population Registry and matched for age, sex, and county of residence. Recruitment took place between September 2000 and January 2004.

The same person interviewed participants in a uniform way, although it is unlikely that the interviewer was blind to case/control status given the nature of examinations. Detailed information was gathered on exposure to snus, including lifetime exposure, consumption per day, duration of use per day, form of snus used, placement of quid, and whether fermented snus was ever used, ie prior to 1984. Whether a minimum level of snus use was required for classification as a snus-user was not stated and no validation of use was undertaken. Recall bias is possible, although if cases tend to overestimate their tobacco use exposure then this bias would suggest that any exposure effect found would be overestimated. 'Ex-snus-users' were those who reported quitting snus use at least six months prior to the interview, and presumably prior to diagnosis, although no information was given concerning the timing of the interview with respect to diagnosis for cases. During the interview, other risk factors and potential confounders were also measured, including clinical examinations and ratings of identified mucosal lesions. Given the detailed assessments made, participation rates were high: 80 per cent and 81 per cent for cases and controls respectively.

Compared with 'never snus users', in multivariate analysis adjusting for alcohol and smoking, no risk for OOSCC was found for 'current snus-users' (OR = 1.1 95% CI, 0.5-2.5), and, unexpectedly, a reduced risk was found for ex-snus users (OR = 0.3 95% CI, 0.1-0.9). There was also no increased risk for users of fermented snus, which included users who later used non-fermented snus, or for users for more than 10 hours per day, or for users reporting at least 30 years of use. Whether any dose-response relationship existed was explored. For higher levels of consumption of >14 g/day, there was a non-significant tendency toward an increased risk of OOSCC (OR = 1.7 95% CI, 0.5-5.7). As the reference group members were never snus users for these analyses, and may have included smokers, there may have been an underestimate of risk for snus use.

The lack of significant evidence of risk for snus use contrasted with significant increased risks for OOSCC for high alcohol consumption and a dose-response effect for smoking. The authors state that oral status, other lifestyle factors that were not described, and HPV infection did not affect any conclusions relating to snus use, although details were not reported. It was not clear whether illicit drug use, nutrition or socio-economic status were considered as potential confounders.

Conclusions

This study found no clear evidence of increased risk for OOSCC as a function of snus use, and a protective effect for ex snus users, in contrast with increased risks associated with high alcohol intake and smoking consumption. As the authors acknowledge, the study sample was small with respect to snus users, with only 13 cases and 31 controls reporting as active users of snus.

Table 4. **Evidence table of the impact of snus on risk for oral, neck and gastrointestinal cancers**

Study & aims	Study and sample characteristics	Measures of exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Hansson et al. 1994) **Country:** Sweden **Study aims:** To examine 'the influence of tobacco and alcohol on the risk of gastric cancer, while controlling for SES and diet.' **Source of funding:** American Cancer Society, Regional Cancer Foundation in Umeå, County Council of Västmanland, Sweden, and the Swedish Tobacco Company (industry).	**Design:** Case-control **Level of evidence:** III.3 **Exposure:** Used moist oral Swedish snuff (snus) **Population:** The study base comprised individuals aged 40-79 years, born in Sweden and living in 5 counties of Sweden from February 1989 through January 1992. The counties included 3 in central Sweden (Uppsala, Västmanland, and Södermanland), and 2 northern counties of Sweden (Västerbotten and Norrbotten). 338 cases (64% males) diagnosed with gastric cancer identified from regional hospital departments and national cancer registries. Mean age = 68 years. Participation rate = 74%. 679 controls drawn by random sampling of 2 controls per case from population registers, stratified by age and gender. Mean age= 67 years. Participation rate = 77%. Number of snus users was not reported. **Exclusion criteria**: Mental or physical illness precluding interview, advanced malignant disease or early death, respondent could not be located. **Observation time:** Recruitment period Feb 1989-Jan 1992	**Exposure:** Face-to-face interviews using structured questionnaire to measure tobacco exposure, alcohol intake and dietary habits, socio-economic status, occupational and medical histories. 'Current smokers' were those who were smoking at least 2 years before the interview (since more cases than controls had quit the year before). Focus on cigarette measures rather than snus. **Outcomes:** Newly diagnosed, histologically confirmed gastric cancer **Confounders:** Adjustment for age, gender, SES, other tobacco exposures, and for snus analysis, vegetable intake.	**Results:** Compared with 'never tobacco-users' in multivariate analysis adjusting for age, gender, SES vegetable intake, and other tobacco use, no evidence of increased risk of gastric cancer for 'snus users' (OR = 0.70 95% CI, 0.47-1.06). In contrast, compared with never tobacco-users, increased adjusted risk for 'current smokers' (OR = 1.72 95% CI, 1.16-2.54). **Author conclusions:** 'Snuff dipping and alcohol intake were not associated with gastric-cancer risk.' (from abstract)	Population-based case-control study Matching of cases with controls on age and gender. Participation rates were moderately high, and slightly higher for controls (77%) than cases (74%). Exposure status measured through retrospective self-report. No definition given of minimum snuff use to satisfy classification as a snuff user. Not validated. Recall bias for retrospective accounts of snus exposure is possible. Not reported whether interviewers and coding were blind to case/control status. Snus use not defined or described. Outcomes histologically confirmed. Number of oral snuff users and non users not described, and therefore cannot assess statistical power. Investigation of several potential confounders. Non-industry and Industry funding sources.

Key: CI = confidence interval, OR = Odds Ratio. SES = socio-economic status.

Table 4. **Evidence table of the impact of snus on risk for oral, neck and gastro-intestinal cancers** *(continued)*

Study & aims	Study and sample characteristics	Measures of exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Lewin et al. 1998) **Country:** Sweden **Study aims:** 'To identify possible factors in the aetiology of cancer of the head and neck among men.' **Source of funding:** Cancer Society of Stockholm, the Swedish Cancer Fund, and the research fund of the Swedish Tobacco Company (Industry).	**Design:** Case-control **Level of evidence:** III.3 **Exposure:** Ever regularly used one packet (50g) per week of Swedish moist oral snuff (snus) **Population:** Swedish males aged 40-79 years living in 2 geographical regions (Stockholm and Southern Healthcare) during the study period. 605 cases diagnosed with squamous cell head and neck cancer, identified in relevant hospital departments and from registrations at the regional cancer registries. 756 controls drawn by random sampling from the population registrations every six months during study period, stratified by region and age. 83 cases and 91 controls had ever used snus **Exclusion criteria**: None stated **Observation time:** Recruitment between January 1988 and January 1991.	**Exposure:** Face-to-face interviews with nurses. Most cases were interviewed in hospital within a month of diagnosis, and controls usually at home. - 'Ever snuff users' defined as having ever regularly used one packet (50g) per week - 'Ever smokers' classified as ever regularly smoking 7 grams of tobacco (about 7 cigarettes) per week (included cigars, cigarillos and pipes) - Current tobacco users defined as using tobacco at least 1 year prior to interview. **Outcomes:** Squamous cell head and neck cancer, including cancers of the oral cavity, oro- and hypopharynx larynx, and the oesophagus (ICD-7, 140, 141, 143-5). **Confounders:** Age and region controlled by matching. Alcohol intake and smoking adjusted for in analyses. Adjustments were also made for age at onset, duration of smoking, oral hygiene, and certain dietary factors (intake of calories, fat carbohydrates, fibers, vitamins). There was little or no impact on results.	**Results:** Compared with never tobacco users, RR for current-users of snus was 3.3 (95% CI, 0.8-12.0), and for ex-snus-users RR was 10.5 (95% CI, 1.4-117.8). Analyses had low precision; only 19 people had used snuff exclusively. In multivariate analysis adjusting for alcohol and smoking compared with never snus users, risk for head and neck cancers was not significantly increased for ever snus users (RR=1.1, 95% CI, 0.7-1.5), for current snus users (RR=1.0, 95% CI 0.6-1.6), or for ex snus users (RR=1.2, 95% CI, 0.7-1.9). High intensity of snus use (>50g per week) was associated with moderately but not significantly higher risk for oral cavity cancer (RR=1.7, C, 0.8-3.9), and for oesophageal cancer (RR=1.9, 95% CI, 0.8-3.9). These results contrast with increased oral cancer risks from smoking, including a four-fold increased risk for head and neck cancers for ever smokers (adjusted RR=4.0, 95% CI 2.8-5.7), adjusted for alcohol but not snus use. **Author conclusions:** 'Tobacco smoking and alcohol intake had a strong interactive effect on the risk of squamous cell carcinoma of the head and neck. No increased risk was found for the use of Swedish oral snuff.' (selected from Abstract)	Population-based case-control study Matching of cases with controls on age and region. Tobacco exposure information collected by face-to-face interview. Site of interview differed between cases and controls. Interviewers not blind to case/control status. High response rates for both cases (90%) and controls (85%). Exposure status clearly defined and described including total consumption, duration, and mean intensity of snus use. Dose-response effects investigated. Tobacco exposure not validated and recall bias possible. The study lacked statistical power and precision for analyses using the referent category of 'never tobacco-users'; only 9 cases and 10 controls used snuff exclusively. Reference group for multivariate analyses included smokers, which may have lead to an underestimate of risk. Outcomes clearly defined by ICD code but unclear how confirmed. Age, region, tobacco use and smoking duration, alcohol intake, oral hygiene and dietary factors considered as potential confounders. Socio-economic status, education and ethnicity not considered. Industry and non-industry funding source

Key: CI = confidence interval, ICD = International Classification of Diseases, RR = Relative Risk

Table 4.   Evidence table of the impact of snus on risk for oral, neck and gastro-intestinal cancers *(continued)*

Study & aims	Study and sample characteristics	Measures of exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Schildt et al. 1998) **Country:** Sweden **Study aims:** 'The risk for oral cancer was evaluated in relation to exposure to moist snuff, smoking and alcohol.' **Source of funding:** Research Foundation of the Department of Oncology, Umeå University, Swedish Tobacco Research Council, Mrs Berta Kamprad Foundation and Örebro County Council Research Committee.	**Design:** Case-control **Level of evidence:** III.3 **Exposure:** Used moist oral Swedish snuff (snus) **Population:** Inhabitants of the four most northern geographical regions in Sweden during the years 1988-1990. 354 cases (117 females, 237 males) diagnosed with squamous cell oral cancer from the four most northern counties in Sweden from 1980-1989 and reported to the Cancer Registry. Mean age was 72.3 years for women, and 69.6 years for men. Of cases, 211 (60%) were deceased. 354 controls (117 females, 237 males) drawn from the National Population Registry, matched for age, sex, county of residence, and vital status (those matched with deceased cases drawn from the National Registry for Causes of Death). 39 cases and 54 controls were active users of snuff. **Exclusion criteria:** Case with wrong diagnosis coding, and deceased cases for whom relatives could not be contacted. Matched counterparts of refusers also excluded. **Observation time:** Cases were diagnosed between 1980 and 1989.	**Exposure:** Mailed questionnaire of exposure supplemented where incomplete by telephone interview completed by subject or where deceased, by their next-of-kin. - Snuff use defined as active (including those quitting within year prior to diagnosis), ex (quit at least one year before diagnosis for case or for respective case) and never. - Cigarette smokers similarly classified. **Outcomes:** Histopathologically verified squamous cell oral cancer; ICD-7 codes 140 (hypolarynx, larynx, oesophageal), 141 (tongue), 143-5 (floor of the mouth, oral cavity not otherwise specified, oropharynx). **Confounders:** In univariate analyses, pairs matched on age, sex, and country of residence. Multivariate analyses (controlling for alcohol and smoking) reported as making little difference to ORs from univariate analyses for snus use.	**Results:** Compared with 'never tobacco-users', univariate ORs were not increased for exclusive snuff users (ie who had never smoked) (OR = 0.7, 95% CI, 0.4-1.2), but there was an increased risk for oral cancer for exclusive smokers (ie who have never used snuff) (OR = 1.7 95% CI, 1.1-2.6). Moderate, but not significantly increased, risk in lip cancer among exsnuff users (OR = 1.8, 95% CI 0.9-3.7), close to unity for current snuff users. No difference in risk among different snuff brands used. In analyses investigating a dose-response effect (for snuff users overall, regardless of smoking status), higher levels of consumption were not associated with risk (for those consuming estimated lifetime >156kg snuff, OR = 1.1, 95% CI 0.5-2.0; and for those consuming <156kg, OR = 0.8, 95% CI 0.4-1.5). **Author conclusions:** 'Tobacco smoking and alcohol intake had a strong interactive effect on the risk of squamous cell carcinoma of the head and neck. No increased risk was found for the use of Swedish oral snuff.' (selected from abstract)	Population-based case-control study Matching of cases with controls on age, sex, county of residence, and vital status. Exposure status measured through retrospective self-report questionnaire, completed by next of kin for 60% of sample. Study hypotheses were concealed. Response rates very high for both cases (96%) and controls (91%), and 86% overall after counterparts of refusers excluded. No definition given of snuff use. Not validated and recall bias possible. Coding of answers and interviews were blind to case/control status. Large proportion (60%) of cases and their matched controls had died, requiring reliance on reports from relatives. Use of deceased controls can be problematic. Authors stated that analyses repeated for live cases and controls alone revealed similar ORs. Attempted to estimate lifetime exposure to snus (and other tobacco), though not clear whether changes in use over time was considered. Brand and type (packet or quid) of snuff considered. Dose-response effects investigated. Outcomes clearly defined by ICD code. Number of active oral snuff users relatively small (n=93). Adjustment for other potential confounders, including socio-economic status, nutrition, and illicit drug use, not reported. Risk for other exposures (including oral infections, dental status, anaemias, occupations and occupational exposures) not reported. Industry and non-industry funding source

Key: CI = confidence interval, ICD-7 = International Classification of Diseases – seventh revision, kg = kilograms, OR = Odds Ratio

Table 4. Evidence table of the impact of snus on risk for oral, neck and gastro-intestinal cancers *(continued)*

Study & aims	Study and sample characteristics	Measures of exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Ye et al. 1999) **Country:** Sweden **Study aims:** 'We analysed the effects of smoking, use of smokeless tobacco, alcohol intake and the risk of gastric cancer by sub-site and histology in a large population-based study.' **Source of funding:** Grant from National Cancer Institute. individual researcher support from UICC fellowship, and Swedish Cancer Society	**Design:** Case-control **Level of evidence:** III.3 **Exposure:** Used moist oral Swedish snuff at least once a week for 6 months or more. **Population:** The study base comprised individuals aged 40-79 years, born in Sweden and living in 5 counties of central and northern Sweden from February 1989 through January 1995. 514 cases diagnosed with gastric cancer identified from regional hospital departments, supplemented by national cancer registries. Mean age = 65 years (cardia and diffuse cancer), 70 years (intestinal). Proportion male: cardia (79%), intestinal (73%), and diffuse (53%). Participation rate = 62% (30% of sample due to death or advanced disease). 1,164 controls drawn by random sampling of 2 controls per case from population registers, stratified by age and gender (by frequency matching). Mean age= 67 years, 67% male. Participation rate = 76%. 83 of male cases (375), 192 of male controls (779), and no females used snuff. **Exclusion criteria**: Mental or physical illness precluding interview, advanced malignant disease or early death, could not be located, missing information, cancer could not be classified. **Observation time:** Recruitment period Feb. 1989 - Jan.1995	**Exposure:** Face-to-face interviews using structured questionnaire to measure tobacco exposure, alcohol intake, dietary habits, BMI, and socio-economic status. 'Current smokers' were those who were smoking at least 2 years before the interview. **Outcomes:** Newly diagnosed, histologically confirmed gastric cancer, with analyses restricted to cardia cancer, and distal stomach cancer (intestinal-type and diffuse-type), defined histologically and according to locality. **Confounders:** Adjustment for age, gender, residence area, BMI, SES, use of alcoholic beverages, and other tobacco exposures. No woman reported having ever used snuff, and so these analyses were restricted to males and excluded the 8 cases and 14 controls who reported ever having chewed tobacco.	**Results:** In multivariate analysis adjusting for age, residence area, BMI, SES, and alcohol intake, for males only: compared with 'never tobacco-users', no evidence of increased risk of gastric and cardia cancer for male exclusive (never smoker) snus-users (OR = 0.5 95% CI, 0.2-1.2). In contrast, compared with never tobacco users, increased risk for exclusive current smokers who had never used snuff (OR = 2.0 95% CI, 1.3-2.9). Analyses also investigated subtypes (cardia, intestinal and distal) and dose-response relationships within sub-types, and found no excesses of risk in any strata and no clear trends. However, cell sample sizes were small and results lacked precision. **Author conclusions:** 'Neither intake of alcoholic beverages nor snuff dipping was associated with an increased risk of any type of cardia or gastric cancer.' (from Abstract)	Population-based case-control study Frequency matching of cases with controls on age and gender. Snus analyses restricted to men. Participation rates were higher for controls (76%) than for cases (62%) and about 3% (28) of cases and 16% (245) of controls refused to participate. This may have introduced bias of unknown direction. A significant (30%) number of cases died or rapidly became too ill to be interviewed. If tobacco and alcohol exposure are related to prognosis, the deficit in cases who had used tobacco and alcohol would bias results towards null. Exposure status measured through retrospective self-report and age at start, duration and daily frequency measured. Recall bias for retrospective accounts of snus exposure possible. Interviewers were not blind to case/control status but were blind to study hypotheses. Not reported whether coding was blind. Outcomes histologically confirmed. Very thorough investigation of potential confounders. Non-industry funding sources.

Key: BMI = Body Mass Index, CI = confidence interval, OR = Odds Ratio. SES = socio-economic status. UICC = International Union Against Cancer (Union Internationale Contre le Cancer)

Table 4.   Evidence table of the impact of snus on risk for oral, neck and gastro-intestinal cancers *(continued)*

Study & aims	Study and sample characteristics	Measures of exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Lagergren et al. 2000) **Country:** Sweden **Study Aims:** 'We have investigated the role of tobacco smoking, snuff dipping and alcohol drinking in a nationwide case-control study of oesophageal and cardia cancer.' **Source of funding:** Grants from National Cancer Institute, and Swedish Cancer Society	**Design:** Case-control **Level of evidence:** III.3 **Exposure:** Used a quid of moist oral Swedish snuff at least once a week for 6 months or more **Population:** Study base comprised individuals aged 0-79 years in Sweden from 1995-1997. 618 cases newly diagnosed with gastric cardia adenocarcinoma (cardia AC), oesophageal adenocarcinoma (oesophageal AC), and half of cases of oesophageal squamous cell carcinoma (SCC), born on even dates and identified from hospital departments, supplemented by national cancer registries, including: - 262 gastric cardia AC, median age 66 years, 85% male, 83% participation rate - 189 oesophageal AC, median age 69 years, 87% male, 83% participation rate - 262 oesophageal SCC, median age 67 years, 72% male, 73% participation rate 1,164 controls drawn by random sampling of population registers, stratified by age and gender (by frequency matching). Median age= 68 years, 83% male. Participation rate = 73%. 123 cases (35 oesophageal AC, 53 gastric cardia AC, 33 oesophageal SCC) and 126 controls had ever used snuff.	**Exposure:** Face-to-face interviews using structured questionnaire to measure tobacco exposure, alcohol intake, dietary habits, BMI, and socio-economic status. 'Current tobacco-users' were those who were snuff dipping/smoking at least 2 years before the interview. **Outcomes:** Newly diagnosed, histologically confirmed gastric cardia adenocarcinoma, oesophageal adenocarcinoma, and oesophageal squamous cell carcinoma, defined histologically and according to locality. 97% confirmed by biopsies and/or surgical specimens by a pathologist. **Confounders:** Adjustment for age, gender, other tobacco smoking, alcohol use, educational level, BMI, reflux symptoms, intake of fruit and vegetables, energy intake, and physical activity.	**Results:** In multivariate analysis with multiple adjustments, compared with 'never snus-users', 'ever-snuff users' were not significantly at risk for oesophageal AC (OR = 1.2 95% CI 0.7-2.0), ever snuff users were not significantly at risk for gastric cardia AC (OR = 1.2 95% CI 0.8-1.8), ever snuff users were non-significantly at 40% excess risk for oesophageal SCC (OR = 1.4 95% CI 0.9-2.3). No dose-response relationships or trends were evident in terms of duration of use (in years), or intensity (quids per week). Some point estimates of borderline significance observed in single categories. Compared with non-snus-users, for those using moderate intensity of 15-35 quids per week, two-fold risk for oesophageal ACC (OR = 2.0 95% CI 1.0-4.3) and for oesophageal SCC (OR = 2.1 95% CI 1.0-4.4). ORs were close to 1 for use <15 quids per week, and use >35 quids per week. In contrast, compared with 'never tobacco-users', significant increased risks associated with current smoking and gastric cardia AC (OR = 4.5 95% CI, 2.9-7.1), and oesophageal SCC (OR = 9.3 95% CI 5.1-17.0). Borderline association for oesophageal AC (OR 1.6 95% CI 0.9-2.7). Dose-response and duration-response relationships observed for gastric cardia AC and oesophageal SCC only.	National population-based case-control study Frequency matching of cases with controls on age and gender. Participation rates were higher for some cases (73-83%) than for controls (73%), and about 3% (23) of cases and 19% (210) of control refused to participate. This may have introduced bias of unknown direction. Authors state that analysis of 24 controls who had initially refused to participate suggested that their smoking and alcohol habits were strikingly similar to those of participants (data not reported). Comprehensive and rapid case ascertainment attempted with most cases interviewed shortly after diagnosis. However, 116 (15%) of cases had died or become too ill to be interviewed. Exposure status comprehensively measured. Recall bias for retrospective accounts of snus exposure possible. Interviewers were not blind to case/control status, were blind to study hypotheses, not reported if blind to coding. Outcomes histologically confirmed. Reference group (never snus users) for relative risks for ever snus use included smokers which may have lead to an underestimate of risk. Very thorough investigation of potential confounders. Given the number of statistical tests performed, some positive findings, particularly results of borderline significance for point estimates in the absence of trends, could be the result of type I error and may be chance findings. Non-industry funding sources.

Key: BMI = Body Mass Index, CI = confidence interval, gastric cardia AC = gastric cardia adenocarcinoma, OR = Odds Ratio, AC = adenocarcinoma , SCC = squamous cell carcinoma

Table 4. **Evidence table of the impact of snus on risk for oral, neck and gastro-intestinal cancers** *(continued)*

Study & aims	Study and sample characteristics	Measures of exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Lagergren et al. 2000) **Country:** Sweden *Continued*	**Exclusion criteria**: Born abroad, had mental or physical impediments precluding interview, advanced malignant disease or early death, could not be located. **Observation time:** Recruitment period 1995-1997		**Author conclusions:** 'We found no strong association between snuff dipping and any of the 3 cancer types.'	

Key: BMI = Body Mass Index, CI = confidence interval, gastric cardia AC = gastric cardia adenocarcinoma, OR = Odds Ratio, AC = adenocarcinoma , SCC = squamous cell carcinoma

Table 4.   Evidence table of the impact of snus on risk for oral, neck and gastro-intestinal cancers *(continued)*

Study & aims	Study and sample characteristics	Measures of exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Rosenquist et al. 2005) **Country:** Sweden **Study aims:** 'To establish the risk estimates for tobacco in terms of smoking and alcohol consumption and to evaluate whether Swedish moist snuff is a risk factor for oropharyngeal squamous cell carcinoma (OOSCC).' **Source of funding:** Cancer Foundation of Malmö University Hospital, Gunnar Nilsson Cancer Foundation, Berta Kamprad Foundation, Swedish Dental Society, Faculty of Odontology in Malmö University, Alfred Österlund Foundation, Swedish Cancer Society, King Gustaf V Jubillee fund.	**Design:** Case-control **Level of evidence:** III.3 **Exposure:** Used moist oral Swedish snuff (snus) **Population:** Inhabitants of the Southern Healthcare region of Sweden between September 2000 and January 2004. 132 cases (41 females, 91 males) diagnosed with OOSCC identified in relevant ENT departments of two hospitals in the region, where almost all patients with cancer were treated. Median age was 69 years for women, and 59 years for men. Participation rate of 80%. 320 controls (105 females, 215 males) drawn by stratified random sampling of 3 controls per case from the Swedish Population Registry, matched for age, sex, county of residence. Median age was 66 years for women, and 60 years for men. Participation rate of 81%. Only 44 people (13 cases and 31 controls) were active users of snuff. **Exclusion criteria**: Case with previous cancer (except skin) diagnosis, not born in Sweden. **Observation time:** Recruitment period was September 2000 to January 2004.	**Exposure:** Interviews with nurse/dental surgeon for tobacco exposure, medical history, sexual habits, medication, and lifestyle factors; clinical ratings of mucosal lesions, oral hygiene, and dental status; panoramic radiographs and cell sampling. Retrospective account of lifetime tobacco exposure, including form used, duration, daily consumption, and placement of quid. Ex use of snuff defined as stopped taking snuff at least 6 months before the interview. Use of fermented snuff defined as those who had been snuff users in 1983 or earlier. **Outcomes:** Oropharyngeal squamous cell carcinoma; ICD-7 codes 141 (tongue), 143-5 (floor of the mouth, oral cavity not otherwise specified, oropharynx). **Confounders:** In univariate analyses, pairs matched on age, sex, and country of residence. Multivariate analyses were adjusted for alcohol and tobacco smoking. Oral status, other lifestyle factors (not identified), and HPV infection were said to not have affected any of the conclusions of risk for OOSCC due to snus user.	**Results:** Compared with 'never snus-users', in multivariate analysis adjusting for alcohol and smoking, no risk for OOSCC for current users (OR = 1.1 95% CI, 0.5-2.5), or ex-users (OR = 0.3 95% CI, 0.1-0.9). No increased risk for users of fermented snuff (where use included pre-1984 snus use), for users of more than 10 hours per day, or for users with at least 30 years of use. In analyses investigating a dose-response effect, for higher levels of consumption of >14 g/day there was a non-significant tendency toward an increased risk of OOSCC (OR = 1.7 95% CI, 0.5-5.7). Note: lack of risk for snus contrasted with increased risks found for smoking; eg compared with non-smokers, increased risk of OOSCC for those with total lifetime consumption of >250kg tobacco, OR = 4.7 95% CI 2.4-9.1, adjusted for alcohol use. **Author conclusions:** 'We found no increased risk of OOSCC associated with the use of Swedish moist snuff.' (from abstract)	Population-based case-control study Matching of cases with controls on age, sex, and county of residence. Measurement of exposure undertaken by face-to-face interview. Participation rates were high for both cases (80%) and controls (81%). Exposure status measured through retrospective self-report. No definition given of snuff use to satisfy classification as a snuff user. Not validated. Recall bias possible. Interviewer likely to be aware of case/control status due to nature of examinations performed. Whether coding of answers blind not stated. Snus use investigated thoroughly. Dose-response effects from total consumption investigated. Outcomes clearly defined by ICD code but unclear how confirmed. Reference group (never snus-users) for relative risks for snus use included smokers which may have lead to an underestimate of risk. Number of current oral snuff users was relatively small (*n*=44). Oral status, other lifestyle factors (not identified), and HPV infection said not to have affected conclusions relating to snus use. Not clear whether illicit drug use, nutrition or socio-economic status considered as potential confounders. Non-industry funding source

Key: CI = confidence interval , ICD-7 = International Classification of Diseases – seventh revision, HPV = human papilloma virus, kg = kilograms, OR = Odds Ratio, OOSCC = oropharyngeal squamous cell carcinoma.

Summary and conclusions

Six population-based case-control studies were appraised which considered oral, neck and gastro-intestinal cancer outcomes. Two reported analyses considered males only (Lagergren et al. 2000; Ye et al. 1999) while the other four studies reported on results which were adjusted for gender. The regional areas considered in the study bases varied, ranging from one region (Rosenquist et al. 2005) to the whole of Sweden (Lagergren et al. 2000)). The three earlier studies (Hansson et al. 1994; Lewin et al. 1998; Schildt et al. 1998) received some of their funding from industry sources whereas the three more recent studies did not report receiving industry support. Studies were generally of high quality. Key confounders such as alcohol use were generally controlled for, except in Hansson et al's 1994 study, with particularly extensive adjustment for potential confounders by Lagergren et al (2000).

As seen in **Table 5**, no included study reported a statistically significant association between snus use and oral, neck and gastric cancer, and there was no clear pattern of outcomes varying as a function of cancer type. However, risk estimates lacked precision due to the small numbers in comparison groups. Numbers were restricted in those analyses in an attempt to control for current or previous tobacco use history. Some studies employed reference groups of never snus users, thus including smokers, which may have led to an underestimate of risks for snus users despite attempts to adjust for smoking. However, it is interesting to note that studies with never tobacco users as the reference group reported the lowest risk estimates for snus use (Hansson et al, 1994; Schildt et al, 1998; Ye et al, 1999). While there were no significant effects in the main comparisons, there were some point estimates of borderline significance for analyses exploring different levels of snus exposure (Lagergren et al. 2000; Lewin et al. 1998; Rosenquist et al. 2005; Schildt et al. 1998), particular for moderate levels of exposure. These sub-group analyses were also limited by very small sample sizes and given the number of statistical tests performed these may be chance marginal associations in the absence of linear dose response relationships for snus exposure. In sum, given the lack of statistical power, small increases in risk cannot be ruled out, particularly for at least moderate doses of snus use.

Table 5.   Summary of key results for risks for oral, neck and gastrointestinal cancers associated with snus use

Study	Exposure	Reference	Outcome	Results
Hansson et al. 1994	Snus users	Never tobacco users	gastric cancer	OR = 0.70 (95% CI, 0.47-1.06)
Lewin et al. 1998*	Current snus users (males)	Never snus users (adjusted for smoking) (males)	squamous cell cancers (oral cavity, larynx, oesophagus)	RR=1.0 (95% CI 0.6-1.6)
Schildt et al. 1998	Exclusive snus users (never smoked)	Never tobacco users	squamous cell oral cancer	OR = 0.7 (95% CI, 0.4-1.2)
Ye et al. 1999	Exclusive snus users (never smoked) (males)	Never tobacco users (males)	gastric and cardia cancer	OR = 0.5 (95% CI, 0.2-1.2)
Lagergren et al. 2000	Ever snus users	Never snus users (adjusted for other tobacco use)	oesophageal adenocarcinoma	OR = 1.2 (95% CI 0.7-2.0)
			gastric cardia adenocarcinoma	OR = 1.2 (95% CI 0.8-1.8)
			oesophageal squamous-cell cancers	OR = 1.4 (95% CI 0.9-2.3)
Rosenquist et al. 2005	Current snus users	Never snus users (adjusted for tobacco smoking)	oropharyngeal squamous-cell carcinoma (OOSCC)	OR = 1.1 (95% CI, 0.5-2.5)

* Compared with never tobacco-users, RR for current-users of snus was 3.3 (95% CI, 0.8-12.0). However this analysis lacked precision as there were very few people (9 cases, 10 controls) who had used snuff exclusively (ie never smoked).

In contrast to the lack of statistically significant risks for snus use, significant risks, approaching two to more than four-fold, were associated with smoking and the various cancer types considered in the six

studies. The only exception was in Lagergren et al's study where the OR of 1.6 was of borderline significance for current smoking and oesophageal adenocarcinoma (95% CI 0.9-2.7) (**Table 4, pages 33-34**). Dose-response relationships were also evident in many analyses.

The findings from these generally well-conducted studies are consistent with the conclusion that there is no evidence for strong associations between snus use and oral, neck and gastro-intestinal cancers considered. However, estimates lacked precision and the possibility of small increases of risk associated with snus use cannot be excluded. Nor, given the trends in some studies and significant effect in one, is it possible to rule out a protective effect. At this point it seems reasonable to assume no effect.

CARDIOVASCULAR DISEASE

The search identified six eligible primary research studies which considered cardio-vascular disease outcomes including major manifestations of atherothrombotic disease, myocardial infarction and stroke. Summaries of the appraisal results for each study are presented below in chronological order, followed by the evidence table for all six papers (**Table 6, pages 44-54).**

Huhtasaari et al (1992)

Huhtasaari et al's (1992) population-based case-control study (**Table 6, pages 44-45**) considered risks for myocardial infarction. The study base comprised men aged 35-64 years old living in two northern counties of Sweden (Västerbotten and Norrbotten) and surveyed within the framework of the WHO's MONICA project in 1990. Cases (*n*=585) with an acute myocardial infarction between April 1989 and April 1991 were identified from general practitioners, nine regional acute-care hospitals, discharge registers, and screening of death certificates. A fifth, or 21 per cent of cases were deceased. Controls (*n*=589) were drawn by random sampling from continuously updated population records and group-matched by age and sex.

For surviving cases, tobacco exposure was measured by interviews with a trained nurse unblinded to case/control status. By contrast, controls and family members of deceased cases were asked to complete a questionnaire in local health centres. Participation rates were higher for cases at 93 per cent than controls at 81 per cent. A telephone survey of 40 per cent of non-participating controls suggested that tobacco consumption was similar in both groups, although there were more former smokers in the non-participating group at 48 per cent than the participating controls at 26 per cent. Cardiovascular disease risk factors ,including blood pressure, total cholesterol, and fasting lipids, were also measured.

The study identified 146 men (59 cases and 87 controls) as active regular users of snuff. Compared with 'non tobacco users', the age adjusted odds ratio for myocardial infarction in non-smoking regular snuff users was not significant (OR = 0.89 95% CI, 0.62-1.29). The ORs were non-significant for both younger (35-54 years) and older (55-64 years) age groups. By comparison, again compared with 'non tobacco-users', the age-adjusted odds ratio for myocardial infarction in non snus using regular smokers was significantly increased (OR = 1.87 95% CI, 1.40-2.48). In analyses by age group, the increase was significant for the 55-64 year age group (OR=3.11 95% CI 2.09-4.63), but not in the younger 35-54 year group (OR=1.35, 95% CI 0.87-2.10). In analyses investigating a dose-response effect, there was no clear significant effect for snuff use, but OR was increased for smokers of more than 10 cigarettes per day compared with non-tobacco users (OR=1.77 95% CI 1.31-2.39). In a logistic regression model for MI, with smoking, snuff, low level of education, and age as predictors, snuff use was not significant. Other potential confounders were not adjusted for in analyses, including illicit drug use, nutrition, socio-economic status, alcohol abuse, physical exercise, BMI, CVD history and some cardiovascular disease risk factors.

As with other case-control studies relying on retrospective recall of tobacco exposure, this study was open to recall biases, particularly given the reliance on family members or significant others for exposure data for 21 per cent of deceased cases. Cases or their family members could exaggerate tobacco exposure due to increased awareness and recall of perceived causal events. Such biases would lead to an overestimate of risk attributed to tobacco exposure. However, a limitation more specific to this study was that tobacco use categories used in analyses were somewhat indistinct. Regular tobacco use was defined as smoking or snus use at least once daily, whereas former tobacco use was defined as no longer regularly using snus or

smoking. Cases who may have given up tobacco use due to emergent symptoms just prior to their MI event would therefore be removed from tobacco user groups, and this may dilute an exposure affect on risk in the case group. Moreover, former snus users, former smokers, and occasional smokers were included with never tobacco users in the reference category of non tobacco users, which may increase the risk associated with that category and underestimate relative risks for current snus users compared with this group.

Conclusion

This study had the advantage of comprehensive case ascertainment. However, the results were limited by indistinct tobacco use categories, which may have diluted exposure effects. As the authors acknowledged, the study was underpowered to detect the effects of snus exposure. Confidence in the results would also have been enhanced by adjustment for a wider range of potential confounders and more careful controlling of tobacco use.

Bolinder et al (1994)

The large population-based prospective cohort study of Bolinder et al (1994) (**Table 6, pages 46-47**) considered risks for myocardial infarction. The study base comprised 135,036 Swedish construction industry workers attending preventive health check-up clinics between 1971-1974 who were alive on 1 January 1974. The participation rate for accepting a free check-up in this period was 'about 75 per cent'. Twelve-year follow-up through to 1985 identified cause-specific mortality through record linkage to the nationwide Cause of Death Registry, validated as being almost 100 per cent complete. Specifically considered outcomes included ischemic heart disease, cerebrovascular disorders, all cardiovascular diagnoses and malignant neoplasms. Lung cancer was also investigated to validate the smokeless classification. Cardiovascular disease was the most common cause of death, and ischemic heart disease caused 38 per cent of the deaths in the whole study population. (Note that data on mortality for all cancers, and from all causes, are reported separately in a later section of this chapter).

The study identified 1,672 people aged 35-54 years, and 1,734 aged 55-64 years who were users of snuff at study entry. Questionnaires were completed with the aid of a nurse and measured tobacco habits, ie kind, amount, duration of habit as well as, medical history, medication, BMI, and intermediate CVD risk factors. Snuff users were defined as exclusive current users of snuff. Ex tobacco users were defined as tobacco users who had quit.

A total of 8,293 people died during 12-year follow-up. Women (fewer than 0.5% of the sample), mixed tobacco (snus and smoking) users, and cigar or pipe users were excluded from analyses. Results were adjusted for age. In men, compared with never tobacco users, age-adjusted relative risk was significantly increased for all cardiovascular disease mortality in exclusive snuff users (RR=1.4 95% CI 1.2-1.6). Risks were stated to be higher in younger age groups: for men aged 35-54 years, RR=2.1 (95% CI 1.5-2.9), and for men aged 55 years and over, RR=1.1 (95% CI 1.0-1.4). However, statistical tests were not reported and so it is not clear whether there was a significant age effect.

Risks for cardiovascular disease were increased by an even greater degree in exclusive smokers. For smokers of up to 15 cigarettes a day, RR was 1.8 (95% CI 1.6-2.0), and for smokers of more than 15 cigarettes per day, RR was 1.9 (95% CI 1.7-2.2). In smokers, a dose-response effect was observed, and risks diminished for ex smokers.

The participation rate , ie those attending check-up, was only 75 per cent and the study base included physically fit, actively working construction workers attending health check-up clinics. These aspects could introduce a healthy worker selection for study participants, which could reduce the power to detect CVD outcomes. Another methodological limitation is that tobacco exposure status and duration were classified through self report at baseline only, and not verified again. Changes in tobacco use during follow-up would mean that risk estimates for tobacco exposure were less valid. Thus if tobacco users tended to quit tobacco use during follow-up, risks would be underestimated, whereas if cohort members took up tobacco, the risks would be exaggerated. Bolinder et al (1994) state that most non-smoking smokeless tobacco users had had their habit for over 15 years and argued that such changes may be expected to be small.

Possible confounders including age, region of residence, and several major CVD risk factors at study entry including blood pressure, blood pressure medication, previous cardiac symptoms, diabetes, and BMI were analysed, with relative risk estimates said to have remained essentially unchanged (data not reported). However, other potential confounders including plasma cholesterol, dietary habits, physical exercise, and alcohol abuse, and family history of CVD were not measured. The authors argued that alcohol consumption would have a comparable confounding effect for snuff users as for smokers.

Conclusion

This study was well conducted and the statistical power high given the sample size and number of deaths during follow-up. Another strength was that comparison groups were exclusive snuff users and exclusive smokers, compared with never tobacco users. Dose-response effects for snus use were not investigated, which limits inferences about causality. The dates during which snus was used in this older study, where participants were recruited in the early 1970s and observed to 1985, is also an important consideration. Most of the period when participants used snuff predated the change in about 1983 from fermentation to non-fermentation production methods of snus in Sweden, when TSNA levels may have been reduced (Foulds et al. 2003).

Huhtasaari et al (1999)

Huhtasaari et al's (1999) population-based case-control study (**Table 6, pages 48-49**) is similar to, but did not overlap with, the earlier case-control study appraised above (Huhtasaari et al. 1992). Also representing a sub-study of the WHO's MONICA project, the broader study base here were men aged 25-64 years old (mean 55.6 years) living in northern Sweden between May 1991 and December 1993 inclusive. Cases (*n*=687) were those with first-time acute myocardial infarction (AMI), fatal (death within 28 days) for 17 per cent of the sample. Cases were identified from general practitioners' reports, hospital discharge registers and screening of death certificates. Refusal rates were very low. Controls (*n*=687) were drawn from continuously updated population records and matched for age, by date of birth, and place of living. Case-control pairs were excluded where there was incomplete data on tobacco use in either person, which led to a participation rate of 68 per cent.

Exposure information was collected in a similar way within pairs. Thus surviving cases and their matched controls were interviewed, in person for cases and by telephone for controls, whereas family members of deceased cases and their matching controls were asked to complete a questionnaire. Interviewers were not blind to case/control status. Response rates were slightly higher for the interview (96%) compared with the questionnaire (90%). Detailed exposure information was gathered including habit onset, duration, type, amount of snuff, and whether snuff was taken up upon quitting. Regular tobacco use was defined as smoking or use of snus least once daily. To validate recall by relatives of deceased cases, recall by 51 spouses of surviving patients was assessed two months after hospitalisation. Agreement was very high at 98 per cent for snuff use, but was less accurate for duration at 82 per cent agreement on age of onset. The study identified 149 current regular snuff users (59 cases and 90 controls) who did not currently smoke.

Of 687 cases of AMI identified, there were 117 fatalities. Univariate ORs indicated that, compared with 'never tobacco-users', non-smoking current snuff users were at no increased risk for first MI (OR = 0.96, 95% CI, 0.65-1.41). For former snuff users who had never smoked the risk was also not significant OR = 1.23 (95% CI, 0.54-2.82). These results contrast with dramatically increased risks of first MI for current smokers who were not currently snuff users (OR = 3.65, 95% CI, 2.67-4.99). In conditional logistic regressions, odds ratios were adjusted for various cardiovascular risk factors and social variables including hypertension, diabetes, high cholesterol, family history of early cardiac death, low level of education, and whether married/cohabiting. In a conditional logistic regression excluding smokers, the adjusted OR for acute MI in regular snuff users was 0.58 (95% CI, 0.35-0.94), an unexpected significant protective effect. The adjusted OR for fatal AMI suggested a non significant increased risk of 1.50 (95% CI, 0.45-5.03). The authors caution that the number of fatal cases was small and confidence intervals large for this analysis. Other factors including illicit drug use, nutrition, physical exercise, BMI, and alcohol abuse were not considered as potential confounders. Regular intake of alcohol is usually associated with a decreased risk of AMI. Dose-response effects from daily consumption of snuff were not investigated.

More than a fifth, or 22 per cent of pairs were excluded due to missing information on tobacco use, particularly for fatal pairs, in 60 of 190 pairs) Comparisons between participants and people excluded

because of missing data identified some social status differences between cases, but not between controls. Participating patients were more likely to be married or cohabiting but less likely to have education above primary school, differences which the authors suggest tend to counterbalance each other (presumably in terms of SES). There were no differences between participating and excluded controls.

Recall biases were possible such that cases may be more likely to remember potentially hazardous exposures than controls. A bias in this direction would mean that any effect was overestimated, which would not alter the finding here of no significant risk. The authors state that the median age of starting snuff use was 31.5 years, which they suggest is older than usual tobacco uptake because snuff use commonly commenced upon quitting smoking, for 49 per cent of snuffing cases, and 41 per cent of snuffing referents. This means that current snuff users were often ex-smokers. However, former smokers who had never used snuff were not at increased risk for AMI (OR=1.05 95% CI 0.77-1.43) and therefore former smoking may not have confounded risk for the current snuff user category.

Conclusion

Results suggest no increased risk of acute myocardial infarction for current non-smoking snuff users, or former tobacco users, and possibly a protective effect for regular non-smoking snuff users. These results are in contrast with a significantly increased risk for current smokers who were not using snuff. Risks were adjusted for a range of confounders. A small increased risk in sudden death from MI based on a small number of fatalities could not be excluded.

Asplund et al (2003)

Asplund et al's 2003 nested case-control study (**Table 6, pages 50-51**) combined data from two separate cohorts with cases matched with controls within each. Both cohorts were from northern Sweden and had a mean age of 55 years. The first cohort was from the Northern Sweden MONICA project. A random sample was identified from Västerbotten and Norrbotten counties, aged 25-74 years, stratified for age and sex, and surveyed in 1986, 1990, 1994, and 1999. The mean participation rate was 77 per cent. The other cohort was from the Västerbotten Intervention Project (VIP). Between 1985 and September 2000, all residents in Västerbotten were invited to a health examination when they turned 30, 40, 50, and 60 years of age. The mean participation rate was 60 per cent. For this study, the two cohorts were combined and data from the two cohorts was not compared or analysed separately. Only men were considered. Cases (*n*=276) were first-ever events of stroke, fatal (death within 28 days) or non-fatal, identified from a population-based stroke register between 1985 and 2000. Clearly defined and validated criteria for case ascertainment were used. Controls (*n*=551), recruited two per case, were matched for sex, age, geographical area, year of baseline examination and cohort.

Tobacco exposure was determined based on the initial baseline assessment only, and follow-up data was not reported. Questionnaires were 'harmonised' for both surveys/cohorts, with the VIP cohort using a simplified version of that used for the MONICA cohort. Regular tobacco use was defined as use of smoking or snus at least once daily. The study identified 95 people as current snuff users who were also non-smokers, 42 of whom were exclusive snus users who had never smoked.

Compared with 'never tobacco users', univariate comparisons of risk for first stroke suggested no increased risk for exclusive snuff users who were never smokers (OR = 1.05 95% CI 0.37-2.94), or for current snuff users who did not currently smoke (OR = 1.16 95% CI, 0.60-2.22). In contrast, smokers who did not currently use snuff were at twice the risk for stroke (OR = 2.21 95% CI, 1.29-3.79). In conditional logistic regression analyses, independent variables included hypertension, diabetes, serum cholesterol levels, level of education, and marital status, from baseline assessments. In this analysis, excluding smokers, the adjusted OR of regular snuff use for first stroke, both fatal and non-fatal, was 0.87 (95% CI 0.41-1.83). Other potential confounders including illicit drug use, nutrition, physical exercise, BMI, and alcohol abuse were not considered. Small numbers precluded analyses of risk for subtypes of stroke, or fatal stroke (*n*=22). Dose-response effects were not investigated.

Participation rates were as low as 60 per cent in the VIP cohort with missing tobacco exposure data for 55 subjects (30 cases, 25 controls). Non-participants in the study base may have had higher prevalence of smoking, according to analyses in the MONICA cohort, that would lead to some dilution of exposure in participants. However, as surveying occurred prior to the stroke outcomes, participant bias seems unlikely.

A particular strength of this study was its nested case-control design such that tobacco use was measured through retrospective self-report prior to the stroke event. This precluded recall biases relating to case status. However, as exposure was measured at baseline only, changes in tobacco use during follow-up may have occurred. If tobacco users reduced tobacco use, risk would be underestimated; if they increased use of tobacco, risks would be exaggerated. As the average time between baseline and stroke was only 4.5 years, the authors argue that tobacco habits were likely to have been relatively stable in this period for men who were aged on average 55 years at baseline.

Conclusion

This nested case-control study's findings suggest no difference in risk of stroke for exclusive snuff users compared with double the risk for smokers who were not currently using snuff at baseline. Risks were adjusted for a range of confounders, including cardiovascular risk factors. The use of two cohorts using non-identical exposure collection methods is a limitation, as is the 60 per cent response rate of one cohort which may have introduced a selection bias. The confidence intervals range to over 2.0 and the authors acknowledge that the possibility of an increase in risk for stroke from snus use cannot be ruled out.

Hergens et al (2005)

Hergens et al's 2005 population-based case-control study (**Table 6, page 52**) combined its sample from two 'methodologically equivalent' case-control studies from separate Swedish counties, Stockholm and Västernorrland. The study base comprised men aged 45-70 years living in Stockholm in 1992-1993, and men aged 45-65 years living in Västernorrland County in 1993-1994. Cases (*n*=1,432) were first-ever events of acute myocardial infarction (AMI), fatal (death within 28 days) or non-fatal, identified from county hospital departments of medicine, hospital discharge registers, and the national mortality register. Controls (*n*=1,810 controls) were randomly sampled from each study base after matching for age and hospital catchment area.

Tobacco exposure was measured only by mailed questionnaire that was identical for both counties, followed by telephone interview. Controls and non-fatal cases also attended a medical examination three months after recruitment. For fatal cases (*n*=259, 18 per cent of cases), next of kin answered the questionnaire. Current snus use was defined as using snuff during the last two years. Former snuff use was defined as quitting at least two years before whereas former smokers were those who had quit at least one year before. The study identified 38 people as exclusive current snuff users who had never smoked (7 non-fatal and 3 fatal cases, 28 controls).

Compared with 'never tobacco users', OR for first MI for exclusive never smoking snuff users was 0.73 (95% CI, 0.35-1.5) and for exclusive never snus using smokers was 2.8 95% CI, 2.3-3.4). Analyses limited to either non-fatal cases or fatal cases did not alter the results. The authors stated that adjusting odds ratios for various CVD risk factors including hypertension, diabetes, hyperlipidemia, overweight, physical inactivity and job strain had negligible effect on risk estimates. Other potential confounders including illicit drug use, nutrition, family history of cardiac disease, level of education, and alcohol abuse were not adjusted for.

Exposure status measurement was limited, based on unvalidated self report at baseline. There were no details of snus use duration, apart from being current or former users, or frequency, or daily consumption. Dose-response effects were not investigated. No attempt was made to validate next of kin reports of tobacco exposure, which were relied on for fatal cases. As current use was defined as being for at least the last two years, recall biases relating to changes to tobacco exposure around the time of diagnosis for cases are unlikely. The participation rates were reasonably high at 77 per cent for cases, and 78 per cent for controls, but response rates were only 65 per cent for next of kin of fatal cases.

Conclusion

Results from Hergens et al (2005) suggest no difference in risk of acute myocardial infarction for current never smoking snuff users compared with a significantly increased risk for current smokers who were not using snuff. Risks are well adjusted for a range of confounders including cardiovascular risk factors. The study results controlled for tobacco exposure such that comparison groups were exclusive snuff users and exclusive smokers, compared with never-tobacco-users. However, this reduced the sample sizes in

comparison groups. The number of never smoking snus users was small (*n*=38), and only 10 of these were cases, 3 of which were fatal. The statistical power of ORs for these comparisons is therefore low and likely to be underpowered to detect effects of snus exposure.

Johannson et al (2005)

Johannson et al's 2005 population-based prospective cohort study (**Table 6, pages 53-54**) considered 3,120 men aged 30-74 years who were randomly sampled from the Swedish population resident between 1988 and 1989. Respondents were followed up until the end of 2000, a mean time of 11.2 years, with regard to fatal and non-fatal coronary heart disease. They were identified from national hospital discharge and cause of death registries) The sample excluded people who indicated that their general health was bad or 'anywhere between good and bad' (*n*=907), those hospitalised with a CHD event within the previous two years, those interviewed with aid of relatives, and those with missing data on weight or height.

Exposure data were collected by face-to-face interview as part of the Swedish Annual Level-of-Living Survey. Tobacco use status was established in the initial survey and current use was defined as daily snuff use.

After follow-up there were 277 CHD events. The number of deaths was not reported and data were reported relating to incidence of CHD events. Cox regression models estimated the hazard ratios for fatal and non-fatal CHD, adjusted for age. In men, compared with non-smokers, the age adjusted hazard ratio for coronary heart disease was not significant for exclusive never smoking snuff users (HR=1.62 95% CI 0.70-3.75). Associations were decreased after adjustment for other explanatory variables including physical activity, BMI, diabetes, and hypertension (HR=1.41 95% CI 0.66-3.28). Including socio-economics status in the model reportedly made no difference to results.

Compared with non-smokers, the age adjusted HR for coronary heart disease in daily smokers was significantly increased (HR=2.19 95% CI 1.59-3.03). After adjustment for other explanatory variables, the HR was 2.30 (95% CI 1.66-3.19). An increased risk was also found for those who were both snus users and smokers, with an age adjusted HR of 2.66 (95% CI 1.32-5.36).

For the baseline survey, the participation rate was 78 per cent; 70 per cent of non-participants were refusals whose mortality rates did not differ from respondents, and the remaining 30 per cent could not be located or were too ill to participate and these had a higher mortality risk than respondents. The study also systematically excluded those who reported that their health was not entirely 'good'. For these reasons, the respondents were likely to be healthier than the general population, which may have reduced both the number of CHD events occurring and the number of tobacco users in the sample. A strength of the study in terms of recruitment was that, compared to Bolinder et al's (1994) study of construction workers, this study included a wide range of SES groups in its population-based sample.

While the reliability of self reported tobacco use at baseline was extremely high, changes in tobacco use during follow-up were not recorded and may have biased results. If smokeless users quit tobacco, risk would be underestimated, whereas if they took up tobacco use, risks would be exaggerated. Another study limitation was that snuff use was simply defined as daily use, but frequency, duration or dose of use was not recorded and dose-response relationships were therefore not investigated.

The primary limitation of the study was its small size, with only 107 exclusive snus users identified. While the study did remove former and current smokers from its snus use category in analyses, the referent category of non-smokers included former snus users. Including former snus users in the referent category may have lead to an underestimate of any risk associated with former snus use. In analyses, several potential confounders were considered, although the CVD risk factors were measured by self report, and so were likely to have been underestimated and unreliably quantified. Moreover, other potential confounders including plasma cholesterol, family history of cardiac disease, alcohol abuse, illicit drug use, and nutrition/diet were not measured or adjusted for.

Conclusions

This small cohort study (Johansson et al. 2005) identified no significant increase in risk for coronary heart disease for exclusive (never smoking) snus users, but the confidence intervals were wide, ranging up to

greater than 3.0 and the study lacked statistical power due to the relatively small number of snus users (n=107). The measurement of tobacco exposure was basic and dose-response relationships were not explored. The sample itself, while being nationally recruited, selectively included healthier people which may also have reduced the likelihood of identifying CHD events.

Table 6. **Evidence table of the impact of snus on risk for cardiovascular disease**

Study & aims	Study and sample characteristics	Measures of exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Huhtasaari et al. 1992) **Country:** Sweden **Study aims:** 'To estimate the risk of myocardial infarction in snuff users, cigarette smokers and non-tobacco users in northern Sweden'. **Source of funding:** Swedish Medical Research Council, Heart and Chest Fund, King Gustaf V's and Queen Victoria's Foundation, 1987 Stroke Fund, and the Joint Committee of the Northern Sweden Health Care Region.	**Design:** Case-control **Level of evidence:** III.3 **Exposure:** Regularly used moist oral Swedish snuff (snus) at least once daily **Population:** Men aged 35-64 years old living in two northern counties of Sweden (Västerbotten and Norrbotten) (identified within the framework of the WHO's MONICA project) between April 1989 and April 1991. 585 cases who had had a myocardial infarction identified from general practitioners, 9 acute care hospitals in the region, checks of discharge registers, and screening of death certificates. Participation rate of 93%. Included 21% of sample who were deceased. 589 controls drawn by random sampling from continuously updated population records, stratified by age and sex. Participation rate of 81%. 146 people (59 cases and 87 controls) were active regular users of snuff. (In addition, 104 were former snuff users, and 63 were concomitant smokers and snuff users. **Exclusion criteria:** Controls who had had a myocardial infarction	**Exposure:** Interviews with subject or, where deceased, by family member or significant other. Surviving cases interviewed by trained nurse. Family members of deceased cases, and controls, were asked to complete questionnaire in local health centres. Measures included tobacco habits, social background, medical history, drugs taken, and intermediate CVD risk factors. Retrospective account of tobacco exposure. Non smokers included occasional and never smokers. Regular tobacco use defined as smoking or snus at least once daily. Former tobacco users were former regular users who had now stopped. Data collected on daily consumption to permit investigation of dose-response relationships. **Outcomes:** Acute myocardial infarction (MI) using clearly defined criteria from MONICA protocol.	**Results:** Compared with 'non tobacco-users' (which included ex-snus users and ex-smokers), the age adjusted odds ratio for myocardial infarction in (non-smoking) regular snuff users was not significant (OR = 0.89 95% CI, 0.62-1.29). The ORs were non-significant for both younger (35-54 years) and older age groups (55-64 years). By comparison, also compared with 'non tobacco-users', the age adjusted odds ratio for myocardial infarction in (non-snus-using) regular smokers was significantly increased (OR = 1.87 95% CI, 1.40-2.48). In analyses by age group, the increase was only significant for the older 55-64 year old group (OR=3.11 95% CI 2.09-4.63), and not the younger 35-54 year old group (OR=1.35, 95% CI 0.87-2.10). In analyses investigating a dose-response effect, there was no clear significant effect for snuff use, but OR was increased for smokers of more than 10 cigarettes per day compared with non-tobacco users (OR=1.77 95% CI 1.31-2.39). In a logistic regression model for MI, with smoking, snuff, low level of education, and age as predictors, snuff use was not significant.	Population-based case-control study Measurement of exposure undertaken by face-to-face interview for surviving cases, and questionnaire completion in health centres for deceased case relatives and controls. Participation rates higher for cases (93%) than controls (81%). A telephone survey of 40% of non-participating controls suggested that tobacco consumption was similar in both groups, although there were more former smokers in the non-participating group (48%) than the participating controls (26%). Exposure status measured through retrospective self-report. Tobacco use well defined but not validated. Recall bias possible. Former tobacco use defined as no longer regularly using snus or smoking, therefore cases who may have given up tobacco use at the onset of symptoms would be removed from regular user groups. Interviewers were not blinded to case/control status. Whether coding was blinded was not stated. Dose-response effects from daily consumption investigated. Outcomes clearly defined. The non-tobacco user reference group included ex-snus users and ex-smokers. As cases may have stopped tobacco use around their MI event, they would have been more likely to be classified as former users which would dilute excess risk from tobacco exposure.

Key: CI = confidence interval, CVD = cardiovascular disease, ICD-7 = International Classification of Diseases – seventh revision, MI = myocardial infarction, MONICA = Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases, OR = odds ratio, WHO = World Health Organization

Table 6.   Evidence table of the impact of snus on risk for cardiovascular disease *(continued)*

Study & aims	Study and sample characteristics	Measures of exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Huhtasaari et al. 1992) **Country:** Sweden *Continued*	**Observation time:** Recruitment period for cases was April 1989 to April 1991. Controls were surveyed in 1990.	**Confounders:** Adjusted for smoking, and age. Analyses of MI excluded people who were concomitant smokers and snus users, and users of tobacco other than snus and cigarettes Logistic regression analyses considered low level of education, tobacco use and age.	**Author conclusions:** 'In middle aged men snuff dipping is associated with a lower risk of myocardial infarction than cigarette smoking' 'A considerably larger study than ours is needed to finally rule out any detrimental effects of snuff sipping on the risk of developing ischaemic heart disease and myocardial infarction'.	Authors suggest that the limited study size may have reduced statistical power to detect small effect of tobacco use in the older age group, and precluded analyses of mortality outcomes. Potential confounders including illicit drug use, nutrition, physical exercise socio-economic status and alcohol use not considered. Non-industry funding sources.

Key: CI = confidence interval, CVD = cardiovascular disease, ICD-7 = International Classification of Diseases – seventh revision, MI = myocardial infarction, MONICA = Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases, OR = odds ratio, WHO = World Health Organization

Table 6.   Evidence table of the impact of snus on risk for cardiovascular disease *(continued)*

Study & aims	Study and sample characteristics	Exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Bolinder et al. 1994) **Country:** Sweden **Study Aims:** 'To investigate whether long-term exposure to smokeless tobacco is associated with an excess risk of dying from cardiovascular disease in users compared with nonusers and to compare this potential excess risk among smokeless tobacco users with the corresponding excess risk among cigarette smokers.' **Source of funding:** Swedish Council for Social Research, and the Swedish Heart and Lung Foundation.	**Design:** Prospective cohort **Level of evidence:** II **Exposure:** Exclusive current users of smokeless tobacco (Swedish snuff) **Population:** 135,036 Swedish construction industry workers attending preventive health check-up clinics between 1971-1974 and who were alive on 1 January 1974. Participation rate for check-ups 'about 75%'. 6,297 snus users, 2,891 aged under 35 years, 1,672 aged 35-54 years and 1,734 aged 55-64 years (at study entry) **Exclusion criteria**: Excluded women (less than 0.5% of the sample), and mixed tobacco users and cigar or pipe users. **Observation time:** From date of entry at health check-up (between 1971 and 1974) and followed up to 1985 (12 years).	**Exposure:** Questionnaires (between 1971 and 1974) completed with aid of a nurse. Tobacco use status and duration established at date of entry (first visit). Measures included tobacco habits (kind, amount, duration of habit), medical history, medication, BMI, and intermediate CVD risk factors. Referent category was never tobacco users. Smokers were exclusive current cigarette smokers (excluding former smoking and other tobacco use), categorised by dose (<15 per day, or 15 per day or more). Smokeless/snuff users were exclusive current users. Ex-smokers were exclusive smokers who had quit, categorised by time since quitting (<5 years, and 5 years of more). **Outcomes:** Cause-specific mortality identified through record linkage to the nationwide Cause of Death Registry (said to be almost 100% complete, and validated), classified according to ICD-8. Specifically considered ischemic heart disease, cerebrovascular disorders, all cardiovascular diagnoses, and all malignant neoplasms (outcomes for mortality from all cancers and all causes reported in **Table 8**, p. 58).	**Results:** After follow-up, 8,293 people died, 38% caused by ischemic heart disease (IHD). Compared with non-tobacco users, the age-adjusted relative risks in male exclusive snuff users for death from all cardiovascular disease was 1.4, 95% CI 1.2-1.6. Higher risks were states for younger age groups, however no statistical comparisons were reported to investigate an age effect. For 35-54 year old men, compared with never tobacco-users, exclusive snuff users age-adjusted relative risks for mortality caused by the following outcomes were: - IHD, RR=2.0 95% CI 1.4-2.9 - stroke, RR=1.9 95% CI 0.6-5.7, based on 4 deaths - all cardiovascular disease, RR=2.1 95% CI 1.5-2.9. For men aged 55 years and over: - IHD, RR=1.2 95% CI 1.0-1.5 - stroke, RR=1.2 95% CI 0.7-1.8 - all cardiovascular disease, RR=1.1 95% CI 1.0-1.4. Lung cancer was also investigated to validate the smokeless category based on the expectation that lung cancer would be rare (only 3 case deaths aged over 35 years).	Population-based prospective cohort study Participation rate (attending check-up) was only 75%. Could be a healthy worker effect of physically fit actively working construction workers attending check-up clinics. Tobacco exposure status and duration classified through (unvalidated) self-report at baseline only, and not verified again. Therefore, changes in tobacco use during follow-up not recorded. If smokeless users quit, risk would be underestimated, if they took up smoking, risks would be exaggerated. Authors state that most ST users had had habit without smoking for over 15 years. Whether a minimum snuff use was required to satisfy classification as snuff user not clear. Frequency of use and dose-response relationship explored for cigarettes only. Outcomes clearly defined by ICD-8 codes. The statistical power of the study is high given sample size and deaths, but not for stroke mortality. Potential confounders extensively considered without change to relative risks. However, SES, education level, plasma cholesterol, alcohol use, physical exercise, family history of CVD, and nutrition/diet not considered as potential confounders. Authors argue that alcohol consumption similarly higher in ST users as for smokers. Funded by non-Industry sources.

Key: BMI = Body mass index, CI = Confidence interval, CVD = cardiovascular disease, ICD –8 = International Classification of Diseases eighth edition, IHD = ischemic heart disease, ST = smokeless tobacco

Table 6.   Evidence table of the impact of snus on risk for cardiovascular disease *(continued)*

Study & aims	Study and sample characteristics	Exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Bolinder et al. 1994) **Country:** Sweden *Continued*		**Confounders:** Results adjusted for age. RR essentially unchanged when age, region of residence, blood pressure, blood pressure medication, previous cardiac symptoms, diabetes, and BMI at study entry analysed.	Higher risks for death from all cardiovascular disease were found for exclusive smokers; for smokers of up to 15 cigarettes per day RR=1.8 (95% CI 1.6-2.0), and for smokers of more than 15 cigarettes a day RR=1.9 (95% CI 1.7-2.2). A dose-response effect for smokers observed. Risks diminished for ex-smokers. **Author conclusions:** 'Both smokeless tobacco users and smokers face a higher risk of dying from cardiovascular disease than non users. Although the risk was lower for smokeless tobacco users than for smokers, the excess risk gives cause for preventive actions.'	

Key: BMI = Body mass index, CI = Confidence interval, CVD = cardiovascular disease, ICD –8 = International Classification of Diseases eighth edition, IHD = ischemic heart disease, ST = smokeless tobacco

Table 6.   Evidence table of the impact of snus on risk for cardiovascular disease *(continued)*

Study & aims	Study and sample characteristics	Measures of exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Huhtasaari et al. 1999) **Country:** Sweden **Study aims:** 'To explore whether the use of snuff affects the risk of myocardial infarction (MI)'. **Source of funding:** Swedish Medical Research Council, Heart and Chest Fund, Västerbotten and Norrbotten County Councils, Umeå and Luleå, and the Swedish Public Health Institute.	**Design:** Case-control **Level of evidence:** III.3 **Exposure:** Regularly used moist oral Swedish snuff (snus) at least once daily **Population:** Men aged 25-64 years (mean 55.6 years) old living in two northern counties of Sweden (Västerbotten and Norrbotten) (a sub-study of the WHO's MONICA project) between May 1991 and December 1993 inclusive. 687 cases identified from general practitioners' reports, hospital discharge registers and screening of death certificates. Refusals less than 0.5% per year. Included 17% of sample who were deceased. 687 controls from continuously updated population records, matched for age and place of living. 149 people (59 cases and 90 controls) were exclusive (not smoking) current snuff users. 117 cases fatal (of 687). **Exclusion criteria:** Controls who had had a myocardial infarction. Participants with incomplete data on tobacco use in either person of matched pair. **Observation time:** May 1991 to end of 1993. (does not overlap with Huhtasaari et al, 1994).	**Exposure:** Interviews with subject or, where deceased, by family member. Surviving cases interviewed by trained nurse. Spouses of deceased cases and matching referents completed a questionnaire. Controls matched with surviving cases were interviewed over the telephone by the same trained person. Response rates for interview 96% and questionnaire 90%. Recall validated through comparisons with recall by 51 spouses of surviving patients 2 months after hospitalisation. For snuff use, 98% agreement on current use, 92% on former use, 82% on age of onset, and 90% on whether snuff taken up upon quitting. Retrospective detailed account of lifetime tobacco exposure including onset, duration, type, amount of snuff, and whether snuff was taken up upon quitting (by 49% snuffing cases, and 41% snuffing referents). Regular tobacco use defined as (smoking or snus) at least once daily.	**Results:** Compared with 'never tobacco-users', univariate ORs for first MI for different combinations of snuff use were as follows: - current snuff users who were current non-smokers: OR = 0.96, 95% CI, 0.65-1.41) - current smokers, who were current non-snuffers: OR = 3.65 (95% CI, 2.67-4.99) - current snuffers who were current smokers: OR = 2.66 (95% CI, 1.24-5.71) - former snuff user, never smoked (OR = 1.23, 95% CI, 0.54-2.82) - former snuff user and former smoker: OR = 0.99 (95% CI, 0.62-1.59). In conditional logistic regression, excluding smokers, adjusted OR of regular snuff use for acute MI (fatal and non-fatal): OR = 0.58, (95% CI, 0.35-0.94). In conditional logistic regression, excluding smokers, adjusted OR of regular snuff use for fatal AMI only was 1.50 (95% CI, 0.45-5.03). **Author 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.' (abstract)	Population-based case-control study Measurement of exposure undertaken by same mode (interview or questionnaire) for matched case-referent pairs. 21.8% pairs excluded due to missing information on tobacco use, particularly for fatal pairs (in 60 of 190 pairs). Exposure status measured through retrospective self-report. Tobacco use well defined with several questions but otherwise unvalidated. Spouse recall validated and was high for snuff use but not so reliable for duration of use. Recall bias possible. Median age of starting snuff use was 31.5 years, commonly started upon quitting smoking. This means that snuff users were often ex smokers and the current snuff user category could have included ex smokers. Former tobacco use appears to have been defined as no longer regularly using snus or smoking, therefore cases who may have given up tobacco use at the onset of symptoms would be removed from regular user groups. Interviewer not blinded to case/control status. Whether coding blinded, not stated. Dose-response effects from daily consumption not investigated. Outcomes clearly defined. As cases may have stopped tobacco use around their MI event, they would have been more likely to be classified as former users, which would dilute excess risk from snus user group. Referent was never used tobacco. The authors suggest that the statistical power was low for the analysis of fatal AMI.

Key: AMI = acute myocardial infarction, CI = confidence interval, ICD = International Classification of Diseases, MONICA = Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases, OR = odds ratio, WHO = World Health Organization

Table 6. **Evidence table of the impact of snus on risk for cardiovascular disease** *(continued)*

Study & aims	Study and sample characteristics	Measures of exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Huhtasaari et al. 1999) **Country:** Sweden *Continued*		**Outcomes:** Fatal (death within 28 days) or first-time non-fatal acute myocardial infarction (AMI), and sudden death, using clearly defined criteria from MONICA protocol; ICD codes 410-414. **Confounders:** Men matched for age. Odds ratios adjusted for hypertension, diabetes, high cholesterol, family history of early cardiac death, low level of education, married/cohabitating.		Cardiovascular risk factors adjusted for. Potential confounders including illicit drug use, nutrition, physical exercise, BMI, and alcohol use, were not adjusted for. Non-industry funding source

Key: AMI = acute myocardial infarction, BMI = mody mass index, CI = confidence interval, ICD = International Classification of Diseases, MONICA = Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases, OR = odds ratio, WHO = World Health Organization

Table 6. **Evidence table of the impact of snus on risk for cardiovascular disease** *(continued)*

Study & aims	Study and sample characteristics	Measures of exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Asplund et al. 2003) **Country:** Sweden **Study aims:** 'The purpose of this study was to explore whether the use of snuff, a smokeless tobacco product, increases the risk of stroke in men'. **Source of funding:** Swedish Medical Research Council, Council for Worklife and Social Research, the Heart and Chest Fund, the Foundation for Strategic Research, King Gustaf V's and QueenVictoria's Foundation, and Västerbotten and Norrbotten County Councils.	**Design:** Nested case-control study **Level of evidence:** III.3 **Exposure:** Used moist oral Swedish snuff (snus) at least once daily **Population:** Men aged 25-74 years old (mean age 55 years) living in 2 northern counties of Sweden obtained from 2 cohorts: (i) WHO's MONICA project, where random sample aged 25-74 years, stratified for age and sex, surveyed in 1986, 1990, 1994, and 1999 (mean participation 77.2%). Non-participants have higher prevalence of smoking. (ii) Västerbotten Intervention Project (VIP), where all residents in county invited to a health examination when they turned 30, 40, 50, and 60 years of age. There was a 60% participation rate. 276 cases identified from population-based stroke register. 551 controls (2 per case), matched for sex, age, area of residence, year of baseline examination, and cohort. 95 people (30 cases, 65 controls) were current snuff users, including 53 ex-smokers, and 42 never smokers. **Exclusion criteria**: Women (few used snus). Cases who had cancer during follow-up, or had subarachnoid haemorrhage.	**Exposure:** Questionnaires, 'harmonised' for both surveys/cohorts, measured tobacco exposure (more detailed for MONICA cohort) at baseline. Regular tobacco use defined as (smoking or snus) at least once daily. A former user had quit at least one month previously. Also measured cardiovascular risk factors. **Outcomes:** First-ever events of stroke, fatal (death within 28 days) or non-fatal, using clearly defined criteria from MONICA protocol. 96% of cases confirmed by CT scan, or if fatal, subjected to an autopsy. **Confounders:** Men matched for age, geographical area, follow-up time, and cohort. In multiple logistic regression analyses, snuff dippers excluded in first model, and smokers in second. Independent variables included hypertension, diabetes, serum cholesterol levels, level of education, and marital status (from baseline assessments).	**Results:** There were 22 cases fatalities (of 276) Compared with 'never tobacco-users', univariate ORs for first stroke for exclusive snuff users (never smokers): OR = 1.05 (95% CI 0.37-2.94), for current snuff users (including ex smokers): OR = 1.16 (95% CI, 0.60-2.22), and for smokers (including ex-snuffers: OR = 2.21 (95% CI, 1.29-3.79). In conditional logistic regression, excluding smokers, adjusted OR of regular snuff use for first stroke (fatal and non-fatal): OR = 0.87 (95% CI 0.41-1.83). **Author conclusions:** 'Whereas regular smoking doubles the risk of stroke in men, snuff use is not associated with any apparent excess risk.' (abstract)	Population-based nested case-control study. Sample recruited from 2 cohorts, but matching of cases with controls performed within cohort. Missing data for 55 subjects (30 cases, 25 controls). Missing data more common for men with low level of education (which was not a predictor of stroke in regression analyses). Participation rates were as low as 60%, but as this occurred prior to the stroke outcomes the authors argue that non-participation would 'probably be of similar magnitude in cases and their matched control'. Tobacco use unvalidated but measured through retrospective self-report prior to the event (stroke), therefore removing recall biases due to case status. Exposure measured at baseline only, therefore, changes in tobacco use during follow-up not recorded. If snus users quit smoking, risk would be underestimated; if they took up smoking, risks would be exaggerated. As average time from baseline to stroke was only 4.5 years, the authors argued that tobacco habits are likely to be relatively stable in this period for this age group (mean age at baseline was 55 years). Whether coding blinded, not stated. Outcomes clearly defined and validated. Stroke patients were relatively young; proportion with cardioembolic stroke was low, few had ischemic heart disease and case fatality was 8%. Analyses of risk for subtypes of stroke, or fatal stroke not performed, due to low numbers. Data from 2 cohorts not analysed separately. Dose-response effects from daily consumption not investigated.

Key: AMI = acute myocardial infarction, CI = confidence interval, ICD = International Classification of Diseases, MONICA = Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases, OR = odds ratio, VIP = Västerbotten Intervention Project, WHO = World Health Organization

Table 6. Evidence table of the impact of snus on risk for cardiovascular disease *(continued)*

Study & aims	Study and sample characteristics	Measures of exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Asplund et al. 2003) **Country:** Sweden *Continued*	Controls with a history of myocardial infarction or cancer. Those with missing data on tobacco exposure. **Observation time:** Cases identified between 1985 and 2000.			Various cardiovascular risk factors adjusted for. Potential confounders including illicit drug use, nutrition, physical exercise, BMI, and alcohol use were not adjusted for. Non-industry funding source

Key: AMI = acute myocardial infarction, CI = confidence interval, ICD = International Classification of Diseases, MONICA = Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases, OR = odds ratio, VIP = Västerbotten Intervention Project, WHO = World Health Organization

Table 6. **Evidence table of the impact of snus on risk for cardiovascular disease** *(continued)*

Study & aims	Study and sample characteristics	Measures of exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Hergens et al. 2005) **Country:** Sweden **Study aims:** 'To assess whether long-term use of Swedish smokeless tobacco increases the risk of first-time acute myocardial infarction in men'. **Source of funding:** Swedish Council for Social Research, and the Swedish Council for Work Life, and Stockholm and Västernorrland County Councils.	**Design:** Case-control study **Level of evidence:** III.3 **Exposure:** Used moist oral Swedish snuff (snus) over last two years. **Population:** Men aged 45-70 years old living in Sweden obtained from 2 cohorts: (i) Stockholm Heart Epidemiology Program, Swedish citizens living in Stockholm in 1992-1993 with no previous MI aged 45-70 years; (ii) Västernorrland Heart Epidemiology Program, aged 45-65 years living in Västernorrland County in 1993-1994. 1,432 cases identified from hospital departments of medicine, hospital discharge registers, and the national mortality register. Included 18% of sample who were deceased. Participation rate was 77%. 1,810 controls randomly sampled from study base after matching for age and hospital catchment area. Participation rate was 78%. 38 exclusive (never smoking) current snus users (7 non-fatal and 3 fatal cases, 28 controls). 259 fatalities (of 1432 cases). **Exclusion criteria**: Controls who had had a myocardial infarction. Participants with incomplete data on tobacco use. **Observation time:** Cases identified in 1992 -1994	**Exposure:** Mailed questionnaires sent to non-fatal cases and controls, followed by telephone interview. Also attended medical examination 3 months after recruitment. For fatal cases, next of kin answered questionnaire. Current snus users were those who reportedly had been using snuff in the last two years. Former snuff use defined as quitting >2 years before, former smokers quit 1 year before. Comparisons between exclusive never smoking current snuff users, exclusive never snus using current smokers, with never-tobacco-users (referent). **Outcomes:** First-time fatal (death within 28 days) or non-fatal acute myocardial infarction (AMI). **Confounders:** Men matched for age and hospital catchment area. Stated that adjusting odds ratios for hypertension, diabetes, hyperlipidemia, overweight, physical inactivity, and job strain had negligible effect on risk estimates.	**Results:** Compared with 'never tobacco users', OR for first MI for exclusive snuff users was 0.73 (95% CI, 0.35-1.5) and for exclusive smokers was 2.8 (95% CI, 2.3-3.4). Analyses limited to either non-fatal cases or fatal cases did not alter the results. For non-fatal MI (*n*=1173 cases), compared with 'never tobacco-users', OR for first non-fatal MI for exclusive snuff users was 0.59(95% CI, 0.25-1.4) based on 7 cases, and for exclusive smokers was 2.7 (95% CI, 2.3-3.4). For fatal MI (*n*=259 cases), compared with 'never tobacco-users', OR for first fatal MI for exclusive snuff users was 1.7(95% CI, 0.48-5.5) based on 3 cases, and for exclusive smokers was 3.6 (95% CI, 2.4-5.2). **Author conclusions:** 'The hypothesis that smokeless tobacco increases the risk for myocardial infarction is not supported in the present study.' (abstract)	Population-based case-control study Exposure status measured through retrospective self-report by questionnaire and telephone interview. Participation rates were 77% among cases (89% among non-fatal, 65% for next of kin of fatal cases), and 78% among controls. No details of snus use duration (apart from being current or former user), frequency, or daily consumption, and unvalidated. Minimum snuff use to satisfy classification as snuff user not defined beyond current use in the last 2 years. Spouse recall not validated. Recall bias possible but current snus use defined as including last 2 years. Not reported whether interviewer blinded to case/control status or whether coding blinded. Dose-response effects not investigated for snus use. Outcomes defined. The number of never smoking snus users were small (*n*=38), with only 10 cases, only 3 of which were fatal. The statistical power of ORs for these comparisons is therefore very low. Some cardiovascular risk factors adjusted for. Potential confounders including illicit drug use, family history of cardiac disease, level education, nutrition, and alcohol use were not adjusted for. Non-industry funding sources.

Key: AMI = acute myocardial infarction, CI = confidence interval, ICD = International Classification of Diseases, OR = odds ratio

Table 6. Evidence table of the impact of snus on risk for cardiovascular disease *(continued)*

Study & aims	Study and sample characteristics	Exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Johansson et al. 2005) **Country:** Sweden **Study aims:** To analyse the association of smoking and snuffing habits and the incidence rate of coronary heart disease (CHD). To examine whether these hypothesised associations remain after adjusting for socio-economic status and the four CHD risk factors: physical inactivity, obesity, diabetes and high blood pressure. **Source of funding:** National Institutes of Health, Knut and Alice Wallenberg Foundation, Stockholm County Council, Karolinska Institute, Swedish Research Council, and the Swedish Council for Working Life and Social Research.	**Design:** Prospective cohort **Level of evidence:** II **Exposure:** Daily, current users of smokeless tobacco (Swedish snuff or snus) **Population:** 3,120 men aged 30-74 years randomly sampled from national non-institutionalised Swedish population between 1988 and 1989. Participation rate of 78% Of 22% non-respondents, 70% were refusals, 30% could not be located or were too ill to participate. 107 exclusive never smoking current daily snus users **Exclusion criteria**: Excluded people who responded that their general health was bad or 'anywhere between good and bad' (*n*=907), those hospitalised with a CHD event within previous 2 years, those interviewed with aid of relatives, those with missing data on weight or height. **Observation time:** From date of entry (between 1988 and 1989) and followed up to death, CHD event or 31 December 2000 (mean time of 11.2 years).	**Exposure:** Interviewed face-to-face by trained interviewers. Tobacco use status established at date of initial survey and determined whether daily current or never snuffers, and current, former or never smokers. Referent category were never-smokers, including former snuffers. No further details of tobacco use or definitions of former use given. **Outcomes:** Time to hospitalisation for fatal or non-fatal CHD event classified as ICD 9 (410-414) and ICD 10 (120-125). CHD events identified from the Swedish National Hospital Discharge Register and the Cause-of-death Register. **Confounders:** Age-adjusted CHD incidence rates (per 10,000 individuals per year) calculated for the follow-up period. Cox regression model estimated the HR for CHD, adjusted for age. Additional models adjusted for other risk factors including physical activity, BMI, diabetes, and hypertension. Including socio-economics status reportedly made no difference.	**Results:** After follow-up, there were 277 CHD events. The number of deaths were not reported and data were reported relating to CHD events. In men, compared with non-smokers, the age adjusted hazard ratio for coronary heart disease was not significant for exclusive (never smoking) snuff users: HR=1.62 95% CI 0.70-3.75. Associations were decreased after adjustment for other explanatory variables (HR=1.41 95% CI 0.66-3.28). Compared with non-smokers, the age adjusted HR for coronary heart disease in daily smokers was significantly increased, HR=2.19 95% CI 1.59-3.03), and was similar after adjustment for other explanatory variables HR=2.30 95% CI 1.66-3.19. Increased risk also found for those who concomitantly were snus users and smokers, with an age adjusted HR of 2.66 (95% CI 1.32-5.36). **Author conclusions:** 'Even though the association between daily snuffing and coronary heart disease was non-significant, the hazard ratio was markedly increased. Therefore smokers should not use smokeless tobacco in order to quit smoking, especially as safer alternatives are available.' 'Such a strategy could lead to concomitant use of both snuff and cigarettes, which was the most hazardous category of tobacco habits in this study.'	Population based prospective cohort study Participation rate of 78%, and 'little or no' loss to follow-up. Of the non-respondents, 30% were too ill to participate, and these had a higher mortality risk than respondents. The study also systematically excluded those who reported that their health was not entirely 'good'. For these reasons, the respondents were likely to be healthier than the general population, which may have reduced both the number of CHD events occurring and the number of tobacco users in the sample. A range of SES groups were represented in the nationwide sample. Refusers had the same mortality risk as non-respondents (not comparison for CHD incidence not reported). Test-retest reliability of self-reported tobacco use extremely high, kappa coefficients of 0.96-0.99. Tobacco exposure status classified through (unvalidated) self-report at baseline only, and not verified again. Therefore, changes in tobacco use during follow-up not recorded. If smokeless users quit, risk would be underestimated, if they took up smoking, risks would be exaggerated. Snuff use defined as daily, but no further details given. Frequency, duration or dose of use not reported and dose-response relationship not explored. Outcomes clearly defined by ICD codes. The statistical power of the study is low given the small sample size, and few number of exclusive snus users (*n*=107). The number of fatal CHD cases was not reported. The referent category were non-smokers, not never tobacco-users, and therefore included former snus users. Former smokers were a separate category. Including former snus users in the referent category may lead to an under-estimate of a snus use effect.

Key: BMI = Body mass index, CI = Confidence interval, CHD = coronary heart disease, HR = hazard ratio, ICD 9 = International Classification of Diseases 9th edition, ICD 10 = International Classification of Diseases 10th edition

Table 6.   Evidence table of the impact of snus on risk for cardiovascular disease *(continued)*

Study & aims	Study and sample characteristics	Exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Johansson et al. 2005) **Country:** Sweden *Continued*				However the number of ex snus users was not reported and may have been small. Several potential confounders considered. However, plasma cholesterol, family history of cardiac disease, alcohol use, illicit drug use, and nutrition/diet were not considered as potential confounders. Hypertension, diabetes and BMI were determined by self report and may be unreliable and underestimated. Funded by non-Industry sources.

Key: BMI = Body mass index, CI = Confidence interval, CHD = coronary heart disease, HR = hazard ratio, ICD 9 = International Classification of Diseases 9th edition, ICD 10 = International Classification of Diseases 10th edition

Summary and conclusions

The search identified six eligible primary research studies that considered cardiovascular disease outcomes. There were two prospective cohort studies (Bolinder et al. 1994; Johansson et al. 2005), one nested case-control study (Asplund et al. 2003), and three population-based case-control studies (Hergens et al. 2005; Huhtasaari et al. 1992; Huhtasaari et al. 1999). All were conducted in Sweden and reported on males only. Three were based on counties in northern Sweden (Asplund et al. 2003; Huhtasaari et al. 1992; Huhtasaari et al. 1999), one was based on two other counties of Sweden (Hergens et al. 2005), and the other two cohort studies (Bolinder et al. 1994; Johansson et al. 2005) considered the whole country as their study base, though Bolinder et al's study was restricted to workers from the construction industry. No studies reported receiving funding from industry sources.

As seen in **Table 7**, risk estimates for a range of CVD outcomes were generally close to 1.0 and were non-significant for five of the six studies. In one of these studies (Johansson et al. 2005), a hazard ratio for risk of coronary heart disease for exclusive snuff users compared with non-smokers, adjusted for several risk factors, was elevated at 1.41 but was non-significant and very imprecise. This small cohort study lacked statistical power due to the low numbers of snus users. In addition, logistic analyses were performed in three studies and did not find snus use a significant predictor for acute myocardial infarction (Huhtasaari et al. 1992; Huhtasaari et al. 1999) or first stroke (Asplund et al. 2003).

In contrast to these findings, the cohort study by Bolinder et al (1994) reported significant excess risks for all cardiovascular disease mortality in exclusive snuff users compared with non tobacco users, during the 12-year follow-up period (RR=1.4 95% CI 1.2-1.6).

Table 7. **Summary of key results for risks for cardiovascular disease associated with snus use**

Study	Exposure	Comparator	Outcome	Results
Huhtasaari et al. 1992	Current, regular, non-smoking snus users	Non tobacco users (includes former tobacco users, occasional smokers)	Myocardial infarction	OR = 0.89 (95% CI, 0.62-1.29)
Bolinder et al. 1994	Exclusive snus users	Never tobacco users	All cardiovascular disease mortality	RR=1.4 (95% CI 1.2-1.6)
Huhtasaari et al. 1999	Current, regular, non-smoking snus users	Never tobacco users	Dirst MI	OR = 0.96 (95% CI, 0.65-1.41)
Asplund et al. 2003	Exclusive snuff users (never smoked)	Never tobacco users	First stroke	OR = 1.05 (95% CI, 0.37-2.94)
	Current, regular, non-smoking snus users			OR = 1.16 (95% CI, 0.60-2.22).
Hergens et al. 2005	Exclusive snuff users (never smoked)	Never tobacco users	First MI	OR = 0.73 (95% CI 0.35-1.5)
Johansson et al. 2005	Exclusive snuff users (never smoked)	Non smokers	Coronary heart disease	HR = 1.41 (95% CI, 0.66-3.28) adjusted for age and risk factors

Associations between smoking and CVD outcomes were also investigated. Smokers were found to have around two-to-three fold excess risks for various outcomes including: acute myocardial infarction (Hergens et al. 2005; Huhtasaari et al. 1992; Huhtasaari et al. 1999); coronary heart disease (Johansson et al. 2005); stroke (Asplund et al. 2003); and deaths from cardiovascular and cerebrovascular disease (Bolinder et al. 1994). Dose response effects were commonly indicated and risks for ex-smokers were diminished (Bolinder et al. 1994) or absent (Huhtasaari et al, 1999).

Most of the evidence from studies appraised here suggests that, in contrast to smoking, there is no evidence for strong associations between use of snus and the prevalence of various CVD outcomes. However, the evidence base was of variable quality and studies were limited by a range of problems to varying degrees. Commonly, there were limited and varying participation rates between groups, imprecise measurement of tobacco exposure, either retrospective in case-control studies or based on baseline assessments only in cohort studies, and a lack of investigation of dose-response relationships for snus use. While cardiovascular intermediate risk factors were often measured and adjusted for,

other potential confounders were commonly not controlled. Alcohol use, illicit drug use and diet were not considered in any of the appraised studies and physical exercise, BMI, family history of CVD, and plasma cholesterol were not measured in several studies. Regular intake of alcohol is associated with a decreased risk of acute myocardial infarction.

Notably, several studies were underpowered to detect small increases in CVD risk for snus users, with imprecise risk estimates surrounded by wide confidence intervals. The possibility of small increases in risk can therefore not be excluded, particularly given the findings of Bolinder et al's 1994 large cohort study. As nicotine has immediate increases in the heart rate, snuff may initiate arrhythmias and enhance the risk of cardiovascular sudden death. It has been suggested that studies published since Bolinder et al's 1994 study have not been designed, or had the statistical power, to detect a small increase in cardiovascular and cerebrovascular disease risk (Asplund 2001; Asplund 2003; Benowitz 1999).

The applicability of this research to snus on the market in Sweden today has also been queried. In Bolinder et al's (1994) study, cohort participants were recruited in the early 1970s, when tobacco exposure was assessed, and observed through to 1985. Most of the period when participants used snuff therefore pre-dated the change in 1983 from fermentation to non-fermentation production methods of snus in Sweden, when TSNA levels may have been reduced (Foulds et al. 2003). By comparison, Asplund et al's 2003 nested case-control study considered cohorts recruited from the mid-1980s and followed up to 1999-2000. Historical exposure to non-fermented, and potentially more toxic, snus is therefore likely to be reduced for more recent cohorts and this may contribute to the varying results.

While Bolinder et al's (1994) findings of an excess risk of death from cardiovascular and cerebrovascular disease associated in snus users have not been replicated, an association cannot be excluded from the evidence base, which is of variable quality and commonly lacked statistical power. The possibility that when snus users have a heart attack it is more likely to be fatal requires further investigation.

OTHER HEALTH EFFECTS

Five primary research papers were identified that investigated the impact of snus on other health effects including, in chronological order of publication: all-cause mortality and all-cancer mortality (Bolinder et al. 1994); inflammatory bowel disease (Persson et al. 1993), pregnancy outcomes (England et al. 2003), diabetes (Eliasson et al. 2004), and malignant lymphomas (Fernberg et al. 2006).

Bolinder et al (1994)

The population-based prospective cohort study of Bolinder et al (1994) (**Table 8, page 58**) considered the effects of tobacco use on mortality outcomes. The study base comprised 135,036 Swedish construction industry workers attending preventive health check-up clinics between 1971 and 1974 who were alive on 1 January 1974. Twelve-year follow-up through to 1985 identified cause-specific mortality through record linkage to the nationwide Cause of Death Registry (validated as almost 100 per cent complete). Specifically considered outcomes included malignant neoplasms, and reported with respect to CVD above, ischemic heart disease, cerebrovascular disorders, and all cardiovascular diagnoses.

The study identified 1,672 people aged 35-54 years, and 1,734 aged 55-64 years who were users of snuff at study entry. Questionnaires were completed with aid of a nurse and measured tobacco habits ie kind, amount, duration of habit as well as medical history, medication, BMI, and intermediate CVD risk factors. Snuff-user was defined as exclusive current use of 'snuff'. Ex tobacco users were defined as tobacco users who had quit.

A total of 8,293 people died during 12-year follow-up. Women, who were fewer than 0.5 per cent of the sample, mixed tobacco (snus and smoking) users, and cigar or pipe users were excluded from analyses, which precluded the investigation of dual use on mortality outcomes. Results were adjusted for age. In men, exclusive snuff users' age-adjusted relative risks for death was significantly increased for all causes (RR=1.4 95% CI 1.3-1.8) compared with never-tobacco-users, but not for all cancers (RR=1.1 95% CI 0.9-1.4). These risks compare with higher RRs for both outcomes when never-

tobacco users were compared with exclusive smokers of more than 15 cigarettes a day: all-cause mortality (RR=2.2 95% CI 2.0-2.4), and all-cancer mortality (RR=2.5 95% CI 2.2-3.0). In smokers, a dose-response effect was observed, and risks diminished for ex-smokers.

Risks of death from all causes were nominally higher for younger age groups, aged 35-54 years compared to those aged 55 years of more. However, statistical tests investigating whether a significant age effect existed were not reported. Lung cancer was also investigated to validate the smokeless classification and was, as expected, rare with only three cases occurring in 3,406 snus users, with a RR of 0.9 (95% CI=0.2-3.0).

The participation rate attending check-up was only 75 per cent and the study base included physically fit actively working construction workers attending check-up clinics. These aspects could introduce a healthy worker selection for study participants. Another methodological limitation is that tobacco exposure status and duration were classified through self-report at baseline only, and not verified again. Changes in tobacco use during follow-up would mean that risk estimates for tobacco exposure were less valid. Thus if tobacco users tended to quit tobacco use during follow-up, risks would be under-estimated, whereas if cohort members took up tobacco, the risks would be exaggerated. Bolinder et al (1994) state that most non-smoking smokeless tobacco users had had their habit for more than 15 years and argued that such changes may be expected to be small.

Possible confounders including age, region of residence and several major CVD risk factors at study entry including blood pressure, blood pressure medication, previous cardiac symptoms, diabetes, and BMI were analysed, with relative risk estimates said to have remained essentially unchanged (data not reported). However, other potential confounders including plasma cholesterol, diet, physical exercise, family history of CVD and alcohol abuse were not measured. The authors argued that alcohol consumption would have a comparable confounding effect for snuff users as for smokers. However, as the referent category were never tobacco users, this does not allay concerns about the lack of adjustment for alcohol consumption.

Conclusion

This cohort study estimated a 40 per cent (RR=1.4 95% CI 1.3-1.8) increased risk of death from snus use compared with never tobacco users. The study was well conducted and the statistical power is high given the sample size and number of deaths during follow-up. Another strength was that comparison groups were exclusive snuff users and exclusive smokers, compared with never tobacco users, although dual users were excluded. The lack of confounding for alcohol and diet is an important study limitation (Foulds et al. 2003) and dose-response effects for snus use were not investigated, which limits inferences about causality. Most of the period when participants used snuff pre-dated the change in 1983 from fermentation to non-fermentation production methods of snus in Sweden, when TSNA levels may have been reduced (Foulds et al. 2003). Therefore results may be less applicable to users of snus currently on the market.

Table 8.   Evidence table of the impact of snus on risk for all-cause cancer and all-cause mortality

Study & aims	Study and sample characteristics	Exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Bolinder et al. 1994) **Country:** Sweden **Study Aims:** 'To investigate whether long-term exposure to smokeless tobacco is associated with an excess risk of dying from cardiovascular disease in users compared with nonusers and to compare this potential excess risk among smokeless tobacco users with the corresponding excess risk among cigarette smokers.' **Source of funding:** Swedish Council for Social Research, and the Swedish Heart and Lung Foundation.	**Design:** Prospective cohort **Level of evidence:** II **Exposure:** Exclusive current users of smokeless tobacco (Swedish snuff or snus) **Population:** 135,036 Swedish construction industry workers, attending preventive health check-up clinics between 1971-1974 and who were alive on 1 January 1974. Participation rate for check-ups 'about 75%'. 6,297 snus users, 2891 aged under 35 years, 1,672 aged 35-54 years and 1,734 aged 55-64 years (at study entry) **Exclusion criteria**: Women (less than 0.5% of the sample). Mixed tobacco users and cigar or pipe users. **Observation time:** From date of entry at health check-up (between 1971 and 1974) and followed up to 1985 (12 years).	**Exposure:** Questionnaires (between 1971 and 1974) completed with aid of a nurse. Tobacco use status and duration established at date of entry (first visit). Measures included tobacco habits (kind, amount, duration of habit), medical history, medication, BMI, and intermediate CVD risk factors. Referent category were never tobacco users. Smokers were exclusive current cigarette smokers (excluding former smoking and other tobacco use), categorised by dose (<15 per day, or 15 per day or more). Smokeless/snuff users were exclusive current users. Ex-smokers were exclusive smokers who had quit, categorised by time since quitting (<5 years, and 5 years or more). **Outcomes:** Cause-specific mortality identified through record linkage to the nationwide Cause of Death Registry (said to be almost 100% complete, and validated), classified according to ICD-8. Specifically considered all malignant neoplasms (and ischemic heart disease, cerebrovascular disorders, and all cardiovascular diagnoses, which are reported in **Table 6** with respect to CVD outcomes). **Confounders:** Results adjusted for age. When age, region of residence, blood pressure, blood pressure medication, previous cardiac symptoms, diabetes, and BMI at study entry analysed, RR essentially unchanged.	**Results:** After follow-up, 8,293 people died. In men, compared with never tobacco users, exclusive snuff users' age-adjusted relative risks for death from the following outcomes were: - all cancer, RR=1.1 95% CI 0.9-1.4 - all causes, RR=1.4 95% CI 1.3-1.8. This contrasts with, again compared with never tobacco users, higher risks for exclusive smokers of more than 15 cigarettes a day as follows: - all cancer, RR=2.5 95% CI 2.2-3.0 - all causes, RR=2.2 95% CI 2.0-2.4 A dose-response effect for smokers observed. Risks diminished for ex-smokers. Higher risks of death from all causes were observed for younger age groups. However statistical tests investigating whether a significant age effect existed were not reported. For 35-54 year old men: RR=1.9 95% CI 1.6-2.4. For men aged 55 years and over: RR=1.2 95% CI 1.0-1.3. Lung cancer was also investigated to validate the smokeless category (only 3 case deaths aged over 35 years). **Author conclusions:** 'Both smokeless tobacco users and smokers face a higher risk of dying from cardiovascular disease than non users. Although the risk was lower for smokeless tobacco users than for smokers, the excess risk gives cause for preventive actions.'	Population-based prospective cohort study Participation rate (attending check-up) was only 75%. Could be a healthy worker effect of physically fit actively working construction workers attending check-up clinics. Authors suggest that this may explain why higher risks observed for younger groups, with healthy worker selection more pronounced for older men. Tobacco exposure status and duration classified through (unvalidated) self-report at baseline only, and not verified again. Therefore, changes in tobacco use during follow-up not recorded. If smokeless users quit, risk would be underestimated, if they took up smoking, risks would be exaggerated. Authors state that most ST users had had habit without smoking for over 15 years. Whether a minimum snuff use was required to satisfy classification as snuff user not clear. Frequency of use and dose-response relationship explored for cigarettes only. Outcomes clearly defined by ICD-8 codes. The statistical power of the study is high given sample size and deaths. Potential confounders extensively considered without change to relative risks. However, SES, education level, plasma cholesterol, alcohol abuse, physical exercise/inactivity, family history of CVD, and nutrition/diet not considered as potential confounders. Authors argue that alcohol consumption similarly higher in ST users as for smokers. Funded by non-Industry sources.

Key: BMI = Body mass index, CI = Confidence interval, CVD = cardiovascular disease, ICD –8 = International Classification of Diseases eighth edition, IHD = ischemic heart disease, ST = smokeless to

Persson et al (1993)

A population-based case-control study (Persson et al. 1993) was identified which considered the effect of snus use on inflammatory bowel disease. The appraisal summary and results are presented in **Table 9, page 60**). This study considered the impact of snus use on inflammatory bowel disease in male inhabitants of Stockholm County. Cases (*n*=145) were randomly selected from patients admitted to all local hospitals with diagnoses of Crohn's Disease and ulcerative colitis between 1980 and 1984. During the same period, the controls (*n*=145) were selected from a register of residents of Stockholm County aged between 15 and 79 years, stratified by age and gender. No other matching was undertaken.

Tobacco exposure was measured by retrospective self-report via questionnaire and supplementary telephone interviews. Participants were asked about snus and cigarette use five years prior, which for 94 per cent of cases was at least one year prior to diagnosis. There was no attempt to validate tobacco exposure or minimise recall bias. Snus use was somewhat vaguely defined as having ever used oral moist snuff regularly, with no information on frequency, quantity or duration of snuff use to permit investigation of dose-response relationships. Diagnoses of Crohn's Disease (*n*=63) and ulcerative colitis (*n*=82) were confirmed from hospital records using strict diagnostic criteria.

Compared with 'non tobacco-users', relative risk estimates for Crohn's Disease were not significantly increased for exclusive ever snuff but never smoked users (adjusted RR = 0.9, 95% CI, 0.3-3.1), or for 'current smokers' who have never regularly used snuff (adjusted RR = 1.1, 95% CI, 0.5-2.3). Similarly for ulcerative colitis, compared with non tobacco-users, relative risk estimates were not significantly increased for exclusive ever snuff users (adjusted RR = 1.1, 95% CI, 0.4-3.1), or for current smokers who had never used snuff (adjusted RR = 0.7, 95% CI, 0.3-1.5). Risks were increased for current smokers who were ever-snus users had increased risk for Crohn's Disease (RR=3.7, 95% CI, 1.1-13.1), and borderline increased risk for ulcerative colitis (RR=3.3, 95% CI, 1.0-10.9). However, these analyses were based on only 14 people.

Conclusions

This population-based case-control study identified no increased risk for Crohn's Disease or ulcerative colitis among users of snuff alone, or of cigarettes alone. The lack of any association for smokers was unexpected and in contrast to previous research. Studies have attributed a three-fold to five-fold higher risk of developing Crohn's Disease to smoking (Rhodes and Thomas 1994), whereas current smoking has been shown to be protective for the development of ulcerative colitis, with a pooled OR of 0.41 (Thomas et al. 2000). The lack of similar smoking-related associations places doubt on the results for snus in this study, which had several limitations. The most significant is likely to be the small sample size for comparisons, with only 11 exclusive snus users and 46 exclusive smokers. There was a low number of cases of Crohn's Disease and ulcerative colitis for exposure groups, eg under 10 for each outcome for exclusive snus users, which would reduce statistical power for risk estimates. Cases and controls were only broadly matched for age and adjustment for other important potential confounders, including socio-economic status, nutrition, or alcohol and illicit drug use, was not mentioned. Tobacco use was poorly defined, unquantified and unvalidated. Measurement of exposure also relied on retrospective self-report of tobacco use five years earlier, allowing for the possibility of recall bias such that tobacco exposure could have been underestimated for cases. These results need to be treated with caution given study limitations. Larger studies, preferably following cohorts prospectively, and using more valid measurement of exposure and adequate adjustment for confounding, are necessary to provide more reliable information on risks for IBD for snus users.

Table 9. **Evidence table of the impact of snus on risk for inflammatory bowel disease**

Study & aims	Study and sample characteristics	Measures of exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Persson et al. 1993) Country: Sweden Study aims: 'To evaluate the relationship of inflammatory bowel disease (IBD) to oral moist snuff use.' Source of funding: Swedish Council for Planning and Coordination of Research, and the Swedish Medical Research Council.	Design: Case-control Level of evidence: III.3 Exposure: Ever regularly used moist oral Swedish snuff (snus) Population: Male residents in Stockholm County aged 15-79 years between 1980 and 1984. 145 cases identified from central register of all hospital admissions in Stockholm county. 147 controls selected from random sample of residents of Stockholm County with listed phone numbers, stratified by age and gender. Only 20 people had ever regularly used snuff exclusively (never smoked), and 46 were current exclusive smokers. Exclusion criteria: Cases whose medical records could not be reviewed within four years of diagnosis. Smokers of pipe or cigars. Observation time: Cases and controls identified between 1980 and 1984. Questionnaire sent out between 1984 and 1987, i.e for cases, up to four years after the date of diagnosis.	Exposure: Retrospective account of tobacco use for previous five years (by questionnaire and supplemented by telephone interview), including (in 94% of cases) period of at least one year prior to diagnosis. Snuff use defined as agreeing to having (ever) used oral moist snuff regularly Outcomes: Confirmed incident cases (from hospital records) of: -Crohn's Disease (n=63) - ulcerative colitis (n=82) Confounders: Relative risks adjusted for age. Cigarette smoking controlled in analyses by reporting on exclusive snuff users.	Results: Compared with 'non tobacco-users', relative risk estimates for Crohn's Disease were not increased for 'exclusive ever-snus users' (adjusted RR = 0.9, 95% CI, 0.3-3.1), or for 'current smokers' who have never used snuff (adjusted RR = 1.1, 95% CI, 0.5-2.3). Compared with non-tobacco-users, relative risk estimates for ulcerative colitis were not increased for exclusive ever snus users (adjusted RR = 1.1, 95% CI, 0.4-3.1), or for current smoker, never snuff users (adjusted RR = 0.7, 95% CI, 0.3-1.5). Current smokers who were ever snus users had increased risk for Crohn's Disease (RR=3.7, 95% CI, 1.1-13.1), and borderline increased risk for ulcerative colitis (RR=3.3, 95% CI, 1.0-10.9). However, analyses based on only 14 people. Author conclusions: 'The RR were not increased for snuff use alone, but a marked potentiation was found among snuff dippers who were also cigarette smokers'	Population-based case-control study Basic matching of cases with controls on age. Tobacco exposure information collected by questionnaire and supplementary telephone follow-up with response rates similar across cases (83% for Crohn's Disease, and 80% for ulcerative colitis) and controls (78%). Exposure status measured through retrospective self-report in vague categories covering 5-year period overlapping with time of diagnosis. Not validated and recall bias possible. Not reported whether interviewers or data coding were blind to case/control status. No data on frequency, quantity or duration of snuff use to permit investigation of dose-response relationships. Outcomes clearly defined. Low incidence of cases of Crohn's Disease and ulcerative colitis for exposure groups (eg under 10 for each outcome for exclusive snus users) which would reduce statistical power. Likewise analyses indicating possible increased risk for dual users were based on only 14 people. Only age and tobacco use considered as potential confounders, and tobacco use was poorly defined and not validated. Adjustment for other potential confounders, including socio-economic status, nutrition, or alcohol and illicit drug use, was not reported. Results from dual (smoking and snus) use were also reported suggesting an increased risk for IBD. Non-industry funding sources.

Key: IBD = inflammatory bowel disease, CI = confidence interval, g = grams, RR = Relative Risk

England et al (2003)

A population-based prospective cohort study (England et al. 2003) was identified which considered adverse pregnancy outcomes of snus use. The appraisal summary and results are presented in **Table 10, page 63**).

This study investigated adverse health outcomes for women exposed to snus in pregnancy. Women who were pregnant and/or delivered singleton infants between 1999 and 2000 were identified from the Swedish birth registry. Tobacco exposure status was determined from information obtained by women's midwives during their first ante-natal visit, which occurred before 15 weeks of gestation in 95 per cent of women. Exposure was not validated. The self-reporting of exposure to potentially harmful substances in pregnancy could be open to reporting biases, particularly given that broadly defined categories of use were employed and snus use was defined as 'daily' use. Self-reporting smoking data can be unreliable in pregnancy as pregnant women advised to quit tend to under-report smoking because of the stigma attached to this practice (Kendrick et al. 1995), and such biases may also apply to snus use. Details on frequency, consistency or duration of use throughout pregnancy were limited to records of current exposure at the ante-natal visit, retrospective recall of use prior to becoming pregnant, and current exposure in late pregnancy, ie 32-34 weeks gestation. Women who reported using tobacco within three months prior to pregnancy, who reported having quit or taken up tobacco use by late pregnancy, or who were combined snus/cigarette users, were excluded from analyses. However, data was incomplete with data on tobacco use in late pregnancy only available for 40 per cent of women.

Mutually exclusive groups of snus users (*n*=789) and cigarette smokers (*n*=11,240) were compared to 'non tobacco-users' (*n*=11,495) on validated measures of adverse birth outcomes including: fetal birth weight adjusted for gestational age, pre-term delivery and preeclampsia. Several confounders were adjusted for in multivariate analyses including maternal age, parity, body mass index, height, gestational age at delivery and infant gender. However, data on other potential confounders was not available including socio-economic status (SES), education, nutrition, comorbidities/general health, alcohol intake and illicit drug use. These factors may be expected to have affected outcomes for smoking use as well as for snuff use.

Compared with non tobacco-users, adjusted mean birth weight was reduced in snus users by 39 grams (95% CI, 6-72g), and reduced for smokers by 190 grams (95% CI, 178-202g). When repeated for the restricted sample of women for whom late pregnancy tobacco status was available, ie 40 per cent of the sample, even greater reductions in birth weight were found for tobacco users. This could be explained by there being unidentified quitters in the original sample of women as quitters were removed only where tobacco status was recorded in late pregnancy. Compared with non tobacco-users, pre-term delivery was increased in snuff users (adjusted OR 1.98, 95% CI 1.46-2.68), and in smokers (adjusted OR 1.57, 95% CI 1.38-2.80), with no difference between snus users and smokers in risk for pre-term delivery. When women with preeclampsia were removed from the analysis, risk for pre-term delivery for snus users was slightly attenuated (adjusted OR 1.79, 95% CI 1.27-2.52). Compared with non tobacco-users, preeclampsia was increased in snus users (adjusted OR 1.58, 95% CI 1.09-2.27, p<0.01), but reduced in smokers (adjusted OR 0.63, 95% CI 0.53-0.75). Analyses for pre-term delivery and preeclampsia were not repeated for the restricted sample as these outcomes confounded with the likelihood of having data available for tobacco use in late pregnancy. However it is possible that analyses for these outcomes underestimate the effect of tobacco use, as for birth-weight, possibly due to the inclusion of unidentified quitters.

Conclusions

Results suggest that snus use was associated with increased risk for adverse pregnancy outcomes, including reduced birth-weight, pre-term delivery and preeclampsia. The risk, compared with non tobacco-users, appeared to be somewhat less for snus users than for smokers for reduced birth weight, was similar for both tobacco users groups for pre-term delivery, and was present for snus users and not smokers for preeclampsia. The authors hypothesise that nicotine is a candidate for causing these adverse pregnancy outcomes, although it was not understood why the risks would vary between snus and smoking, or why the known protective effect of smoking on preeclampsia was not observed for snus. While this prospective cohort study was relatively well conducted, tobacco exposure was not precisely or reliably measured. Possible recall and self-report biases on tobacco use, and the presence

of quitters in some analyses, are likely to lead to an under-estimate of the negative health effects of tobacco use. The possible confounding effects of SES, illicit drug use and alcohol use with smoking and snus use could not be investigated. Further high quality and ideally prospective research is needed to corroborate these findings and explore possible dose-response effects. That said, it is reasonable to tentatively conclude that there are adverse effects and that snus should not be encouraged as a safe alternative to smoking among pregnant women.

Table 10.   Evidence table of the impact of snus on risk for adverse pregnancy outcomes

Study & aims	Study and sample characteristics	Exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(England et al. 2003) **Country:** Sweden **Study Aims:** 'To evaluate the effects of smokeless tobacco use during pregnancy.' **Source of funding:** National Institute of Child Health and Human Development.	**Design:** Prospective cohort **Level of evidence:** III.1 **Exposure:** Daily use of moist oral Swedish snuff (snus) **Population:** Swedish-born women who delivered singleton infants (identified from Swedish Birth Registry) Snuff users = 789 Smokers = 11,240 Nonusers of tobacco = 11,495 **Baseline characteristics:** Differences between comparison groups at baseline such that snuff users and smokers were less likely to be living with a partner, were shorter, had a greater body mass index. These were adjusted for in analyses. **Exclusion criteria**: Excluded mothers of stillborn infants, had congenital malformations, or with missing confounder data. Also excluded mothers whose tobacco use changed between early and late pregnancy, non-tobacco users who reported using tobacco prior to getting pregnant, and combined users of snus and cigarettes. **Observation time:** 3 months before pregnancy until delivery (during 1999-2000)	**Exposure:** Mutually exclusive categories of tobacco use (snuff use daily, 1-9 cigarettes daily, 10 or more cigarettes daily, or non tobacco use) for early pregnancy reported at first ante-natal visit, before 15 weeks of gestation, for 95% of women. Late pregnancy (>36 weeks) exposure also recorded (for 40% of women) and used to exclude women whose tobacco use status had changed (quit, initiated or changed status for tobacco use). Analyses compare exclusive snuff use with exclusive cigarette use. **Outcomes:** In live-born infants: - birth weight (>2 SD below mean, gender-specific fetal weight for gestational age) - preterm delivery (less than 37 weeks gestation, verified by ultrasound scan) - preeclampsia (validated use of ICD-10 codes from hospital discharge notes) **Confounders:** Results adjusted for maternal age, parity, body mass index, height, gestational age at delivery and infant gender. Results only reported for women with complete data on covariates. Living with a partner (as a SES proxy) considered as a confounder but not associated with any outcomes. Cigarette smoking controlled in analyses (by reporting on exclusive snuff users).	**Results:** Compared with 'non tobacco users', adjusted mean birth weight was reduced in snuff users by 39g (95% CI, 6-72g), and reduced for smokers by 190g (95% CI, 178-202g). For restricted sample of women for whom late pregnancy tobacco status was available, the adjusted mean birth weight was reduced in snuff users by 93g (95% CI, 38-147) compared with non tobacco-users. Compared with non tobacco users, pre-term delivery was increased in exclusive snuff users (adjusted OR 1.98, 95% CI 1.46-2.68, p<0.01), and in exclusive smokers (adjusted OR 1.57, 95% CI 1.38-2.80, p<0.01) (no difference between snuff users and smokers). When women with preeclampsia were removed from the analysis, risk for pre term delivery for snuff users was slightly attenuated (adjusted OR 1.79, 95% CI 1.27-2.52, p<0.001). Compared with non tobacco users, preeclampsia was increased in snus users (adjusted OR 1.58, 95% CI 1.09-2.27, p<0.01), but reduced in smokers (adjusted OR 0.63, 95% CI 0.53-0.75, p<0.0001). **Author conclusions:** 'Snuff use was associated with increased risk of pre-term delivery and preeclampsia. Snuff does not appear to be a safe alternative to cigarettes during pregnancy.' (from abstract)'	Population-based prospective cohort study with reasonable sample size. Cases and controls identified in broad categories through self-report in early pregnancy. Not validated. Possibility of recall bias such that cases could possibly underestimate their tobacco use to the midwife. Less than daily use classified as no use. No data on frequency of snuff use. Duration of use over the study period not recorded excepting with respect to whether woman was a snus user in late pregnancy, which was only available for 40% of the sample. Outcomes clearly defined. Several important potential confounders adjusted for, but others were not including socio-economic status (whether partnered used as a weak proxy), education, nutrition, comorbidities, or alcohol and illicit drug use. Analysis for the restricted sample of women for whom late pregnancy tobacco status was available (40% of the total group) revealed even greater reductions in birth weight by tobacco use. This could be explained by there being unidentified quitters in the original sample. Non-industry funding sources.

Key: BMI = Body Mass Index, CI = Confidence interval, g = grams, ICD = International Classification of Diseases, OR = odds ratio, SD = standard deviation, SES = socio-economic status

Eliasson et al (2004)

A prospective cohort study, including cross-sectional data not reported here, (Eliasson et al. 2004) was identified which considered the effect of snus use on diabetes. The appraisal summary and results are presented in **Table 11 (page 65)**. This study was part of the World Health Organization's MONICA study and included participants randomly selected from population registers, stratified for age and gender, in the two most northern counties of Sweden. Three separate population-based cohorts provided baseline data by questionnaire for men aged 24-74 years in 1986, 1990, or 1994 with follow-up for 69.2 per cent in 1999 after 5, 9, and 13 years respectively (mean of 8.7 years, or 15,726 person years). At follow-up, those without diabetes at baseline were categorised into six mutually exclusive tobacco exposure categories based on self-reported exposure at baseline and follow-up (*n*=1,275). Exposure was biochemically validated for a randomly selected subgroup.

Outcomes included incidence of self-reported, clinically diagnosed, known type 2 diabetes, verified from case records, and pathological glucose tolerance (PGT), determined by oral glucose tolerance test). There were no cases in the group of 'exclusive snus users' (therefore precluding exploration of dose-effects. Compared with consistent 'non tobacco-users', the age and follow-up adjusted risk of developing clinically diagnosed type 2 diabetes during follow-up was increased for 'consistent smokers' (adjusted OR 4.63, 95% CI 1.37-15.6), and also increased for 'ex-smokers' (adjusted OR 3.20, 95% CI 1.16-8.81). Compared with non tobacco users, the risk of PGT during follow-up was not increased for 'consistent tobacco-users' of snus or cigarettes) but there was a non-significant trend for increased risk in 'ex-snus users' (OR 1.85, 95% CI 0.60-5.7). Dual use was not investigated as such users were excluded.

Several important potential confounders were adjusted for including age, follow-up, waist circumference and annual percentage weight gain. Family history was not adjusted for, but cross-sectional data in 1999 suggested that family history of diabetes was no more common in snus users than in non users, though it was not clear whether non users included smokers. Adjustment for self-reported leisure time physical activity and alcohol consumption did not significantly alter findings. Duration of use was not measured and date of diagnosis of diabetes was not determined which limited the statistical analyses possible.

The authors raised the possibility that diabetes may be investigated and diagnosed more actively for smokers by general practitioners as part of cardiovascular risk reduction, and that this could inflate risk estimates. It is suggested that this could also apply for snus users. The determination of PGT in the study avoided the possibility of diagnostic bias.

Conclusions

This well conducted and carefully measured study confirmed the accepted association between diabetes and smoking, in both exclusive current smokers and ex-smokers. No significant risk of diabetes was observed for snus users. These conclusions are limited by the small number of cases of diabetes identified during follow-up, with just 27 cases of clinically diagnosed diabetes. This reduces the statistical power of determining accurate risk estimates. The authors also noted that the study participants were 'rather young' and were below the diabetes prone age groups but unfortunately, mean age at entry was not reported. More investigation from longer-term prospective studies is recommended, particularly in light of mixed results from cross-sectional research (Persson et al. 2000).

Table 11. Evidence table of the impact of snus on risk for diabetes

Study & aims	Study and sample characteristics	Exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Eliasson et al. 2004) **Country:** Sweden **Study Aims:** 'To explore the effect of smoking and smokeless tobacco, "snus", on the risk of type 2 diabetes.' **Source of funding:** Swedish Research Council, Research Council for Social Sciences, Heart and Chest Fund, King Gustav V's and Queen Victoria's Foundation, Västerbotten and Norbotten County Councils, Swedish Public Health Institute. Dr Rodu supported in part by an unrestricted gift from the United States Smokeless Tobacco Company (industry). Statement given that there was no financial or personal conflict of interest and sponsors had no influence over the project or paper.	**Design:** Prospective cohort **Level of evidence:** II **Exposure:** Daily use of moist oral Swedish snuff (snus) **Population:** 2,540 men aged 25-74 years, randomly selected from population registers, stratified for age and gender, in the 2 most northern counties of Sweden (as component of the WHO's MONICA study). 78% participation rate. At follow-up (*n*=1,275) included Exclusive snuff users = 103 Exclusive smokers = 112 Exclusive non tobacco users = 585 **Baseline characteristics:** Snus users (current or ex) were younger and ex smokers older and heavier. **Exclusion criteria:** From follow-up analyses, excluded: users of pipes/cigars, those with missing data on tobacco use or diabetes, those with kDM or diabetes at OGTT at baseline (see next column), and those not fitting in 6 tobacco exposure categories (ie excludes combined snus/smoking). **Observation time:** Entry in 1986, 1990, or 1994, with 69.2% of these participants followed up in 1999 after 5, 9, and 13 years respectively (mean 8.7 years).	**Exposure:** Six mutually exclusive groups (ex, current, and never use of snus, and of cigarettes) identified based on tobacco use by questionnaire. Snus use defined as being at least daily use and smokers defined as at least one cigarette per day. In 1990 cohort, self-reported tobacco habits validated in random sample of 321 participants using plasma nicotine and cotonine measures. **Outcomes:** Prevalence and incidence of (i) self-reported clinically-diagnosed, known diabetes mellitus (kDM) (verified as type 2 diabetes from case records in 2002), and of (ii) pathological glucose tolerance (PGT) determined by a 75g OGTT after overnight fast for random subset of 774 participants without kDM. **Confounders:** Results adjusted for age, follow-up, waist circumference, and annual percentage weight gain. Further adjustment for leisure time physical activity and alcohol consumption did not alter direction or significance of results. Cigarette smoking controlled in analyses (by reporting on exclusive snuff users).	**Results:** After average follow-up of 8.7 years, or 15,726 person years, 27 eligible participants developed known diabetes mellitus. Compared with consistent 'non tobacco-users', the age and follow-up adjusted risk of developing clinically diagnosed diabetes during follow-up was increased for 'consistent smokers' with five cases occurring (adjusted OR 4.63, 95% CI 1.37-15.6) (with no attenuation after adjustment of confounders), and was also increased for 'ex-smokers' with 12 cases (adjusted OR 3.20, 95% CI 1.16-8.81). There were no cases in 'exclusive snus users' (dose-effects could therefore not be estimated). Compared with consistent non tobacco-users, the risk of PGT during follow-up was not increased for 'consistent tobacco users' (snus or cigarettes), but there was a non-significant trend for increased risk in 'ex-snus users' with 5 of 20 having PGT (OR 1.85, 95% CI 0.60-5.7). **Author conclusions:** 'The risk of diabetes for snus users was not significantly increased. Smoking was associated with prevalent and incident cases of diabetes. Ex tobacco users tended towards more PGT.' (from abstract)	Population-based cross-sectional and prospective follow-up study (only follow-up data reported here). Reasonably good participation rate at entry and follow-up. However, outcomes reported for only 1,275 of 1,757 followed up, with no breakdown of reasons for omission from analyses. Not reported whether follow-up duration or person years of observation differed between exposure groups. Past and current tobacco exposure classified through biochemically validated self-report at baseline and follow-up. Less than daily use classified as no use. Frequency of snus use and dose-response relationship explored. Duration of use (apart from during follow-up) not measured. Date of diagnosis of kDM not known. Outcomes clearly defined and validated by scrutiny of case records and use of OGTT. Statistical power of analyses limited by small number of new diabetes cases (*n*=27) occurring during the mean follow-up period of 8.7 years. There were fewer than six cases of kDM and of PGT for 'exclusive snus users' or for 'exclusive smokers'. Dual users were explicitly excluded in the study. Several important potential confounders adjusted for. Other potential confounders including family history and comorbidities were not adjusted, but cross-sectional data in 1999 suggested that family history of diabetes was no more common in snus users than non users (not clear whether non users included smokers). Physical activity defined as that done in leisure time only. Supported by non-industry sources, but industry support given to one author (Dr Rodu).

Key: BMI = Body Mass Index, CI = Confidence interval, g = grams, kDM = known diabetes mellitus, ICD = International Classification of Diseases, MONICA = Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases, OGTT = oral glucose tolerance test, OR = odds ratio, PGT = pathological glucose tolerance, WHO = World Health Organization

Fernberg et al (2006)

A large population-based prospective cohort research study investigated Hodgkin's disease (HD)and non-Hodgkin's lymphoma (NHL) (Fernberg et al. 2006). This study (**see Table 12, page 68)** considered 335,612 Swedish construction workers who were regularly invited to attend preventive health check-up clinics between 1971 and 1992 and was the same cohort as used in Bolinder et al's study investigating mortality outcomes. Participation rate for attending check-ups was not stated. Outcomes followed up for 96 per cent of participants were histologically verified incidence of Hodgkin's disease and non-Hodgkin's lymphoma identified from record linkage with the Swedish Cancer Registry, Migration Registry and Cause of Death Registry. After follow-up of, on average, 19.1 years, 1,309 people were diagnosed with NHL, including chronic lymphocytic leukemia, and 205 with HD. Analyses excluded participants visiting the clinic between 1975-1977, when smoking data were not collected, and individuals diagnosed with cancer before study entry.

Tobacco exposure was measured through self-administered questionnaires between 1971 and 1974, and personal interviews with a nurse from 1978 onwards. Not all of the cohort participants attended check-ups more than once. The authors argue that, in order to avoid participation biases, tobacco use status and duration were established at date of entry, on the first visit, only. Tobacco exposure was not validated.

Fewer than 5 per cent were women, and only one woman had ever used snuff, therefore results were only reported for men, of whom 12 per cent had ever used snuff and not smoked, and 30 per cent had ever smoked cigarettes exclusively. Results were adjusted for age, tobacco use and BMI. In men, compared with 'never tobacco-users' at baseline, the adjusted risk of developing NHL during follow-up was not increased for 'exclusive snus users' (IRR 0.77, 95% CI 0.59-1.01), or for 'exclusive cigarette smokers' (IRR 1.00, 95% CI 0.86-1.16). Similarly, compared with never tobacco users, the risk of developing HD was not increased for exclusive snuff users (IRR 0.88, 95% CI 0.49-1.58), or for exclusive cigarette smokers (IRR 1.32, 95% CI 0.91-1.91).

However, in analyses investigating possible dose-response relationships, some point estimates were significant. Compared with never tobacco users, men who had used snuff exclusively for more than 30 years were at significantly increased risk for developing HD, (IRR 3.78 95% CI 1.23-11.60) but not for developing NHL (IRR 0.69, 95% CI 0.41-1.15). The finding of increased risk for HD was based on four cases of snus users. Linear dose-response relationships were not demonstrated for dose or years of smoking. While, compared with never tobacco users, men who smoked 11-20 cigarettes per day at baseline were at increased risk for developing HD (IRR 1.73 95% CI 1.14-2.63), there was no change in risk for men who smoked fewer or more than this dose at baseline. In the absence of consistent linear dose-response trends and the few cases for such analyses, these findings could be the result of type I error and may be chance findings.

The strengths of this study include its large sample size and the prospective nature of collection of exposure data. However, there are several limitations. The participation rate, for attendance at check-ups where exposure data was recorded, is not reported although earlier reports on this cohort noted that 25 per cent of workers did not attend (Bolinder et al. 1994). Tobacco exposure was based on self reporting and given the context of a health check-up, could be open to reporting biases. Of particular concern is the fact that tobacco exposure, ie status, daily dose, and duration, was based on that reported at study entry. This was designed to avoid any potential bias if failure to repeat check-ups was related to tobacco use and outcome of cancer. However, data to support these hypotheses were not reported. Relying on baseline assessment of tobacco exposure in analyses means that any change in tobacco exposure during the study period could not be taken into account in risk estimates. Given the substantial changes in tobacco use in Sweden over the study period in terms of increased snus use, decreased cigarette smoking, and in the age groups where snus use is prevalent, it is likely that tobacco exposure changed over time for this cohort, particularly given the extensive follow-up period of, on average, 19 years. Other confounders not adjusted for include SES, education, other indices of overweight and risk factors such as immunosuppressive status, immunosuppressive therapy, autoimmune diseases and a history of Epstein-Barr infection.

Conclusions

This large prospective cohort study generally did not identify a relationship between snus or smoking and Hodgkin's disease or non-Hodgkin's lymphoma. An exception was the finding of an increased risk for developing HD in long-term snuff users, based on four cases, though such exposure would relate to products that may not be comparable to those available on the market today. However, confidence in these findings is moderated by methodological limitations relating to possible participation biases, reliance on baseline measurement of tobacco exposure, and lack of consideration of some potential confounders. Further research is required to verify a lack of association between tobacco use and Hodgkin's disease or non-Hodgkin's lymphoma.

Table 12.   Evidence table of the impact of snus on risk for malignant lymphomas

Study & aims	Study and sample characteristics	Exposure, outcomes & confounders	Results and author conclusions	Reviewer comments
(Fernberg et al. 2006) **Country:** Sweden **Study Aims:** **(**we have) 'the objective of investigating the role of tobacco use and BMI on development of lymphomas.' **Source of funding:** Funding source not stated. Researchers affiliated with the Karolinska Institutet (Sweden) and the International Agency for Research on Cancer.	**Design:** Prospective cohort **Level of evidence:** II **Exposure:** Use of oral moist Swedish snuff (snus) **Population:** 335,612 construction workers, mean age at entry of 44.6 years (range 14-82), attending preventive health check-up clinics between 1971-1992. On average, cohort members attended 2.6 check-ups. Participation rate for check-ups not stated. Loss to follow-up of 4%. Of males, 28% had ever used moist snuff, and 12% had used snuff exclusively, 30% used cigarettes exclusively. Of females, only one woman had ever used snuff (0.07%), 48% used cigarettes exclusively. **Exclusion criteria**: From follow-up analyses, excluded those participants visiting the clinic between 1975-1977 (when smoking data were not collected), individuals with cancer before study entry, workers with incorrect national identification numbers (assigned to all Swedish residents allowing linkage to registries). **Observation time:** From date of entry (between 1971 and 1992) and 96% followed up to death, emigration, date of cancer diagnosis or December 31st 2000.	**Exposure:** Self-administered questionnaires (between 1971 and 1974) and personal interviews with a nurse of more detailed information on tobacco use (1978 onwards). Not all cohort participants attended check-up more than once and therefore tobacco use status and duration established at date of entry (first visit). **Outcomes:** Histologically verified incidence of Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) identified through record linkage to the nationwide Swedish Cancer Registry, Migration Registry, and Cause of Death Registry. **Confounders:** Fewer than 5% were women, and so results analysed separately for men and women. Results adjusted for age, tobacco use, and BMI.	**Results:** After average follow-up of 19.1 years. 1'309 people were diagnosed with NHL, including chronic lymphocytic leukemia (CLL) and 205 with HD. In men, compared with 'never tobacco users' at baseline, the adjusted risk of developing NHL during follow-up was not increased for 'exclusive snuff users' (IRR 0.77, 95% CI 0.59-1.01), or for 'exclusive cigarette smokers' (IRR 1.00, 95% CI 0.86-1.16). Similarly, compared with never tobacco users, the risk of developing HD was not increased for exclusive snuff users (IRR 0.88, 95% CI 0.49-1.58), or for exclusive cigarette smokers (IRR 1.32, 95% CI 0.91-1.91). Only one female used snus (she did not develop NHL or HD). Compared with never tobacco users, men who had used snuff exclusively for more than 30 years were at significantly increased risk for developing HD (IRR 3.78 95% CI 1.23-11.60, based on 4 cases of snus users), but not for developing NHL (IRR 0.69, 95% CI 0.41-1.15). Linear dose-response relationships not found for dose or years of smoking. One point estimate significant: compared with never tobacco users, men who smoked 11-20 cigarettes per day at baseline were at increased risk for developing HD (IRR 1.73 95% CI 1.14-2.63). No effect for smoking fewer than 11 or more than 20 cigarettes per day. **Author conclusions:** 'No link was found between NHL and usage of smokeless tobacco.' 'Our novel finding of an increased risk of HD with long-term snuff dipping in males needs to be verified by additional studies.'	Population-based prospective cohort study Participation rate (attending check-up) not stated. Could be a healthy worker effect such that those who were more at risk of illness (including snus users) were less likely to attend check-up clinics. Loss to follow-up only 4%. Tobacco exposure status and duration classified through unvalidated self-report at baseline only, and not verified again. Therefore, changes in tobacco use during follow-up not recorded. Minimum snuff use to satisfy classification as snuff user not defined. Frequency of snuff use and dose-response relationship explored based on use at first visit. Outcomes clearly defined by ICD-7 codes. Histologically verified. Outcomes for women not reported here as only one female used snus (she did not develop NHL or HD). Given the number of statistical tests performed, some positive findings, particularly in the absence of dose-response trends and based on few cases, could be the result of type I error and may be chance findings. Other potential confounders not adjusted for including SES, education, other indices of overweight, and risk factors such as immunosuppressive status, immunosuppressive therapy, autoimmune diseases and a history of Epstein-Barr infection. Appears to not have been funded by Industry.

Key: BMI = Body mass index, CI = Confidence interval, CLL = chronic lymphocytic leukemia, ICD 7= International Classification of Diseases seventh edition, HD = Hodgkin's disease, IRR = incidence rate ratios
NHL = non-Hodgkin's lymphoma

Chapter 4: Discussion

SUMMARY OF EVIDENCE

Overview

This report systematically reviewed the international evidence for health effects of using modified smokeless tobacco. Approximately 217 articles were identified by the search strategy. From 71 articles identified as potentially eligible for inclusion and retrieved as full text, a final group of 18 papers was selected for appraisal. These included two systematic reviews and 16 primary studies of which five were cohort and 11 case-control. All primary studies considered Swedish oral moist snuff and were conducted in Sweden. The 16 appraised studies reported on the following areas (note that some studies reported on outcomes within more than one group): head, neck and gastrointestinal cancers (six studies); cardiovascular disease (six studies); other health effects, including inflammatory bowel disease, diabetes, pregnancy outcomes, and malignant lymphomas (four studies); all-cancer mortality outcomes (one study).

Results for included, appraised secondary and primary studies are summarised and discussed below.

Secondary literature

Two systematic reviews were identified which were eligible for inclusion. Discussion in the literature has tended to be in the form of narrative reviews, commentaries, and opinion pieces. While several older reports considered the health risks of smokeless tobacco generally, they did not include any primary studies eligible for review here and were therefore excluded on this basis.

A comprehensive and carefully conducted systematic review of all forms of smokeless tobacco (ST) was undertaken by Critchley and Unal (2003; 2004), funded by the UK's Health Development Agency. The review involved an extensive search strategy and independent appraisal of study quality by two reviewers using extensive checklists. Of papers published since 1980 meeting minimum quality criteria, eight reported on Scandinavian snus, seven of which met criteria for inclusion in the current review. The authors commented on heterogeneity in findings between ST types and regions, concluding that while chewing betel quid and tobacco was associated with a substantial risk of oral cancers in India, most recent studies from the US and Scandinavia did not indicate statistically significant increased health risks. However moderate positive associations cannot be ruled out due to lack of power. The reviewers also commented that many studies were not designed to evaluate ST, few considered non-cancer outcomes, and many had imprecise measurement of ST exposure and poor control of important confounders such as smoking. The reviewers noted that the toxicities of smokeless tobacco have changed over time, observing that the health impacts of newer types would take some years to establish. Recommendations for future research included improved validation of tobacco exposure, provision of trend information, and consideration of risks associated with individual brands.

More recently, Roth, Roth and Liu (2005) conducted a more circumscribed systematic review, funded by Swedish Match (North Europe Division). Its focus was on snus use for harm reduction compared with smoking, and it was limited to reviewing analytic epidemiological studies that provided quantitative risk estimates associated with Swedish snus and cigarette smoking in a single population, using a common references group. A number of unspecified bibliographic databases were employed to identify studies reporting on specific outcomes, which omitted pregnancy outcomes, dental diseases, or diabetes. From seven included papers, all of which are included in the current review, the reviewers concluded that the health risks associated with snus are lower than those associated with smoking. The review was limited by the somewhat selective reporting and interpretation of results, exclusion of important health consequences and the scant critique of methodological limitations in the field.

Head, neck and gastrointestinal cancers

The search identified six eligible primary research studies that considered oral, neck and gastro-intestinal cancer outcomes. Meta-analyses were not possible due to study and outcome heterogeneity. All were population-based case-control studies conducted in Sweden and were generally well conducted and of moderately high quality. No study reported a statistically significantly increased risk for snus users of oral, neck and gastro-intestinal cancer compared to never tobacco users or never snus users, controlling for tobacco use. Risk estimates ranged from 0.5 (Ye et al. 1999) to 1.4 (Lagergren et al. 2000), with most being close to or below 1.0. Risk estimates did not vary as a function of cancer type in any discernible way. There were some point estimates of borderline significance for analyses exploring different levels of snus exposure (Lagergren et al. 2000; Lewin et al. 1998; Rosenquist et al. 2005; Schildt et al. 1998), particularly for moderate levels of exposure. However, these sub-group analyses were limited by very small sample sizes and may be chance effects given the multiple statistical tests performed and the lack of linear dose-response relationships for snus exposure. In contrast to the lack of any strong association of cancer outcomes with snus use, significant cancer risks ranging from 1.7 to greater than four-fold were associated with smoking across the six studies, and dose-response effects were also usually evident.

The findings from the six population-based case-control studies are consistent with the conclusion that there is no evidence for strong associations between snus use and oral, neck and gastro-intestinal cancers considered. However, risk estimates lacked precision due to the low numbers in comparator groups and the possibility of small increases of risk associated with snus use cannot be excluded. As these cancer forms are not very common, it has been suggested that these studies do not have the statistical power to exclude a very modest excess risk (Asplund 2001). Studies reporting on these outcomes for larger numbers of snus users compared with non-tobacco users, and with ex-smokers, given that snus is being suggested as a substitute for smoking, are required to increase the precision of these risk estimates. Results also consistently show that snus use is associated with significantly reduced harm of a range of head, neck and gastrointestinal cancers compared to smoking.

Cardiovascular disease

Six studies were eligible for appraisal in this review reporting on CVD events including myocardial infarction and stroke. Meta-analyses were not possible due to study heterogeneity. Bolinder et al's 12-year follow-up of a large cohort of construction workers undergoing health examinations in the early 1970s found a 40 per cent excess risk of death from cardiovascular and cerebrovascular disease in those who used snus at baseline compared with those who were non tobacco users at baseline. The study base for Bolinder et al's study comprised construction workers attending health-check-ups.

Bolinder et al's findings received some corroboration from the case-control study of Huhtasaari et al (1999). In conditional logistic regression excluding smokers, adjusted OR of regular snuff use for fatal AMI was 1.50 (95% CI, 0.45-5.03) (**Table 6, pages 46-47**). The odds ratio was adjusted for various cardiovascular risk factors and social variables, but not nutrition, physical exercise, BMI or alcohol abuse. The OR was statistically non-significant and was surrounded by wide confidence intervals due to the few deaths overall. However, the similar magnitude of risks between the two studies suggests that a slightly increased risk of sudden death cannot be excluded. Other studies considering fatal outcomes did not have sufficient numbers of fatalities to permit meaningful analyses (Asplund et al. 2003; Hergens et al. 2005) or did not report results separately for fatal and non-fatal outcomes, perhaps due to low mortality during follow-up (Johansson et al. 2005).

Apart from Bolinder et al's study, no significantly increased risks for snus users were found in five studies reporting on later cohorts, including three case-control studies (Hergens et al. 2005; Huhtasaari et al. 1992; Huhtasaari et al. 1999), a nested case-control study (Asplund et al. 2003), and a cohort study (Johansson et al, 2005). These five studies generally suggested risk estimates close to 1.0 for non-fatal and fatal CVD events (see **Table 7, page 55**). In contrast, studies consistently demonstrated strong increases, in the order of two-to-three fold, between smoking and major CVD events, accompanied by evidence of dose-response associations. Therefore, with the exception of Bolinder et al's study, most evidence suggests that there are no strong associations between use of snus and various CVD outcomes. Some researchers have suggested that these results indicate that nicotine absorbed from smokeless tobacco is not a significant risk factor for causing acute cardiovascular events or accelerating coronary heart disease (Asplund 2001; Benowitz 1999).

The excess risks for mortality identified in Bolinder et al's study may be associated with population and exposure characteristics specific to that cohort. Why these results diverge from those of studies of later cohorts are not clearly understood and a number of reasons have been suggested for the discrepancy. As nicotine causes immediate increases in the heart rate, snuff may initiate arrhythmias and enhance the risk of cardiovascular sudden death. It has been suggested that later studies have not been designed, or had the statistical power, to detect a small increase in such risk (Asplund 2001; Asplund 2003; Benowitz 1999). Another reason suggested for variations between the construction worker cohort and more recent cohorts is that the toxicity profile of snus appears to have changed over time, with TSNA levels decreasing by 85 per cent since the 1980s (Osterdahl et al. 2004). Bolinder et al's cohort was recruited in the early 1970s and followed up to 1985, and so most exposure to snus would have occurred prior to the change to non-fermentation method of production in the early 1980s. Tobacco exposure and any attendant health risks may therefore reflect higher TSNA levels in contrast to more recently observed cohorts (Asplund 2001; Asplund 2003).

With respect to internal validity, high quality research with better controlling of confounders such as diet, physical exercise and alcohol use and abuse, and family history of CVD, as well as better measurement of tobacco exposure over time, is required to further understand the potential association between snus use and CVD outcome.

Other health effects

Five other studies considered a range of other health outcomes in this review (discussed below in chronological order of publication): all-cause and all-cancer mortality, inflammatory bowel disease, pregnancy outcomes, diabetes and malignant lymphomas.

All-cause and all-cancer mortality

The large population-based prospective cohort study of Bolinder et al (1994) considered risks for death from all cancers and all causes, as well as cardiovascular and cerebrovascular disease mortality reported above, in male Swedish construction workers recruited between 1971-1974 and followed up for 12 years. Compared with never tobacco users, exclusive snuff users' age-adjusted relative risk for death was significantly increased for all causes (RR=1.4 95% CI 1.3-1.8) but not for all cancers. As expected, lung cancer was extremely rare in snus users. Risks were even greater for exclusive smokers of more than 15 cigarettes a day, such that risks were increased more than two-fold for death from all causes, and for all cancers, compared with never tobacco users. A dose-response effect was observed for smokers and risks were diminished for ex-smokers.

This study was well conducted and the statistical power is high given the sample size and number of deaths during follow-up. However, there were some methodological limitations. First, tobacco exposure status and duration were classified through self-report at baseline only and not verified again, which would not consider changes in tobacco use during the follow-up period of, on average, 12 years. The lack of consideration of the potentially confounding effects of alcohol intake and abuse, diet (Foulds et al. 2003) and family history of cardiovascular disease are also important study limitations. Also, dose-response effects for snus use were not investigated, which limits inferences about causality. Finally, the applicability of this research to snus on the market today has been queried given that almost all observed tobacco use pre-dated the introduction of non-fermentation methods of production of snus in Sweden, and given that TSNA levels have decreased substantially since the early 1980s (Osterdahl et al. 2004). This issue is discussed further shortly.

Despite reservations about aspects of this study, it suggests no increased risk for death from all cancers from snus use, and it provides some evidence for a 40 per cent increased risk of death from all causes in snus users. Further research is needed to investigate CVD risks in other populations and to investigate what diseases may have contributed to the increased risk for all-cause mortality, apart from CVD mortality. This requires further investigation from adequately powered prospective cohort studies which adjust for potential confounders and consider changes to tobacco use over time that is ideally validated.

Inflammatory bowel disease

The case-control study of male inhabitants of Stockholm County by Persson et al (1993) found no association between exclusive snus use and Crohn's Disease or ulcerative colitis. However, it also found no association between these outcomes and smoking, in contrast to previous research that indicated increased risks of current smokers developing Crohn's Disease (Rhodes and Thomas, 1994) and decreased risk of developing ulcerative colitis (Thomas et al. 2000). The pathological processes between smoking and inflammatory bowel disease are unknown but nicotine has been postulated as a factor as it affects cellular immunity and reduces blood flow. Therefore, an association between IBD and snus use, which also contains nicotine, is plausible. Persson et al's study was limited by poor measurement of tobacco exposure and lack of statistical power given low incidence of IBD and very small comparison groups, particularly for exclusive ever snus use. The evidence from this one study of limited quality is therefore not sufficient to draw conclusions about whether snus use affects risks for developing Crohn's Disease or ulcerative colitis.

Pregnancy outcomes

Research on pregnancy outcomes relating to smokeless tobacco is rare. This is possibly because historically, women of reproductive age have tended not to use such products (Savitz et al. 2006). One population-based prospective cohort study identified in this review (England et al. 2003) considered adverse pregnancy outcomes of snus use. The results, adjusted for maternal age, parity, body mass index, height, gestational age at delivery and infant gender, are consistent with the conclusion that snus use was associated with increased risk for adverse pregnancy outcomes compared with non tobacco users. The babies of women who used snus exhibited reduced birth weight (by 39g, 95% CI, 6-72g), and increased risks for both pre-term delivery (adjusted OR 1.98, 95% CI 1.46-2.68), and preeclampsia (adjusted OR 1.58, 95% CI 1.09-2.27). By comparison, reductions in birth weight compared to non tobacco use were greater for smokers than for snus users. Risk estimates were similar for both tobacco user groups for pre-term delivery. While the risk of preeclampsia was unexpectedly increased for snus users, it was reduced for smokers. This is consistent with previous research. As nicotine may play a role in decreasing fetal growth through increasing vaso-constriction and decreasing perfusion through the placenta (Verma et al. 1983), the possibility of an association between mothers' snus use and their babies' birth weight is plausible. However, the authors were uncertain why the risks would vary between snus and smoking, and why the known protective effect of smoking on preeclampsia (Stratton et al. 2001) was not found for snus. While this prospective cohort study was well conducted, tobacco exposure was not precisely or reliably measured, recall and self-report biases may have under-estimated risks of tobacco use, and alcohol use and other possible confounders were not investigated. It can be tentatively concluded that there are adverse effects in pregnancy from the use of snus and that snus use should not be encouraged as a safe alternative to smoking among pregnant women. High quality prospective research is needed to corroborate these findings and explore possible dose-response effects.

Diabetes

A prospective cohort study by Eliasson et al (2004) considered the effect of snus use on diabetes in men recruited from the two most northern counties of Sweden, where snus use is most prevalent. This well-conducted study detected no significant risk of diabetes for snus users, but confirmed the established finding of increased risk for diabetes from smoking. Statistical power was limited by the small number of cases of diabetes identified during follow-up (n=27). Follow-up was 8.7 years on average and the authors noted that the study participants were below the diabetes-prone age groups. Further investigation in prospective studies with longer follow-up is recommended, particularly in light of mixed results from cross-sectional research suggesting a link between snus use and type 2 diabetes (Persson et al. 2000).

Malignant lymphomas

A large population-based prospective cohort research study by Fernberg et al (2006) investigated Hodgkin's disease and non-Hodgkin's lymphoma, including chronic lymphocytic leukemia, in male Swedish construction workers. The study did not identify a relationship between snus and Hodgkin's disease (HD), or non-Hodgkin's lymphoma, or between smoking and these outcomes. Some isolated point estimates were significant but as they were based on very few cases and were not supported by linear dose-response relationships, they may have been chance findings. There were several significant

methodological limitations in the study including possible participation biases, ie a 'healthy worker effect', and lack of consideration of potential confounders. Of particular concern is that the study relied on baseline measurement of tobacco exposure. Observed risks attributed to tobacco exposure, and dose-responses relationships, are likely to be influenced by tobacco use throughout the prolonged observation period of, on average, 19 years, as well as status at baseline. Considering these limitations, the lack of an association between tobacco use and Hodgkin's disease and non-Hodgkin's lymphoma requires corroboration.

KEY LIMITATIONS OF CURRENT RESEARCH

The evidence considered in this review exhibited methodological limitations which are discussed in the critical appraisals in Chapter 3. Some key issues for the field to address in the future are highlighted below.

Range of modified smokeless tobacco products evaluated

The range of products evaluated in robust designs eligible for review was limited to snus, which itself has been a changing product over time. Careful investigation of other modified low-nitrosamine smokeless products and other PREPs is needed to establish whether they offer reduced harm. Non-tobacco products including medicinal nicotine and pharmacotherapy also need to be evaluated as long-term alternatives for inveterate smokers, and ways of making them more acceptable and accessible to smokers explored (Tomar et al. 2003). A Cochrane Collaboration systematic review (Stead et al. 2006) is currently underway relating to interventions to reduce harm from continued tobacco use. It focuses mainly on RCT evaluations of non-tobacco nicotine delivery products, eg inhalator and gum (Ms Lindsay Stead, *personal correspondence,* 27 April 2006)[9].

Range of health outcomes considered

The range of health outcomes investigated in long-term epidemiological studies of snus use is small. The emphasis has been on cancers, particularly of the oropharyngeal region, in light of risks associated with these conditions from conventional smokeless products, and cardiovascular disease, perhaps prompted by the findings of increased cardiovascular and cerebrovascular mortality in snus users found in Bolinder et al's study. Research into oral pathologies has been limited to case series, cross-sectional research, and follow-up studies of snus-induced lesions (Roosaar et al. 2006), and therefore such evidence was excluded from this review due to study design criteria. One prospective cohort study conducted in Norway (Boffetta et al. 2005) considered health risks for pancreatic and other cancers. It was ineligible for inclusion and was not formally appraised as it did not report exclusively on snus but considered a range of smokeless tobacco products determined by a broad survey question, ie 'Do you chew tobacco or do you use a snuff?' (Dr Elisabete Weiderpass, *personal correspondence*, 8 December 2006). Therefore, smokeless tobacco included Norwegian snuff, snuff imported from the US and Sweden, and Norwegian chewing tobacco, known as skrå (Boffetta et al. 2006). The cohort was enrolled in 1966 and Swedish snuff was rarely used in Norway in the beginning of the study period (Ramstrom 2006). Moreover, any snus that was used would not be comparable to products on the market in recent years. Nevertheless, the finding of an increased risk for pancreatic cancer in current and former smokeless tobacco users compared with never users (RR=1.67, 95% CI 1.12-2.50) suggests that further research is required into the possible risks for pancreatic cancer associated with snus use. Other health outcomes, and particularly those which may relate to long-term nicotine use, require investigation.

Exposure measurement

Self-reporting, particularly retrospective, data on tobacco use can be unreliable and biochemical validation was only conducted for a sub-sample of tobacco users in one study appraised here (Eliasson et al. 2004). It is possible that cases may over-estimate their exposure to potential hazards due to their increased awareness and recall of perceived causal events. In contrast to this, tobacco users may under-

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9 It is expected to be published around April 2007 in the Cochrane Database of Systematic Reviews, Issue 2 of the Cochrane Library, 2007 (Ms Lindsay Stead, *personal correspondence*, 10 November 2006).

report their tobacco use in efforts to avoid the stigma and guilt attached to admitting behaviours that may have led to their illness. It is also possible that as symptoms emerge prior to diagnosis, cases reduce or even cease exposure to snus and that recall of earlier exposure is under-estimated. Authors have attempted to reduce these biases by defining ex use as being based on a period that preceded the diagnosis by months or even years. However, this does not address reduced use.

Most longitudinal studies ascertained tobacco exposure at study entry. However, snus use could have changed during follow-up, particularly in cohort studies with long-term follow-up of disease outcomes. A recent prospective cohort study using the MONICA protocol (Rodu et al. 2003) tracked changes in tobacco use over time in Northern Sweden. Findings suggested that snus users tended to have fairly stable habits over medium term follow-up of 5-13 years. For the minority where changes in tobacco use status occurred, they tended toward cessation rather than taking up smoking. By comparison, smokers were much more likely to quit. These data are consistent with the trends over time in Sweden toward substantially lower smoking rates and small increases in snus use. From this survey, relying on exposure data at baseline would suggest that unidentified quitters during follow-up would lead to an under-estimate of effects of exposure, and that this is more likely for smokers than snus users. Such a pattern would mean that the extent of reduced harm from snus use compared with smoking would be underestimated. However, such interpretations are sketchy and the results of studies would be much improved if they provided more detailed, repeated, and ideally validated measures of tobacco exposure throughout the observation period of a prospective cohort study. Such information would also permit some investigation of dose-response relationships for snus use.

Confounders and risk modifiers

Potential confounders were not routinely controlled for or adjusted. Alcohol abuse, illicit drug use, diet, physical exercise, BMI and family history of disease were rarely considered. It is acknowledged that some of these variables may have had similar confounding effects for snus users as for smokers, and as strong associations were nevertheless demonstrated for smoking, confounder effects may not fully explain a lack of increased risk for snus in many studies. There may also be unknown factors specific to the study population that impact on risk, such as oncogenes, tumour suppressors and viruses which impact on the pathogenesis of cancer (Scully 1993).

While studies attempted to control for the confounding effects of smoking, the interaction between snus use and other tobacco use is actually very important to investigate. Dual use is being encouraged by marketing of smokeless tobacco for specific smoke-free situations and may become more popular. (This is discussed in the next section). Most results reported in this review have compared exclusive, never smoking snus users with never tobacco users, and many explicitly excluded dual users from analyses (Bolinder et al. 1994).

Past tobacco use also needs consideration in determining risk estimates. If snus is being taken as a harm reduction product or cessation tool, snus users will usually be ex smokers. Risks for smoking-related diseases in ex smokers take time to diminish. It is important to determine whether continued exposure to tobacco, even one such as snus with apparently lower tobacco-related toxicities, allows for reversibility of carcinogenic events and will not foster carcinogenesis (Shields 2002).

Statistical power

While most studies appraised in this review did not find a statistically significant association between snus and certain health outcomes, studies have tended to be underpowered to rule out a small to moderate excess risk associated with snus use. In attempts to control for the effects of other and past tobacco use, studies were hampered by the small number of exclusive snus users who had never-smoked. On a population level, small increased risks may nevertheless be significant if the uptake of snus use is high and the duration of snus use is long. Therefore it is crucial that accurate risk estimates are obtained.

Study designs

There are limitations in relying on epidemiological evidence, even from well-conducted prospective cohort studies that provide the highest quality evidence. These include that important health outcomes,

particularly cancer incidence and mortality, take decades to appear and require large samples along with carefully conducted study designs. Ascertaining risk can be problematic when the constitution of the snus to which patients are exposed can change over time in response to changes in raw materials, production and consumer preferences. Changes in use influenced by marketing, availability, regulation, and behavioural practices can also occur, including form, eg pouch, quantity, frequency, duration and placement of quid, which will impact on dose-response relationships. The impact of storage time and temperature on levels of harmful constituents of smokeless tobacco also needs to be evaluated (Savitz et al. 2006).

Long-term epidemiological studies need to be supported by *in vitro* cell culture studies, animal studies and human clinical studies (Shields 2002; Stratton et al. 2001). More research into snus's cellular and genetic toxicity can assist in investigating the relationship between specific constituents and disease development (Savitz et al. 2006; Stratton et al. 2001). Shields (2002) advises that panels of biomarkers will be critical in clinical studies and short-term epidemiological studies to allow rapid evaluation of exposure, biologically effective dose and potential harm, particularly for newly developed PREPs where there hasn't been time to conduct long-term studies. In such cases, indirect measures of exposure to toxins and measures of surrogate disease endpoints will be necessary (Hatsukami et al. 2002). Research at the cellular and animal level would also allow investigation into the possibility of antimutagenic compounds and chemoprotective agents in extracts of Swedish snus (Nilsson 2006a). PREPs will also need to be evaluated in different groups of people to explore variations in individual susceptibility to disease through carcinogenic metabolism and DNA repair. How harm-reduction products vary as a function of users' behaviour, use of the product, sex, age, genetics and prior tobacco use needs further investigation (Shields 2002).

Industry funding

Another concern in this field as the involvement of the tobacco industry, which has as a stated goal of maintaining profits, in funding studies and researchers (Boffetta et al. 2006). Issues of scientific independence arise when researchers collaborate with private industry (Fox and Cohen 2002). Four of the 18 research studies appraised in this review (Hansson et al. 1994; Lewin et al. 1998; Roth et al. 2005; Schildt et al. 1998) were partly funded by tobacco industry companies, and Rodu, one of the authors for the included study by Eliasson et al (2004), reported having received financial support from industry sources. While there is no evidence that the studies with industry funding have systematically different results to those that has no industry support, it is possible that subtle biases may creep in to the way research is conducted and interpreted. Researchers who are proponents of snus are also more likely to receive future funding from industry, which may encourage some scientists to be less neutral in reporting their work. That said, partial accounts of research findings and interpretations of data can also be seen in the publications of some passionate snus-sceptics. Indeed, the issue of harm-reduction products has polarised public health researchers and advocates dramatically; at times opponents who are snus proponents have been painted as industry stooges while those who are snus-sceptics have been said to condemn smokers to 'quit or die' (Bates et al. 2003; Pierce 2002; Tomar et al. 2003). Neither stance is an accurate or helpful representation of the complexities of this debate.

Research challenges for harm reduction

Many of these limitations in the current evidence base and gaps in knowledge were highlighted by a conference convened to discuss research challenges ahead for tobacco harm reduction (Hatsukami et al. 2002). The focus of this review is on the current evidence base, rather than providing a programme of future research required. However, a list of specific issues raised at the conference of particular relevance to this review is provided below to illustrate the amount of knowledge lacking in this area:

- identify valid biomarkers or predictors of reduced toxin exposure *in vitro*, in animals, and humans;
- estimate the extent of reduction in tobacco toxin exposure that would lead to reduced harm in health, including what part of smoking-related risk is reversible when smoking is reduced and over what timeframe;
- develop a comprehensive surveillance system to monitor PREP marketing, penetration, uptake, and consequences, to health and prevalence of use of PREP and conventional tobacco products;
- develop both rapid and long-term PREP assessment systems;
- examine the impact of messages and marketing of PREPs on consumer and healthcare provider attitudes, knowledge, perception and beliefs;

- develop ways of communicating an accurate perception of the relative hazards of products and make the product more attractive than more dangerous alternatives while retaining the primary messages of prevention and cessation; and
- consider the regulatory framework and requirements to oversee and monitor PREPs.

APPLICATION OF RESULTS

To consider snus as a potential product for harm reduction requires a consideration of socio-cultural and regulatory issues relating to its acceptability, use and accessibility in countries such as Sweden where it has been studied, and how these may translate to other countries. In addition, the relationship of snus use to the use of cigarettes, ie prevalence of dual regular use and whether snus use is a 'gateway' to smoking, and any role snus may have in smoking cessation by increasing it or delaying it is key to understanding the population impact of snus. While these broader issues were not systematically considered in this current review of epidemiological evidence of health outcomes, key issues are summarised below.

Variations in product

All of the primary research studies included in this review were conducted with Swedish populations. This is not because Swedish snus is only used in Sweden, but because studies of its use elsewhere, such as in other Scandinavian countries and the United States, were effectively excluded for reasons set out in Chapter 1.

An important consideration in applicability of the research appraised from Sweden is the differences in product historically, given that cohorts observed in appraised studies included snuff users with a long history of snus use extending over several decades (Nilsson 2006a). In particular, the older epidemiological studies such as Bolinder et al's (1994) considered exposure to snus that overlapped with the period prior to change to non-fermented production. Participants may have been exposed to products delivering higher quantities of harmful substances than current versions (Foulds et al. 2003). While this factor has been frequently raised in the literature as a possible reason for the lack of consistent findings concerning CVD, only one study appraised here attempted to investigate this issue explicitly. Rosenquist et al (2005) considered whether there was any difference in risk for users of snus pre-1984, when snus was fermented and may have had relatively higher TSNA levels, than from 1984 onwards, when a non-fermentation method of production was employed in Sweden. No increased risk for oropharyngeal squamous cell carcinoma was found for either group, but the samples were small for exclusive users of non-fermented snus (*n*=20), and the fermented group was imprecisely defined, including ex users and current users who had used both fermented and unfermented snus over the years. Further investigation of this issue in Swedish cohorts would be useful.

Results from appraised studies may not be generalisable to products available outside Sweden. Notably, snus products made for the US market, such as Swedish Match's product Exalt, appear to have higher TSNA levels than snus products available to Swedish consumers (Tomar et al. 2003). This has been suggested as evidence for the importance of American taste expectations on product manufacturing (Rodu and Jansson 2004). Of concern in regard to these preferences is the finding that, in an assessment of several brands of US moist snuff, Hoffman et al (1995) found that the best-selling brands delivered the highest concentrations of TSNAs. As manufacturers respond to consumer preferences and economic factors, they may make changes to the type of tobacco, additives and blending ingredients, curing methods, pasteurisation processes and storage requirements. Such modifications are likely to lead to changes in the constituents and the toxicity profile of snus (Tomar et al. 2003). For these reasons, research findings relating to snus of Swedish origin may not be applicable to snuff sold or manufactured elsewhere. The potential role of regulatory controls on production and constituents of modified low-nitrosamine products is discussed shortly.

Variations in acceptability and use

To consider how applicable the results of Swedish-based studies are to other countries, including New Zealand, requires careful consideration of a number of factors. First, ethnic, demographic, social and cultural factors relating to Swedish snus users may not transfer to potential ST users in other countries. As mentioned above, there is still much to be learned about how harm-reduction products may vary as

a function of individual susceptibility through factors including: tobacco use behaviour including dose, duration, frequency, placement, use of other tobacco products, prior tobacco use, etc; sociio-demographic variables including sex, age, genetics, and socio-economic status; physical environmental factors; other confounding behaviours such as alcohol use, diet and physical activity; and physiological state, such as in pregnancy or following a myocardial infarction (Hatsukami et al. 2002; Shields 2002). In New Zealand, where the burden of tobacco-related disease rests heavily on Maori and Pacific Islander smokers (Wilson et al. 2006), the implications and impacts of introducing smokeless tobacco require particular consideration (Bullen et al. 2006).

The way snus is used in Sweden varies from the way smokeless tobacco is used in countries such as the US and such variations may be critical to the products' harm-reducing potential. Portion bags, which permit the use of small doses in mini-pouches, for discreet use, have become more popular in Sweden. Compared with loose moist snuff, the use of portion bags seems to be associated with less pronounced oral mucosal changes and less prevalent gingival recessions (Axell 1993). Swedish snus users also tend to place snus under their upper lip, toward the front of the mouth, whereas in the US, moist snuff tends to be placed between the cheek and gums in the lower rear of the mouth. Compared with US snuff dippers, Swedish snus users have less salivation and a very low need to swallow or expectorate tobacco juice, which may have toxicological advantages to the user (Kozlowski et al. 2003b).

The degree to which snus users also continue to smoke, ie dual or concurrent use, is very important. Data from a recent nationwide representative sample of adult Swedes suggested that dual use is rare with just 2 per cent daily dual use in men and 0 per cent in women (Ramstrom and Foulds 2006). Similarly, a low prevalence rate of dual use, at just 2.2 per cent was found in 2004 for men living in Northern Sweden (Stegmayr et al. 2005). However, such habits of use may not apply to other countries, and in the US concomitant use is not uncommon in men, being present in a sixth of all smokeless tobacco users (Asplund 2003). Dual use is likely to reduce the likelihood of complete cessation and the impact of smoking bans on tobacco use. In this regard, it is of concern that new smokeless products which explicitly target people's concerns about smoking restrictions, or smoking in the presence of their children, have been introduced into the US market, thus seemingly using public health efforts to reduce smoking as marketing opportunities for smokeless tobacco (Henningfield et al. 2002). If snus was promoted as a 'way out' of smoking bans at work or in the home, smoking could be maintained at other times to sustain a dual tobacco habit. This is likely to be a key tactic for companies which manufacture both cigarettes and snus-like smokeless products, such as recent arrivals in the snus market, Philip Morris, BAT and RJ Reynolds. The health consequences of dual use have been rarely considered in the literature; in this review outcomes for dual use were infrequently reported and dual users often excluded from studies, perhaps due to the low prevalence of dual use in Sweden (Ramstrom and Foulds 2006). More research is needed into health risks of dual use and the impact of promoting dual use.

Perhaps of even greater consequence with respect to a possible role of snus in harm reduction is that snus's popularity in Sweden may not transfer to other countries and may relate to local factors. There has been a custom of snus use for many decades in Sweden, and to some extent in the US. However it does not exist in New Zealand and many other countries, where there may be social barriers toward use. That snus is rarely used by women in Sweden also suggests that there are strong cultural prescriptions to use and it has been suggested that endorsement of snus as a harm-reduction strategy could cause social disparity (Fox and Cohen 2002) and is a serious limitation (Henningfield and Fagerstrom 2001). However, use in women is on the rise in Sweden with products being developed which may appeal particularly to female and young consumers. These include the sale of little pink and purple tins offering smaller pinches/pouches of snus[10], with flavourings including vanilla, coffee, lemon, eucalyptus, mint, citrus, flowers and blackcurrant[11]. These dramatic changes in a relatively short space of time suggest that snus can be introduced to new markets and made rapidly popular. However, a potential concern is how these changes appear to have been largely outside of the control of the health community and policy makers, and have been market and industry driven.

In recent years, Swedish Match has not been terribly successful in its attempts to introduce snus into other countries including those such as India, where smokeless tobacco is not banned, and there is a history of traditional use along with few regulatory constraints. Disappointing sales suggest that the

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10 http://www.sweden.se/templates/cs/Article____13429.aspx, accessed on 7 November 2006.

11 http://www.gothiatek.com, accessed on 27 November 2006

product is extremely challenging to sell and give support to the view that removing bans on products like snus would lead to only marginal uptake (Chapman 2007). Nevertheless, the use of oral moist snuff has increased dramatically in both Sweden and the US over the last three decades, and use has shifted to younger cohorts, directed by concerted marketing from the manufacturers. The impact of industry efforts to influence ST use should not be under-estimated.

While some commentators have concluded that 'snus has decreased Swedish male smoking and cancer rates' (Laugesen 2006), a direct causal relationship has not been established with certainty (Savitz et al. 2006; Tomar et al. 2003). As discussed in the review's Background section (**Chapter 1**), the contribution of snus to the low smoking rates in Sweden continues to be the subject of much debate (Henningfield and Fagerstrom 2001; Tomar et al. 2003; Vainio and Weiderpass 2003). Low smoking rates have been achieved in other countries including Australia without harm-reduction products such as snus available (Sweanor 2003), and there is no evidence that the promotion of snus in a naive population would overall lead to a large-scale reduction in cigarette smoking (Martinet et al. 2006).

An important consideration of the applicability of the research appraised here is that the studies evaluate use from cohorts who began using snus at an older age than today's users (Martinet et al. 2006). If young people taking up snus continue to use snus long-term, the health risks could be greater than seen in studies of older cohorts. As mentioned above, risks could also be increased if dual use is more common than it has been historically in Sweden. For these reasons, and given the evolving patterns of product content and form, consumer demographics, and user habits in Sweden, the Swedish experience is one that requires continued monitoring and research.

Variations in accessibility and regulatory controls

While there are many uncertainties surrounding the population impact of making snus more widely available, one can be confident that snus companies would attempt to promote use as much as possible in order to increase profits for their shareholders. The harm-reduction potential of PREPs such as snus is already being exploited by industry to gain market share from other tobacco products. However, given that new snus-like products are being sold by companies which also sell cigarettes, one cannot rely on industry to promote snus as being healthier than cigarettes. The marketing of new snus-like low-nitrosamine smokeless products released in the US in 2006 has tended to focus on the convenience and accessibility of snus in smokefree situations, which could imply a promotion of dual use.

Given that it is not in the tobacco industry's interests to decrease tobacco use, and in the case of companies selling cigarettes as well as snus, to decrease smoking, the success of a harm reduction strategy for snus depends on effective regulation (Savitz et al. 2006). Regulatory controls could include mandatory warning labelling, reporting of constituents, restrictions on marketing and sales to minors, setting maximum toxicity levels, and taxation/price regimes that favour safer products (Bates et al. 2003; Savitz et al. 2006).

The regulation of what information is provided to consumers, and the features of health warnings and content labelling, is contentious and complex. It has been suggested that the public be accurately informed about the extent of tobacco toxins they are exposed to through use of harm reduction products. The Canadian government already requires a measuring and disclosure regime for all tobacco products, including smokeless tobacco (Bates et al. 2003). However the impact of such information on public perceptions of these products also needs to be considered and evaluated as it may affect prevalence of tobacco use (Hatsukami et al. 2004). The challenge is to communicate relative hazard information accurately (Hatsukami et al. 2002), so that 'less harmful' products are not perceived as 'safe' (Savitz et al. 2006). Overstating the harm could prevent smokers switching to low nitrosamine smokeless, whereas understating it could lead nonusers to take up smokeless (Savitz et al. 2006). Balancing the 'safer but not safe' message in the minds of consumers is key.

If advocating harm reduction, it would seem counterproductive to allow smoking consumers the right to make informed choices about their risk, but then deny them the very risk information they need to make these choices. The source of the information would seem key to this debate. Simon Chapman (2007) warns that allowing tobacco companies to provide information about their harm-reduction products could lead to calls to relax advertising bans in countries where they exist, such as New Zealand, or to keep bans at bay in countries such as the US where advertising is currently permitted. To avoid risks of confusing and conflicting messages, or attempts by industry to unravel advertising bans,

and of risks of use by starters and relapsers, Chapman (2007) argues that information should come only from government sources and that access be tightly controlled. This includes precluding access by minors. Restricting information to government sources would also help reduce the risk of industry attempts to target children. While overt marketing to children is banned in Sweden, the US places few limits on marketing and fears have been raised that new products such as *Camel* snus are being marketed specifically to children in promotions[12], prompting renewed calls for regulation of smokeless products in the US[13]. In New Zealand, commercial advertising of tobacco products is banned. Information from government-sponsored agencies could provide relative-harm information in balanced, clear and qualified terms.

Given possible variations in snuff, several researchers have suggested that any harm-reduction claims should only be permitted following regulation of the product itself (Bates et al. 2003; Tomar et al. 2003). Evidence of changes in TSNA levels over time, and in particular through the release of products marketed specifically as being relatively low in TSNA levels, suggests that such characteristics can be largely controlled by the choice of raw material, processing procedures and refrigeration practices (Ramstrom 2000). Production, storage and testing practices could be enforced by regulation and ideally apply to smoked as well as smokeless forms of tobacco (Bates et al. 2003). Specifically, a quality standard could set maximum toxin levels that could be internationally applied, similar to the Swedish Match (industry) GothiaTek standard (Bates et al. 2003). Measures have been called for which would reduce levels of toxins to the lowest levels technically feasible (Nilsson 1998), or at least to the lowest level of any product currently available (Chapman 2007). In the US, where there is currently no government regulation of the product, the manufacturer is not compelled to produce the least hazardous product possible (Tomar et al. 2003). Indeed it is ironic that the manufacturers of the least harmful nicotine products, ie medicinal nicotine, are stringently regulated whereas cigarettes, the most harmful nicotine products, are subject to little regulation (Sweanor 2000). While supporting a regulatory approach, McNeill et al (2006) cautioned that monitoring and research would need to ensure that reduction in, say, TSNA, did not lead to increases in other undesirable substances. The risks of interactive effects are also raised by Chapman, and supported by released industry correspondence about the issue (2007).

The role of price in the accessibility of snus may also be significant. In Sweden, cigarettes are three to four times more expensive than snus based on average daily consumption (Ramstrom 2000), which may contribute to the high prevalence of snus use there. In the US, there are data consistent with the conclusion that, as the price of cigarettes increases through higher cigarette excise tax rates, individuals substitute smokeless tobacco use for smoking and that similarly, higher excise taxes on smokeless tobacco use is associated with reductions in use of smokeless tobacco (Chaloupka et al. 1997; Ohsfeldt et al. 1997). It is therefore interesting that tins of low-nitrosamine snuff, containing 12 packets, being test-marketed in the US by cigarette company Philip Morris are being sold at the same price as a packet of cigarettes[14]. As already mentioned, it is not in the tobacco companies' profit margin motivated interests to divert sales away from cigarettes to smokeless tobacco. In the US, tobacco companies that also sell cigarettes are promoting snus-like products as a means of maintaining tobacco use in situations where smoking is banned. From this perspective, interchangeable use of both products may be enhanced where there is not a price variation. It is worth noting that the unit cost of smokeless tobacco is currently less than that of medicinal nicotine agents in the US, and this may favour its use to consumers (Hatsukami et al. 2004). Governments can influence price, and therefore choice of tobacco type, through the use of differential taxation regimes that favour safer products.

Population impact of modified smokeless tobacco products

Evidence evaluated in this review relates to health risks for the individual, and particularly for the individual with exclusive, regular use of snus compared with (i) non-tobacco use, and (ii) often indirectly, with smoking. Whether risks are increased or decreased upon the introduction of a safer tobacco product depends on transitions in tobacco use. Thus risks may be increased when individuals move from non-tobacco use but may be decreased for smokers moving to snus. Therefore determining net health impacts at the population level requires a determination of the numbers of individuals in each tobacco use pathway and the attendant risks. The tobacco use transition pathways can be

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12 http://www.localnewsdaily.com/news/story.php?story_id=116407139289636400, accessed 23 November 2006.

13 http://newstandardnews.net/content/index.cfm/items/, accessed 27 November 2006.

14 http://abcnews.go.com/Health/story?id=2099026&page=, accessed on 29 November 2006.

categorised as being harm reducing or harm increasing. Those in the harm-reducing pathway are smokers who substitute cigarettes with modified smokeless tobacco, and possibly dual users who smoke less because they supplement cigarettes with snus, with the exception of those who defer quitting because the availability of smokeless blunts the motivation to quit from smoking bans. Those in the harm-increasing pathway include the following: *deferred quitters*, who may decide to use a safer tobacco product when they would otherwise have quit tobacco use completely; *relapsers*, former smokers who resume tobacco use in a smokeless form; and *starters*, who are never smokers who initiate tobacco use in a smokeless form, which in turn may or may not facilitate moving to smoking – the so-called gateway effect. These three pathways may be harm increasing by increasing the number of people who are exposed to harmful tobacco-toxins and/or by extending the period over which individuals maintain their tobacco addiction. The use of the term reduced-exposure rather than reduced-harm in the term potential reduced exposure product (PREP) recognises that the net effect of introducing products that reduce individual exposure may not reduce net harm for the general population. However, net effect also has to consider the number of smokers taking the harm reducing pathway who move to a safer modified smokeless product. For these reasons, the impact of PREPs on initiation of smoking and intention to quit smoking are crucial to any determination of the net population effect of introducing a safer tobacco product. Net effect should be considered not only in terms of the situation at baseline but also in terms of what would have occurred in the absence of PREPs (Hatsukami et al. 2002), something that can only be estimated.

As discussed in Chapter 1, how people may respond to a safer modified smokeless tobacco product such as snus being introduced has been greatly debated in the literature and experiences in Sweden in particular have been scrutinised. While a detailed analysis of this issue is beyond the scope of the current review, it would appear from ecological evidence for Swedish men that the availability of snus can have a net population health gain (Chapman 2007; Fagerstrom and Schildt 2003; Hall 2005; Savitz et al. 2006). However the transferability of the Swedish experience to countries such as New Zealand is another question entirely, for reasons already discussed above. Nevertheless, it is worth considering that, if the use of snus was one-tenth as harmful as smoking, as a recent panel of experts concluded it was in relation to mortality (Levy et al. 2004), then the product would need to be used 10 times more often, taking into account duration of habit as well as number of users, in order to offset its benefit to public health (Fagerstrom and Schildt 2003).

What happens to the population as a whole when harm-reduction strategies are introduced, ie what tobacco use pathways are taken, by whom, and at what age, will depend on the regulatory framework surrounding the products' introduction as well as on the marketing permitted to accompany this introduction (Bates 2001), which may take subtle and insidious forms. Levy et al (2006) convened a panel of experts who were asked to estimate, through an iterative and moderated Delphi approach, the net effect of introducing low nitrosamine smokeless tobacco products, such as snus and *Ariva*, in the US under conditions of a hypothetical regulatory framework. This framework would enforce the GothiaTek standard as a minimum for production and manufacturing and require use of warning labels about health risks relative to smoking[15]. The panel concluded that this scenario would accelerate a decrease in smoking prevalence in the US from 1.3 per cent to 3.1 per cent over five years, with a greater effect for males aged 21-25 years who had recently initiated tobacco use. If such results held, there would be a net public health benefit through reduced mortality (Levy et al. 2006).

Regardless of the net impact of introducing PREPs at a population level, it has been argued that, ethically, smokers have the right to be informed about and have access to products that may reduce their individual harm (Kozlowski 2002). An approach to minimise risk for the population from the availability of snus or other PREPs is to ensure that snus is directed toward those who could most benefit (Savitz et al. 2006). If snus was made available for harm reduction, health agencies could target access to consumers who may benefit from substituting smoking with snus, while also restricting unsupported use by non-smokers or former smokers. Priority could be given to inveterate smokers, low-income uninsured smokers, and/or smokers who have failed at existing cessation methods (Hatsukami et al. 2004). Specific guidelines for use could also be advocated. For example, Kozlowski et al (2003b) suggests the following approach for smokers: first, quit any tobacco use; second, try medicinal nicotine; third, try snus as a substitute for smoking, as the Swedes do, ie use a product meeting or exceeding the GothiaTek standard, buy it fresh from a retailer who refrigerates it, use snus

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15 The suggested warning label was: 'This product is addictive and may increase your risk of disease. This product is substantially less harmful than cigarettes, but abstaining from tobacco use altogether is the safest course of action' (p. 1192, Levy et al 2006).

as individual pouches or sachets, place snus under the upper lip toward the front of the mouth; fourth, try to switch from snus to medicinal nicotine; finally, and ideally, stop using any nicotine if possible. Such detailed and specific prescriptions of use and user may benefit from the involvement of a health professional or counsellor. For example, with access mediated by a doctor's prescription and/or through an under-the-counter pharmacy-only point of sale (Chapman 2007).

Regulatory, ethical and legal issues pose profound challenges to public health policy makers, particularly given that many important factors are outside the control of the health community, including competing commercial interests and population preferences (Henningfield and Fagerstrom 2001). Policy approaches may include increasing access to PREPs such as snus for targeted cigarette consumers; regulating production and/or constituents to minimise toxicants; providing supportive public education through government sponsored agencies; continuing to ban commercial advertising; and using a differential taxation regime to make PREPs such as snus cheaper to purchase than cigarettes. In considering the role of snus and other modified smokeless products in harm reduction, the costs and benefits of existing 'cleaner', pharmaceutical nicotine sources also need to be considered, including the appropriate regulatory environment for medicinal nicotine and its long-term effects (Hatsukami et al. 2002; Tomar et al. 2003).

CONCLUSIONS

This report systematically reviewed the international epidemiological evidence relating to the major health effects of using modified smokeless tobacco products for reduced harm compared with conventional combustible tobacco products. The safety of using modified smokeless tobacco products compared with not using any form of tobacco was also considered.

Eighteen papers were eligible for inclusion in this review: 16 primary studies (all conducted in Sweden), and two systematic reviews. This number of epidemiological studies is relatively slight compared to the wealth of literature published relating to smoking.

The evidence appraising six case-control studies in this review suggests that snus use, compared with smoking, has much lower health risks associated with a range of head, neck and gastro-intestinal cancers. Indeed, compared with non tobacco use, snus did not lead to an increased risk for these cancers, although larger studies are required to increase the precision of these risk estimates. Meta-analyses for outcomes were not possible due to study and outcome heterogeneity, and no pattern of findings was observed with respect to different cancer sites.

Five of six studies investigating risks for fatal and/or non-fatal CVD outcomes in men, including three case-control studies, a nested case-control study, and a cohort study, found no significantly increased prevalence of CVD for snus users compared with no tobacco use. However, a large cohort study of construction workers recruited in the early 1970s found a 40 per cent increased risk of death from cerebrovascular and cardiovascular disease in snus users compared with no tobacco use. This finding is in contrast to the five studies of more recently observed cohorts that did not have the statistical power to detect small increases in mortality. The excess risks found in the construction worker study may be associated with population and exposure characteristics specific to the cohort, and findings may be less applicable to snus products currently on the market. Nevertheless, an increased risk for death from cerebrovascular and cardiovascular disease in snus users cannot be excluded, and this risk does not appear to be linked to increased risk for developing CVD. Additional high quality research with better controlling of confounders and measurement of tobacco exposure over time is required to further understand the potential association between snus use and CVD mortality. Notably, all six studies consistently demonstrated strong positive associations between smoking and major CVD events, accompanied by evidence of dose-response associations.

Other outcomes were investigated in five separate studies. The large cohort study of construction workers found no increased mortality from all cancers in snus users, but did find a 40 per cent increased risk for all-cause mortality. One small underpowered case-control study found no association between exclusive snus use, or smoking, and Crohn's Disease or ulcerative colitis. Another underpowered prospective cohort study detected no significant risk of diabetes for snus users, but confirmed the established finding of increased risk for diabetes from smoking. A large population-based prospective cohort research study did not identify a relationship between snus and Hodgkin's

disease (HD), or non-Hodgkin's lymphoma, or between smoking and these outcomes. The study was limited by possible participation biases, lack of consideration of many potential confounders and reliance on baseline measures of tobacco exposure. With respect to pregnancy outcomes, compared with non-tobacco use, snus use was associated with reduced infant birth-weight, and increased risks for both preterm delivery and, in contrast to smoking, preeclampsia. The study was limited by its measurement of tobacco exposure, possible reporting biases and lack of controlling for potential confounders. Nevertheless, the study suggests that there are adverse effects in pregnancy from the use of snus and that snus use should not be encouraged as a safe alternative to smoking among pregnant women. High quality prospective research is needed to corroborate these findings and explore possible dose-response effects.

The evidence from this review suggests that the harm of using snus, relative to non tobacco use, is significantly less than found for smoking with respect to cancers of the head, neck and gastro-intestinal region, and cardiovascular disease events. While studies were underpowered to detect small increases in mortality risk compared with no tobacco use, results suggested that the product does not lead to significant risks for these outcomes. One older cohort study provided some evidence for a 40 per cent increased risk of death from all causes, and a 40 per cent increased risk of death from cerebrovascular and cardiovascular disease in snus users compared with no tobacco users. However, there was no increased risk for all-cancer mortality. Further research is needed to investigate CVD risks in other populations using low-nitrosamine snus products and to investigate what diseases may have contributed to the increased risk for all-cause mortality, apart from CVD mortality. Single investigations of limited quality did not indicate increased risks in snus users for diabetes, inflammatory bowel disease or malignant lymphoma, and suggested increased adverse effects for snus use in pregnancy. Other known risks associated with snus but not included in studies appraised here are the dependence potential of nicotine and oral effects including snus-induced lesions, oral mucosal changes that apparently are reversible upon cessation, and gingival recessions.

Limitations of the evidence base included the following:

- an emphasis on oropharyngeal cancers and cardiovascular disease health outcomes with investigation of other health outcomes limited to single studies;

- reliance on retrospective, unvalidated self-report of tobacco exposure at study entry;

- potential confounders such as alcohol abuse, illicit drug use, diet, physical exercise, BMI and family history of disease often not suitably controlled or adjusted;

- health risks associated with snus use in ex-smokers, or with dual, ie smoking and snus users rarely measured;

- risk estimates tended to be imprecise and studies underpowered to rule out small to moderate excess health risks associated with snus use;

- in five of the 18 papers appraised in the review, the research or in one case, a researcher, received some financial support from the tobacco industry. This may have introduced subtle biases into the design, conduct and interpretation of the research, although no evidence of systematic differences were observed as a function of funding source.

Harm reduction is arguably the most complex, controversial and divisive issue in tobacco control today (Chapman 2007). One point that most scientists and commentators agree on is that complete tobacco cessation is the best outcome for smokers and any efforts to make available products safer need to be part of a comprehensive tobacco control strategy aimed at minimising tobacco use through cessation and prevention (Stratton et al. 2001). Comprehensive prevention and cessation programmes have reduced smoking rates dramatically (Vainio and Weiderpass 2003) and promoting snus for harm reduction should not be at the expense of diverting significant resources away from the public health goal of tobacco elimination (Chapman 2007). Some have argued that it may be better to focus efforts on developing and improving pharmacological therapies than to promote smokeless tobacco (Bullen et al. 2006; Hatsukami et al. 2004; Jorenby et al. 1998). Currently, however, the use of pharmaceutical cessation aids and behavioural support have led to limited success in cessation and it has been argued that means that the majority of current smokers will continue to smoke without acceptable safer alternatives (Britton 2003). Snus and other modified smokeless products may therefore be an additional tool for reducing tobacco related harm when used to target inveterate smokers for whom current cessation programmes have had only limited success (Savitz et al. 2006). Critical to efforts to reduce

tobacco-related harm for population net benefit are appropriate regulatory controls which are not stymied by commercial interests aimed at maximising tobacco consumption.

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Appendix 1: Search strategy

Medline
1   snus.af. (70)
2   Tobacco, Smokeless/ (1789)
3   exp Scandinavia/ (96909)
4   sweden/ (40139)
5   norway/ (20454)
6   finland/ (19217)
7   denmark/ (35162)
8   iceland/ (1963)
9   (swedish or norwegian or finnish or danish or icelandic).mp. (40062)
10   (sweden or norway or finland or denmark or iceland).af. (685479)
11   Nitrosamines/ (6287)
12   low nitrosamine$.mp. (4)
13   (modified adj3 tobacco).mp. (48)
14   (revel or exalt or ariva or stonewall).af. (863)
15   (revel : or stonewall :) (au) (807)
16   14 not 15 (88)
17   or/3-10 (690055)
18   2 and (11 or 17) (396)
19   (lozenge and tobacco).mp. (17)
20   1 or 12 or 13 or 16 or 18 or 19 (561)
21   randomized controlled trial.pt. (226902)
22   meta-analysis.pt. (13423)
23   randomized controlled trials/ or meta-analysis/ (51040)
24   controlled clinical trials/ or controlled clinical trial.pt. (76765)
25   exp clinical trials/ or clinical trial.pt. (557015)
26   random allocation/ or (random$ adj2 allocat$).tw. (67764)
27   single blind method/ or double blind method/ (98229)
28   (clinic$ adj trial$).tw. (101949)
29   ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$ or dumm$)).tw. (84757)
30   (systematic$ adj3 (review$ or overview)).tw. (10695)
31   (meta-analy$ or metaanaly$).tw. (16107)
32   exp review literature/ (2880)
33   (hand search$ or relevant journals or manual search$ or selection criteria or data extraction).ab.
        (12707)
34   or/21-33 (680490)
35   letter.pt. (566621)
36   case report.tw. (114405)
37   (historical article or review of reported cases or review, multicase).pt. (228381)
38   or/35-37 (902595)
39   animal/ (4003642)
40   human/ (9533472)
41   39 not (39 and 40) (3036808)
42   34 not (38 or 41) (631911)
43   exp epidemiologic studies/ (911576)
44   exp case control studies/ (325496)
45   exp cohort studies/ (589040)
46   cross-sectional studies/ (68386)
47   (case control or cohort analy$ or cross sectional).tw. (94592)
48   (longitudinal or retrospective).tw. (187809)

49   (cohort adj (study or studies)).tw. (26092)
50   ((follow-up or observational) adj (study or studies)).tw. (36196)
51   or/43-50 (1012836)
52   20 and 42 (27)
53   20 and 51 (102)
54   52 or 53 (122)
55   20 and random$.af. (32)
56   54 or 55 (132)
56   54 or 55 (132)
57   20 not 56 (429)
58   letter.pt. (567219)
59   news.pt. (102504)
60   57 not (58 or 59) (403)

Embase
1   snus.af. (36)
2   Tobacco, Smokeless/ (632)
3   exp Scandinavia/ (35666)
4   sweden/ (13586)
5   norway/ (6375)
6   finland/ (8485)
7   denmark/ (7391)
8   iceland/ (1120)
9   (swedish or norwegian or finnish or danish or icelandic).mp. (24931)
10   (sweden or norway or finland or denmark or iceland).af. (373768)
11   Nitrosamines/ (1527)
12   low nitrosamine$.mp. (3)
13   (modified adj3 tobacco).mp. (47)
14   (revel or exalt or ariva or stonewall).af. (376)
15   (revel : or stonewall :) (au) (554)
16   14 not 15 (290)
17   or/3-10 (376907)
18   2 and (11 or 17) (134)
19   (lozenge and tobacco).mp. (51)
20   1 or 12 or 13 or 16 or 18 or 19 (531)
21   randomized controlled trial.pt. (0)
22   meta-analysis.pt. (0)
23   randomized controlled trials/ or meta-analysis/ (128561)
24   controlled clinical trials/ or controlled clinical trial.pt. (379907)
25   exp clinical trials/ or clinical trial.pt. (388232)
26   random allocation/ or (random$ adj2 allocat$).tw. (28281)
27   single blind method/ or double blind method/ (60829)
28   (clinic$ adj trial$).tw. (81826)
29   ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$ or dumm$)).tw. (64839)
30   (systematic$ adj3 (review$ or overview)).tw. (9766)
31   (meta-analy$ or metaanaly$).tw. (14310)
32   exp review literature/ (7352)
33   (hand search$ or relevant journals or manual search$ or selection criteria or data extraction).ab.
        (8304)
34   or/21-33 (490330)
35   letter.pt. (315064)
36   case report.tw. (80023)
37   (historical article or review of reported cases or review, multicase).pt. (0)
38   or/35-37 (393735)
39   animal/ (7164)

40 human/ (4544010)
41 39 not (39 and 40) (5766)
42 34 not (38 or 41) (474847)
43 exp epidemiologic studies/ (492298)
44 exp case control studies/ (13524)
45 exp cohort studies/ (34011)
46 cross-sectional studies/ (94845)
47 (case control or cohort analy$ or cross sectional).tw. (78015)
48 (longitudinal or retrospective).tw. (142417)
49 (cohort adj (study or studies)).tw. (23816)
50 ((follow-up or observational) adj (study or studies)).tw. (27373)
51 or/43-50 (693920)
52 20 and 42 (62)
53 20 and 51 (100)
54 52 or 53 (150)
55 20 not 54 (381)
56 letter.pt. (315064)
57 55 not 56 (363)

Cinahl

1 snus.af. (23)
2 Tobacco, Smokeless/ (298)
3 exp scandinavia/ (10409)
4 sweden/ (5051)
5 norway/ (1531)
6 denmark/ (1445)
7 finland/ (2634)
8 iceland/ (286)
9 (swedish or norwegian or finnish or icelandic or danish).mp. (4468)
10 (sweden or norway or denmark or iceland or finland).af. (22748)
11 exp NITROSAMINES/ (16)
12 low nitrosamine.mp. (0)
13 (modified adj3 tobacco).mp. (2)
14 (revel or exalt or stonewall or ariva).mp. (7)
15 (lozenge and tobacco).mp. (3)
16 or/3-10 (23579)
17 2 and 16 (33)
18 1 or 17 or 14 or 15 or (2 and 11) (50)

Psychinfo

1 snus.af. (29)
2 exp Smokeless Tobacco/ (217)
3 (sweden or norway or denmark or finland or iceland).af. (64849)
4 (swedish or norwegian or finnish or danish or icelandic).mp. (9335)
5 2 and (3 or 4) (30)
6 nitrosamine$.mp. (9)
7 2 and 6 (1)
8 (tobacco and lozenge$).mp. (9)
9 (revel or exalt or arica or stonewall).mp. (55)
10 1 or 5 or 7 or 8 or 9 (108)

Current Contents/Web of Science

Snus

Smokeless tobacco
Sweden OR norway OR finland OR iceland OR denmark
Swedish OR norwegian OR finnish OR icelandic OR danish
Low nitrosamine*
Nitrosamine*
Modified SAME tobacco
Lozenge SAME tobacco
Revel OR exalt OR stonewall OR ariva
#2 AND (#3 OR #4 OR #6)
#1 OR #5 OR #7 OR #8 OR #9 OR #10

Cochrane Central Register of Controlled Trials

1   snus.af. (2)
2   tobacco, smokeless/ (52)
3   exp scandinavia/ (1530)
4   sweden/ (773)
5   norway/ (285)
6   finland/ (391)
7   denmark/ (433)
8   iceland/ (23)
9   (swedish or norwegian or finnish or danish or icelandic).mp. (1687)
10   (sweden or norway or finland or denmark or iceland).af. (19214)
11   nitrosamines/ (6)
12   low nitrosamine$.mp. (0)
13   (modified adj3 tobacco).mp. (3)
14   (revel or exalt or ariva or stonewall).af. (33)
15   (revel : or stonewall :) (au) (0)
16   14 not 15 (33)
17   or/3-10 (19724)
18   2 and (11 or 17) (5)
19   (lozenge and tobacco).mp. (5)
20   1 or 12 or 13 or 16 or 18 or 19 (45)

SEARCHES FROM OTHER SOURCES

In databases and all other sources without controlled vocabulary combinations of the index terms and additional keywords from the above strategies, were used in the search.

Appendix 2: Retrieved papers excluded for review

References for papers retrieved as potentially eligible for review and then excluded based on selection criteria are presented below, annotated by reason for exclusion. Note that several criteria may apply.

Accortt, N. A., Waterbor, J. W., Beall, C., & Howard, G. (2002). Chronic disease mortality in a cohort of smokeless tobacco users. American Journal of Epidemiology, 156, 730-737.

Ineligible exposure (US smokeless tobacco with insufficient differentiation of types of smokeless to permit identification of data for modified ST)

Adami, J., Nyren, O., Bergstrom, R., Ekbom, A., Engholm, G., Englund, A., & Glimelius, B. (1998). Smoking and the risk of leukemia, lymphoma, and multiple myeloma (Sweden). Cancer Causes & Control, 9, 49-56.

Univariate analyses of snus use in cohort study did not control or adjust for tobacco use

Asplund, K. (2003). Smokeless tobacco and cardiovascular disease. Progress in Cardiovascular Diseases, 45, 383-394.

Narrative review

Barnekow-Bergkvist, M., Hedberg, G. E., Janlert, U., & Jansson, E. (1998). Health status and health behaviour in men and women at the age of 34 years. European Journal of Public Health, 8, 179-182.

Cross-sectional design

Bates, C. (2001). Clearing the smoke or muddying the water? Tobacco Control, 10, 87-88.

Expert opinion/editorial

Beck, J. D., Koch, G. G., & Offenbacher, S. (1995). Incidence of attachment loss over 3 years in older adults--new and progressing lesions. Community Dentistry & Oral Epidemiology, 23, 291-296.

Ineligible exposure (US smokeless tobacco with insufficient differentiation of types of smokeless to permit identification of data for modified ST)

Boffetta, P., Aagnes, B., Weiderpass, E., & Andersen, A. (2005). Smokeless tobacco use and risk of cancer of the pancreas and other organs. International Journal of Cancer, 114, 992-995.

Same cohort as Heuch et al (1983). Considers range of smokeless products, including Norwegian snuff and Norwegian chewing tobacco or skrå ((Boffetta et al. 2006), letter to the editor)

Bolinder, G., & de Faire, U. (1998). Ambulatory 24-h blood pressure monitoring in healthy, middle-aged smokeless tobacco users, smokers, and nontobacco users. *American Journal of Hypertension*, 11, 1153-1163.

Ineligible outcome (risk factors)

Bolinder, G., Noren, A., de Faire, U., & Wahren, J. (1997a). Smokeless tobacco use and atherosclerosis: an ultrasonographic investigation of carotid intima media thickness in healthy middle-aged men. *Atherosclerosis*, 132, 95-103.

Cross-sectional study

Bolinder, G., Noren, A., Wahren, J., & De Faire, U. (1997b). Long-term use of smokeless tobacco and physical performance in middle-aged men. *European Journal of Clinical Investigation*, 27, 427-433.

Cross-sectional study

Bolinder, G. M., Ahlborg, B. O., & Lindell, J. H. (1992). Use of smokeless tobacco: Blood pressure elevation and other health hazards found in a large-scale population survey. *Journal of Internal Medicine*, 232, 327-334.

Cross-sectional study on CVD risk factors

Carlsson, S., Persson Brobert, G. P., Grill, V., Eliasson, M., Nasic, S., & Rodu, B. (2005). Influence of smoking and snus on the prevalence and incidence of type 2 diabetes amongst men: The northern Sweden MONICA study. *Journal of Internal Medicine*, 257, 481-483.

Letter to the editor (commenting on another study)

Critchley, J. A., & Unal, B. (2004). Is smokeless tobacco a risk factor for coronary heart disease? A systematic review of epidemiological studies. *European Journal of Cardiovascular Prevention & Rehabilitation*, 11, 101-112.

Reports from same review as Critchley and Unal (2003), included, with additional data on intermediary CVD risk factors which are excluded outcomes

Eliasson, M., Asplund, K., Evrin, P. E., & Lundblad, D. (1995). Relationship of cigarette smoking and snuff dipping to plasma fibrinogen, fibrinolytic variables and serum insulin. The Northern Sweden MONICA Study. *Atherosclerosis*, 113, 41-53.

Cross-sectional study

Eliasson, M., Lundblad, D., & Hagg, E. (1991). Cardiovascular risk factors in young snuff-users and cigarette smokers. *Journal of Internal Medicine*, 230, 17-22.

Ineligible outcome (CVD risk factors)

Foulds, J., Steinberg, M. B., Williams, J. M., & Ziedonis, D. M. (2006). Developments in pharmacotherapy for tobacco dependence: past, present and future. *Drug & Alcohol Review*, 25, 59-71.

Narrative review

Furberg, H., Bulik, C. M., Lerman, C., Lichtenstein, P., Pedersen, N. L., & Sullivan, P. F. (2005). Is Swedish snus associated with smoking initiation or smoking cessation? *Tobacco Control*, 14, 422-424.

Cross-sectional

Goodman, M. T., Morgenstern, H., & Wynder, E. L. (1986). A case-control study of factors affecting the development of renal cell cancer. *American Journal of Epidemiology*, 124, 926-941.

Ineligible exposure (US chewing tobacco)

Hardell, L., Eriksson, M., & Degerman, A. (1994). Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma. *Cancer Research*, 54, 2386-2389.

Univariate analysis of snus in a case-control study with no controlling for tobacco use

Hatsukami, D. K., Lemmonds, C., Zhang, Y., Murphy, S. E., Le, C., Carmella, S. G., & Hecht, S. S. (2004). Evaluation of carcinogen exposure in people who used 'reduced exposure' tobacco products. *Journal of the National Cancer Institute*, 96, 844-852.

Ineligible outcome (toxin exposure)

Heuch, I., Kvale, G., Jacobsen, B. K., & Bjelke, E. (1983). Use of alcohol, tobacco and coffee, and risk of pancreatic cancer. *British Journal of Cancer*, 48, 637-643.

Ineligible exposure (chewing tobacco)

Hirsch, J. M., Livian, G., Edward, S., & Noren, J. G. (1991). Tobacco habits among teenagers in the city of Goteborg, Sweden, and possible association with dental caries. *Swedish Dental Journal*, 15, 117-123.

Cross-sectional study

Kneller, R. W., McLaughlin, J. K., Bjelke, E., Schuman, L. M., Blot, W. J., Wacholder, S., Gridley, G., et al. (1991). A cohort study of stomach cancer in a high-risk American population. *Cancer*, 68, 672-678.

Ineligible exposure (US smokeless tobacco with insufficient differentiation of types of smokeless to permit identification of data for modified ST)

Kozlowski, L. T., O'Connor, R. J., Edwards, B. Q., & Flaherty, B. P. (2003). Most smokeless tobacco use is not a causal gateway to cigarettes: using order of product use to evaluate causation in a national US sample. *Addiction*, 98, 1077-1085.

Ineligible exposure (US smokeless tobacco with insufficient differentiation of types of smokeless to permit identification of data for modified ST)

Lindstrom, M., & Isacsson, S. O. (2002). Smoking cessation among daily smokers, aged 45-69 years: a longitudinal study in Malmo, Sweden. *Addiction*, 97, 205-215.

Follow-up of smokers on smoking status (ineligible design)

Lundback, B., Lindberg, A., Lindstrom, M., Ronmark, E., Jonsson, A. C., Jonsson, E., Larsson, L. G., et al. (2003). Not 15 but 50% of smokers develop COPD?--Report from the Obstructive Lung Disease in Northern Sweden Studies. *Respiratory Medicine*, 97, 115-122.

Ineligible exposure (cigarette smoking)

McLaughlin, J. K., Lindblad, P., Mellemgaard, A., McCredie, M., Mandel, J. S., Schlehofer, B., Pommer, W., et al. (1995). International renal-cell cancer study. I. Tobacco use. *International Journal of Cancer*, 60, 194-198.

Multi-centre case-control study including Sweden, but does not report results from Sweden or for snus separately.

Moller, L. F., & Jespersen, J. (1995). Elevated insulin levels in men: An 11-year follow-up study. *Journal of Cardiovascular Risk*, 2, 339-343.

Ineligible exposure (smoked tobacco)

Norstein, J. (1997). Re: Smoking and colorectal cancer: a 20-year follow-up study of Swedish construction workers. *Journal of the National Cancer Institute*, 89, 95-96.

letter

Nyren, O., Bergstrom, R., Nystrom, L., Engholm, G., Ekbom, A., Adami, H. O., Knutsson, A., et al. (1996). Smoking and colorectal cancer: a 20-year follow-up study of Swedish construction workers. *Journal of the National Cancer Institute*, 88, 1302-1307.

Ineligible exposure (cigarette smoking)

Persson, P. G., Carlsson, S., Svanstrom, L., Ostenson, C. G., Efendic, S., & Grill, V. (2000). Cigarette smoking, oral moist snuff use and glucose intolerance. *Journal of Internal Medicine*, 248, 103-110.

Cross-sectional

Ranney, L., Melvin, C., Lux, L., McClain, E., Morgan, L., & Lohr, K. (2006). *Tobacco use: prevention, cessation, and control. Evidence Report/Technology Assessment 140*. Bethesda, MD: Agency for Healthcare Research and Quality.

Does not include any studies eligible for the current review. Review of peripheral tobacco use issues including impact of product marketing of smokeless tobacco

Rodu, B., & Cole, P. (2002). Smokeless tobacco use and cancer of the upper respiratory tract. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology & Endodontics*, 93, 511-515.

Cross-sectional

Rodu, B., & Jansson, C. (2004). Smokeless tobacco and oral cancer: a review of the risks and determinants. *Critical Reviews in Oral Biology & Medicine*, 15, 252-263.

Narrative review

Rodu, B., Stegmayr, B., Nasic, S., & Asplund, K. (2002). Impact of smokeless tobacco use on smoking in northern Sweden. *Journal of Internal Medicine*, 252, 398-404.

Narrative review

Rodu, B., Stegmayr, B., Nasic, S., Cole, P., & Asplund, K. (2003). Evolving patterns of tobacco use in northern Sweden. *Journal of Internal Medicine*, 253, 660-665.

No eligible health outcomes reported (follow-up of tobacco use only)

Rodu, B., Stegmayr, B., Nasic, S., Cole, P., & Asplund, K. (2004). The influence of smoking and smokeless tobacco use on weight amongst men. *Journal of Internal Medicine*, 255, 102-107.

Ineligible outcome (weight gain not specifically considered in this review as it is not a specific disease endpoint)

Rosen, M., Alfredsson, L., Hammar, N., Kahan, T., Spetz, C. L., & Ysberg, A. S. (2000). Attack rate, mortality and case fatality for acute myocardial infarction in Sweden during 1987-95. Results from the national AMI register in Sweden. *Journal of Internal Medicine*, 248, 159-164.

Reported trends in acute myocardial infarction attack and mortality rates. No analysis by snus use.

Shah, N., & Sharma, P. P. (1998). Role of chewing and smoking habits in the etiology of oral submucous fibrosis (OSF): a case-control study. *Journal of Oral Pathology & Medicine*, 27, 475-479.

Ineligible exposure (Indian chewing tobacco)

Sham, A. S. K., Cheung, L. K., Jin, L. J., & Corbet, E. F. (2003). The effects of tobacco use on oral health. *Hong Kong Medical Journal*, 9, 271-277.

Does not include any study eligible for current review. Considers tobacco smoking and oral health.

Suadicani, P., Hein, H. O., & Gyntelberg, F. (1994). Serum validated tobacco use and social inequalities in risk of ischaemic heart disease. *International Journal of Epidemiology*, 23, 293-300.

Ineligible exposure (chewing tobacco and snuff reported together)

Suadicani, P., Hein, H. O., & Gyntelberg, F. (1997). Mortality and morbidity of potentially misclassified smokers. *International Journal of Epidemiology*, 26, 321-327.

Ineligible exposure (chewing tobacco and snuff reported together)

Tillgren, P., Haglund, B. J., Ainetdin, T., & Holm, L. E. (1995). Who is a successful quitter? One-year follow-up of a National Tobacco Quit and Win Contest in Sweden. *Scandinavian Journal of Social Medicine*, 23, 193-201.

No eligible health outcomes reported (follow-up of quitters)

Tomar, S. L., & Henningfield, J. E. (1995). Additional evidence implicating moist snuff as a potent carcinogen. *Journal of the National Cancer Institute*, 87, 1822-1824.

Expert opinion/commentary

Tucker, L. A. (1989). Use of smokeless tobacco, cigarette-smoking, and hypercholesterolemia. *American Journal of Public Health*, 79, 1048-1050.

Ineligible outcome (hypercholesterolemia)

US Department of Health and Human Services (1986). *The health consequences of using smokeless tobacco: a report of the Advisory Committee to the Surgeon General. DHHS Publication no. (NIH) 86-2874*. Bethesda, MD: National Institutes of Health.

Does not include any studies eligible for the current review.

Wallenfeldt, K., Hulthe, J., Bokemark, L., Wikstrand, J., & Fagerberg, B. (2001). Carotid and femoral atherosclerosis, cardiovascular risk factors and C-reactive protein in relation to smokeless tobacco use or smoking in 58-year-old men. *Journal of Internal Medicine*, 250, 492-501.

Cross-sectional study on CVD risk factors

Wickholm, S., Soder, P. O., Galanti, M. R., Soder, B., & Klinge, B. (2004). Periodontal disease in a group of Swedish adult snuff and cigarette users. *Acta Odontologica Scandinavica*, 62, 333-338.

Cross-sectional study

World Health Organisation (1988). Smokeless tobacco control. *WHO Technical Report Series* 773, 1-81.

Does not include any studies eligible for the current review.

Wray, A., & McGuirt, W. F. (1993). Smokeless tobacco usage associated with oral carcinoma. Incidence, treatment, outcome. *Archives of Otolaryngology -- Head & Neck Surgery*, 119, 929-933.

Ineligible exposure (US smokeless tobacco with insufficient differentiation of types of smokeless to permit identification of data for modified ST)

Wynder, E. L., Bross, I. J., & Feldman, R. M. (1957a). A study of the etiological factors in cancer of the mouth *Cancer*, 10, 1300-1323.

Ineligible exposure (US smokeless tobacco with insufficient differentiation of types of smokeless to permit identification of data for modified ST)

Wynder, E. L., Hultberg, S., Jacobsson, F., & Bross, I. J. (1957b). Environmental factors in cancer of the upper alimentary tract; a Swedish study with special reference to Plummer-Vinson (Paterson-Kelly) syndrome. *Cancer*, 10, 470-487.

Ineligible exposure (chewing tobacco), and did not adjust for other tobacco use or age.

Zatterstrom, U. K., Svensson, M., Sand, L., Nordgren, H., & Hirsch, J. M. (2004). Oral cancer after using Swedish snus (smokeless tobacco) for 70 years - a case report. *Oral Diseases*, 10, 50-53.

Case report

Appendix 3: Included studies

Asplund, K., Nasic, S., Janlert, U., & Stegmayr, B. (2003). Smokeless tobacco as a possible risk factor for stroke in men - a nested case-control study. Stroke, 34, 1754-1759.

Bolinder, G., Alfredsson, L., Englund, A., & de Faire, U. (1994). Smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers. American Journal of Public Health, 84, 399-404.

Critchley, J. A., & Unal, B. (2003). Health effects associated with smokeless tobacco: a systematic review. Thorax, 58, 435-443.

Eliasson, M., Asplund, K., Nasic, S., & Rodu, B. (2004). Influence of smoking and snus on the prevalence and incidence of type 2 diabetes amongst men: the northern Sweden MONICA study. Journal of Internal Medicine, 256, 101-110.

England, L. J., Levine, R. J., Mills, J. L., Klebanoff, M. A., Yu, K. F., & Cnattingius, S. (2003). Adverse pregnancy outcomes in snuff users. American Journal of Obstetrics & Gynecology, 189, 939-943.

Fernberg, P., Odenbro, A., Bellocco, R., Boffetta, P., Pawitan, Y., & Adami, J. (2006). Tobacco use, body mass index and the risk of malignant lymphomas--a nationwide cohort study in Sweden. International Journal of Cancer, 118, 2298-2302.

Hansson, L. E., Baron, J., Nyren, O., Bergstrom, R., Wolk, A., & Adami, H. O. (1994). Tobacco, alcohol and the risk of gastric cancer. A population-based case-control study in Sweden. International Journal of Cancer, 57, 26-31.

Hergens, M. P., Ahlbom, A., Andersson, T., & Pershagen, G. (2005). Swedish moist snuff and myocardial infarction among men. Epidemiology, 16, 12-16.

Huhtasaari, F., Asplund, K., Lundberg, V., Stegmayr, B., & Wester, P. O. (1992). Tobacco and myocardial infarction: is snuff less dangerous than cigarettes? BMJ, 305, 1252-1256.

Huhtasaari, F., Lundberg, V., Eliasson, M., Janlert, U., & Asplund, K. (1999). Smokeless tobacco as a possible risk factor for myocardial infarction: A population-based study in middle-aged men. Journal of the American College of Cardiology, 34, 1784-1790.

Johansson, S. E., Sundquist, K., Qvist, J., & Sundquist, J. (2005). Smokeless tobacco and coronary heart disease: A 12-year follow-up study. European Journal of Cardiovascular Prevention & Rehabilitation, 12, 387-392.

Lagergren, J., Bergstrom, R., Lindgren, A., & Nyren, O. (2000). The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. International Journal of Cancer, 85, 340-346.

Lewin, F., Norell, S. E., Johansson, H., Gustavsson, P., Wennerberg, J., Biorklund, A., & Rutqvist, L. E. (1998). Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck - A population-based case-referent study in Sweden. Cancer, 82, 1367-1375.

Persson, P. G., Hellers, G., & Ahlbom, A. (1993). Use of oral moist snuff and inflammatory bowel disease. International Journal of Epidemiology, 22, 1101-1103.

Rosenquist, K., Wennerberg, J., Schildt, E. B., Bladstrom, A., Hansson, B. G., & Andersson, G. (2005). Use of Swedish moist snuff, smoking and alcohol consumption in the aetiology of oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. Acta Oto-Laryngologica, 125, 991-998.

Roth, H. D., Roth, A. B., & Liu, X. (2005). Health risks of smoking compared to Swedish snus. Inhalation Toxicology, 17, 741-748.

Schildt, E. B., Eriksson, M., Hardell, L., & Magnuson, A. (1998). Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. International Journal of Cancer, 77, 341-346.

Ye, W., Ekstrom, A. M., Hansson, L. E., Bergstrom, R., & Nyren, O. (1999). Tobacco, alcohol and the risk of gastric cancer by sub-site and histologic type. International Journal of Cancer, 83, 223-229.

Appendix 4: Critical appraisal checklist

Paper/Study ID: Date:

USE OF CHECKLIST: circle selected response, note in Evidence Table relevant details, noting particularly any problematic issues. MST = modified smokeless tobacco.

SECTION 1: MEASUREMENT EXPOSURE:

Definition and measurement of exposure
Is a 'definition' of MST use provided (eg minimum use to classify as MST user)?

	Yes	**No**

Is use of MST tobacco validated in any way? (eg biochemically, checking sources)

	Yes	**No**

Does the study provide any description of frequency of use? (eg amount used per day/week, frequency of snuff dipping, retention of the snuff in the mouth)

	Yes	**No**

Does the study describe duration of use? (eg, years, and/or age at starting)

	Yes	**No**

OUTCOMES:

Describe what outcomes were studied

Was the outcome of interest clearly defined?   **Yes**   **No**
 (eg ICD, WHO classification)

If <u>oral cancer</u>, is it clearly stated which regions are included (eg lip, tongue, buccal cavity, pharynx, larynx etc)?

	Not applicable	**Yes**	**No**

If <u>cancer outcome</u>, were cases confirmed **(**eg by histology, microscopy)?

	Not applicable	**Yes**	**No**

If <u>cancer outcomes</u>, is the type stated (eg squamous cell or adenocarcinoma)?

	Not applicable	**Yes**	**No**

SECTION 2: Questions for case-control studies only

Is the study of incident or prevalent cases (circle one)?

Incident   **prevalent**   **not clear**

Were controls selected from the same population as cases?

          Yes   **No**   **Unclear**

Were controls matched to cases appropriately?

          Yes   **No**   **Unclear**

Was there any differential treatment of cases and controls (eg cases interviewed, controls sent postal questionnaires to determine smokeless tobacco use?

          Yes   **No**   **Unclear**

Were any steps taken to minimise possible recall bias? (eg cross-checking questionnaires/ interviews with other sources of information on smokeless tobacco use)

          Yes   **No**   **Unclear**

Were interviewers blinded (if possible) to the disease status of patients / hypothesis under investigation?

          Yes   **No**   **Unclear**

Was data entry/coding blinded to the disease status of patients / hypothesis under investigation?

          Yes   **No**   **Unclear**

Does the study calculate or provide sufficient information to calculate the non-response rates for both cases and controls?

          Yes   **No**   **Unclear**

Are they significantly different?

          Yes   **No**   **Unclear**

SECTION 3: Question for cohort studies

Follow-up
Was MST use verified more than once during the follow-up period?

| | **Yes** | **No** | **Unclear** |

Potential for attrition bias
Was there different levels of attrition for the tobacco exposure groups?

| | **Yes** | **No** | **Unclear** |

Was there different levels of missing data on outcomes for the tobacco exposure groups

| | **Yes** | **No** | **Unclear** |

SECTION 4: Confounding

Check whether these confounders were measured and controlled for in the analysis:

	Measured	Controlled for	Measurement quality
i) Age			
ii) Sex (if appropriate)			
iii) Ethnicity			
iv) Socio-economic status			
v) Education			
vi) cigarette smoking (or other tobacco)			
vii) alcohol consumption			
viii) measures of nutritional status or diet (describe)			
ix) oral /dental hygiene *(where applicable)*			
x) use of mouthwash *(where applicable)*			
xi) any co-morbidities (describe)			
xii) others (list)			

Were confounders measured entered into a multi-variate analysis and adjusted results (an odds ratio or relative risk) presented?

	Yes	**No**

IF **YES,** were some confounders NOT adjusted for?   **Yes**   **No**

IF **YES**, was explanation given for not adjusting (e.g., made no difference)?

	Yes	**No**

SECTION 5: Results

Complete the number for each cell, where reported (note where fewer than 10 cases for MST use, or cigarette use)

	Mutually exclusive comparators		
Define (eg, exclusive, current, ever)	**MST user**	**Cigarette smoker**	**Non-user of tobacco**
Total number of patients (total)			
Number of deaths (where reported)			
Number of 'cases' (with outcome 1)			
Number of 'cases' (with outcome 2)			
Number of 'cases' (with outcome 3))			

Were there significant differences between exposure groups for the following:

Person-years of observation **avail.**	**Yes**	**No**	**Unclear/not**
Mean follow-up duration **avail**	**Yes**	**No**	**Unclear/not**
Includes Industry Funding Source **avail**	**Yes**	**No**	**Unclear/not**
Includes conflict of interest statement **avail**	**Yes**	**No**	**Unclear/not**

ANY OTHER COMMENTS: