

REVIEW

Effect of smokeless tobacco (snus) on smoking and public health in Sweden

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Objective: To review the evidence on the effects of moist smokeless tobacco (snus) on smoking and ill health in Sweden.

Method: Narrative review of published papers and other data sources (for example, conference abstracts and internet based information) on snus use, use of other tobacco products, and changes in health status in Sweden.

Results: Snus is manufactured and stored in a manner that causes it to deliver lower concentrations of some harmful chemicals than other tobacco products, although it can deliver high doses of nicotine. It is dependence forming, but does not appear to cause cancer or respiratory diseases. It may cause a slight increase in cardiovascular risks and is likely to be harmful to the unborn fetus, although these risks are lower than those caused by smoking. There has been a larger drop in male daily smoking (from 40% in 1976 to 15% in 2002) than female daily smoking (34% in 1976 to 20% in 2002) in Sweden, with a substantial proportion (around 30%) of male ex-smokers using snus when quitting smoking. Over the same time period, rates of lung cancer and myocardial infarction have dropped significantly faster among Swedish men than women and remain at low levels as compared with other developed countries with a long history of tobacco use.

Conclusions: Snus availability in Sweden appears to have contributed to the unusually low rates of smoking among Swedish men by helping them transfer to a notably less harmful form of nicotine dependence.

In recent times the tobacco industry has been active in developing and marketing new products that might be perceived as less harmful to health than typical cigarettes.^{1,2} At the same time, there has been an increasingly vigorous debate within the public health community over the most appropriate response to the new products being developed by the industry.^{3–5} In this debate, public health advocates have been mindful of the historical precedents set by previous tobacco industry attempts to introduce new product lines that have been perceived as less harmful. It is now clear that so called “light” cigarettes were widely believed to be less harmful (and continue to be by the majority of consumers) but in fact are no less deadly than standard cigarettes.⁶ The introduction and marketing of these products may well have had a serious adverse effect on public health by duping hundreds of millions of smokers into the belief that they could continue to smoke at reduced risk.

In the current debate over tobacco harm reduction, some have cited the “Swedish experience” as an example of tobacco product switching that may have had a positive effect on smoking and public health.⁷ This article aims to review our knowledge about smokeless tobacco use in Sweden and its likely effect on tobacco smoking and public health in that country.

WHAT IS SNUS?

“Snus” is the name given to the form of smokeless snuff tobacco commonly used in Sweden. It is a moist, ground oral tobacco product that is typically placed behind the upper lip, either as loose ground tobacco or contained in sachets appearing like small teabags. The snus is typically held in the mouth (without chewing) for approximately 30 minutes before it is discarded.

MANUFACTURING

Snus both contains and delivers a number of harmful substances, including cancer-causing tobacco specific nitrosamines (TSNAs). It has become clear that different selection and curing methods can affect the levels of nitrites and hence TSNAs present in the raw tobacco before processing.⁸ Over recent decades snus manufacturers have selected tobacco blends that have been air and sun cured (dried), while US moist snuff products tend to include blends high in fire cured tobacco.

After curing, raw cured tobacco is cut into small strips, dried, ground, and sifted before processing. In Sweden, by tradition, snus production has included a process in which the tobacco is heat treated with steam for 24–36 hours (reaching temperatures of approximately 100°C). Ingredients added are: 45–60% water, 1.5–3.5% sodium chloride, 1.5–3.5% humectants, 1.2–3.5% sodium bicarbonate, and less than 1% flavouring. It is claimed that the heating process kills bacteria, producing a relatively sterile product. The product is then packaged in cans and refrigerated during storage. In Sweden the product is also kept in refrigerators by the retailers. One study examined levels of carcinogenic TSNAs in snus kept at temperatures ranging from –20°C to +23°C for 20 weeks.⁹ This exposure to a variety of temperatures over time did not produce a significant increase in concentrations of TSNAs, suggesting that the exposure to heat during

Abbreviations: CI, confidence interval; IOM, US Institute of Medicine; MI, myocardial infarction; OR, odds ratio; OSCC, oesophageal squamous cell carcinoma; RR, relative risk; TSNAs, tobacco specific nitrosamines

manufacturing may itself have prevented microbial activation of nitrites.¹⁰

This manufacturing process contrasts with that traditionally used in the USA, in which the product is fermented (rather than being subject to high temperatures), allowing the continued formation of TSNA. In addition, North American smokeless tobacco is not typically stored in refrigerators. One study found that nitrite and TSNA levels increased significantly in US snuff stored at 37°C for four weeks.¹¹

Although different products vary in their pH levels, snus typically has a pH in the range 7.8–8.5.^{12–13} This is important because only nicotine in the free-base form is rapidly absorbed through the mucosal membrane, and the proportion of free-base nicotine available from tobacco is determined by the pH level. For example Brunnemann and Hoffmann compared two brands and found that one brand with a pH of 5.84 had only 1% of the nicotine in the free-base form and another brand with a pH of 7.99 had 59% of the nicotine available in free-base form for absorption.¹⁴ Another study found that a leading Swedish snus brand had a higher pH (and therefore probably more efficient nicotine delivery) than five comparison brands of US smokeless tobacco.¹³

Delivery of harmful substances

Possibly as a result of the differences in manufacturing and storing procedures, snus has been claimed to contain lower levels of some harmful substances than many of the brands available in North America and notably lower levels than exist in the smokeless tobacco used in the Sudan and India.¹⁰ Table 1 below summarises data from five studies^{13–18} of TSNA levels in various samples of different brands marketed in different countries. The total TSNA concentration varied greatly among the US brands from 4.1 to 128 (µg/g dry tobacco). There is little evidence to support claims that TSNA levels have consistently dropped over the past decade in North American snuff (for example, Copenhagen brand in 1994 had a measured TSNA level of 17.2 and in 2000 it was 41.1). Snus brands selected in Sweden from 1990, 1991, and 2000 have generally been lower and have varied from 9.2 to 11.2 µg/g in the three samples in 1990–91 and 2.8 µg/g in 2000. Brunnemann and Hoffmann¹³ also examined the effects of storage for six months at room temperature and found that in two leading US brands, the TSNA levels increased by between 30–130% whereas in the snus brand there was no increase. More recently the manufacturer of

Table 2 Gothiatek standard.¹⁹ Voluntary market based toxicity standard used for snus products by Swedish Match Tobacco Company

Toxin	Limit
Nitrate	3.5 mg/kg
Tobacco specific nitrosamines (TSNA)	5 mg/kg
N-Nitrosodimethylamine (NDMA)	5 µg/kg
Benz(a)pyrene (BaP)	10 µg/kg
Cadmium	0.5 mg/kg
Lead	1.0 mg/kg
Arsenic	0.25 mg/kg
Nickel	2.25 mg/kg
Chromium	1.5 mg/kg

mg/kg, thousandth gram per kilogram product (based on Snus with 50% water content); µg/kg, millionth gram per kilogram product (based on Snus with 50% water content); double the limits for dry weight equivalents.

snus has created and publicised a quality standard, the Gothiatek standard,¹⁹ for its snus products that includes maximum permissible limits for “undesirable substances” (table 2). It is unclear if all Swedish Match smokeless tobacco products produced in Sweden and abroad adhere to the Gothiatek standard.

One method of assessing the potential harmfulness of a tobacco product is to measure the level of circulating mutagens in body fluid after exposure to the tobacco. Curvall and colleagues²⁰ compared the mutagenic activity of urine from snus users, cigarette smokers, and non-tobacco users. They found that smokers had notably increased urinary mutagenic activity, whereas there was no significant difference between snus users and non-tobacco users.

Nicotine delivery

Swedish snus, like some other brands of smokeless tobacco, contains and delivers quantities of nicotine comparable to those typically absorbed from smoking cigarettes. As shown in fig 1, each dose typically provides a venous nicotine “boost” of around 15 ng/ml after half an hour, with steady state levels around 30 ng/ml being typical.^{21–22} These nicotine levels are very similar to those found in cigarette smokers,²¹ with the main difference from smoked tobacco being the slightly slower nicotine absorption and the lack of a higher concentration arterial “bolus” that results from nicotine inhalation. These nicotine levels obtained from snus are

Table 1 Mean nitrosamine content (and range) of moist snuff products from various sources based on dry weight

Country and brand (year sampled)	Manufacturer	Nicotine (mg/g)	NNK (µg/g)	NNN (µg/g)	Total TSNA (µg/g)
Sweden					
Three brands* (1990–91) ¹⁵	Swed Match		1.4–2.1	5.2–5.7	9.2–11.2
Ettan Snus (2000) ¹³	Swed Match		0.5	1.1	2.8
Sudan (Toombak)					
5 Samples* (1990) ¹⁶		32.2–102.4	630–7870	830–3805	
5 Samples* (1990) ¹⁶		8.4–26.0	1140–2790	420–1550	
3 Samples* (1993) ¹⁷			188–362	241–369	
USA					
2 Samples* (1991) ¹⁵		18.6–20.6	0.5–0.8	4.8–8.0	
1 Sample* (1992) ¹⁵		16.7	0.6	5.6	
Copenhagen (1994) ¹⁸	USSTC	12 (12.7–11.3)	1.9 (1.3–2.5)	8.7 (10.1–7.3)	17.2 (20.2–14.2)
Skool, Original fine cut(1994) ¹⁸	USSTC	11.9 (13.4–10.7)	1.3 (1.4–1.2)	8.2 (9.5–6.9)	14.9 (17.4–12.4)
Skool Bands Straight(1994) ¹⁸	USSTC	10.1 (10.9–9.3)	0.9 (1.2–0.6)	5.1 (6.1–4.1)	8.2 (9.9–6.5)
Kodiak Wintergreen(1994) ¹⁸	Conwood	10.9 (10.1–11.7)	0.6 (0.8–0.4)	6.3 (7.4–5.2)	11.0 (13.4–8.6)
Hawken Wintergreen(1994) ¹⁸	Conwood	3.2 (3.4–3.0)	0.2 (.24–.16)	3.1 (3.4–2.8)	4.1 (4.5–3.7)
Skool (2000) ¹³	USSTC		4.3	20.8	64.0
Copenhagen(2000) ¹³	USSTC		3.4	14.3	41.1
Timber Wolf(2000) ¹³	Swed. Match		0.95	3.0	7.5
Silver Creek(2000) ¹³	Swisher		17.8	41.4	127.9

All available pertinent data from referenced studies is reported. Blank cells indicate that data were not provided in the referenced study.

*Brand not specified in study.

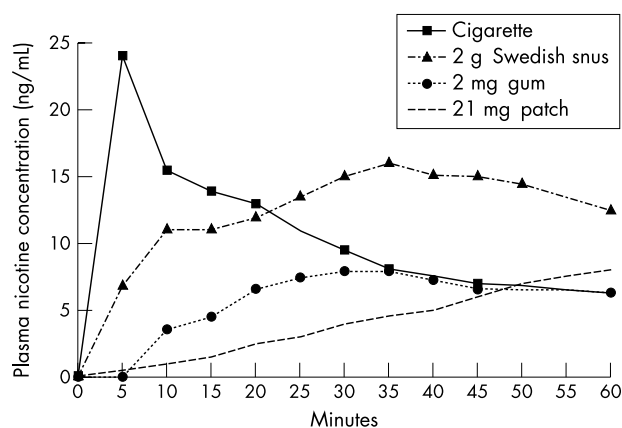


Figure 1 Venous blood concentrations in nanograms of nicotine per millilitre (ng/ml) of plasma as a function of time for various nicotine delivery systems; all plasma nicotine concentrations have been reconfigured such that the pre-absorption level starts at 0 ng/ml (that is, to take out the baseline differences). Cigarette, and 2 mg nicotine gum, adapted from Russell *et al.*,²⁴ and 21 mg patch adapted from Stratton *et al.*,³ page 100. Swedish snus plasma nicotine concentrations in 10 Swedish snus users from a single 2 g pinch of loose snus adapted from Holm *et al.*²¹

about twice as high as the nicotine concentrations typically obtained from nicotine replacement therapy.²³ The nicotine levels shown in fig 1 are from users of loose snus and it is possible that some other brands (particularly portion packed products or those with a lower pH) may give different levels.

IS SNUS HARMFUL TO HEALTH AND IS IT LESS HARMFUL TO AN INDIVIDUAL USER THAN CIGARETTES?

Many of the smokeless tobacco users participating in the older epidemiological studies discussed below may have been exposed to products delivering higher quantities of harmful substances than current versions of these products.

Nicotine dependence

Given the pattern of nicotine absorption described above there can be no doubt that snus is dependence forming in much the same way as other forms of tobacco consumption. There is some evidence that the dependence potential of nicotine and other psychoactive drugs is related to their speed of delivery to the brain^{23, 25} and so one would expect snus and other non-inhaled forms of nicotine delivery to be proportionately less addictive than inhaled tobacco smoke. However, there is clear evidence that users of products with snus-like nicotine delivery profiles develop cravings and nicotine withdrawal symptoms when attempting to abstain, and find it difficult to quit.^{21, 26} While snus probably does not produce stronger nicotine dependence than smoking, it has just minimal, if any, advantages over cigarettes or other smokeless nicotine delivery products in terms of its lower potential to induce dependence. In fact, its high nicotine delivery and hence dependence potential (relative to most other non-smoked delivery modalities) may be a critical factor enabling it to compete with the more rapidly absorbed nicotine from smoked tobacco.

Oral cancer

One of the biggest concerns about the use of smokeless tobacco stems from the relatively large body of evidence from a number of countries showing that oral tobacco use can cause cancer of the mouth, head, and neck. With regards to its use in India, the 2001 US Institute of Medicine (IOM) report³ stated that, "A large number of studies in India,

including cohort, case-control, and intervention studies, support an association between oral cancer and smokeless tobacco, and these studies are consistent, strong, coherent and temporally plausible" (p 427). The IOM report stated that toombak users in Sudan also have a much higher relative risk (RR) of oral cancer than non-users and that "In spite of conflicting US data, it can be concluded that snuff use in the United States also increases the risk of oropharyngeal cancers" (p428). In contrast, there is consistent evidence from two case-control studies in Sweden showing no increased risk of cancer of the head, neck, or mouth among snus users.

Schildt and colleagues²⁷ investigated whether snus leads to increased risk of oral cancer by comparing various risk factors in 410 cases of oral cancer and 410 matched controls identified during the period 1980–89. Ninety six per cent of the identified cases and 91% of identified controls participated in the study (leaving full data from 354 matched pairs) and 20% of the overall sample were current or ex snus users. Univariate analyses found significant increased risk of oral cancer as a result of smoking (odds ratio (OR) 1.8 for active smokers), and alcohol (OR 1.9 for beer drinkers) but no increased risk for active snus use (OR 0.7, 95% confidence interval (CI) 0.4 to 1.1). The authors concluded: "Our results do not support any association between use of oral snuff and oral cancer."

Lewin and colleagues²⁸ conducted a similarly designed study, identifying cases of head and neck cancer in two regions of Sweden between 1988 and 1991 and matched controls. Interviews were conducted with high proportions of identified cases (90%) and controls (85%). This study found significantly increased risks of head and neck cancers associated with alcohol use and smoking, but no increased risk associated with former or current snus use. The RR for head and neck cancer among snus users as compared with non-snus users, after adjusting for age, region, alcohol, and smoking was 1.0 (95% CI 0.6 to 1.6). Similarly there were no significant relations between duration of snus use or lifetime consumption and head/neck cancer.

A recent systematic review of the health effects of smokeless tobacco concluded: "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 statistical power."²⁹ Snus causes a number of non-malignant oral diseases, including oral lesions³⁰ and dental caries.³¹ However, it appears as though the lesions produced by snus are reversible and disappear if snus use ceases.³⁰

Other cancers

Ye and colleagues³² conducted a case control study (504 cases and 1164 controls) examining the effects of smoking, alcohol, and snus use on gastric cancer in Sweden. They found a significant dose and duration related increase in gastric cancer risk with smoking, but no effect of snus or alcohol. They concluded that "smoking, but not the oral use of tobacco in the form of moist snuff, is positively associated with risk of gastric cancer".

Lagergen *et al.*³³ conducted a case-control study designed to test the association between smoking, snus, and alcohol use, and cancer of the oesophagus and gastric cardia in Sweden. Combined smoking and alcohol use was strongly associated with oesophageal squamous cell carcinoma (OSCC) (OR 23.1 for heavy users compared with never users), but snus use was not significantly associated with any of the cancer sites under study in multivariate analyses. There was some indication of a possible link between snus use and OSCC in that the odds ratio was 2.0 for use for over 25 years versus never snus use,

although because of the relatively small size of this sub-sample ($n = 14$ cases) this was not significant (95% CI 0.9 to 4.1). The authors concluded: "we found no statistically significant association between snuff dipping and risk of any of the studied tumors."

It remains possible, but unlikely, that a carcinogenic effect of snus only emerges after very long term use. Bolinder and colleagues³⁴ found a non-significant RR of death from cancer of 1.1 for snus users compared with never tobacco users (95% CI 0.9 to 1.4) in a prospective study of Swedish construction workers that included a relatively large sample, many of whom had used snus for over 40 years. The RR for cancer death was 1.0 (compared with non-tobacco users) for the 1734 snus users aged 55–65 years, most of whom would presumably have used snus for over 35 years. However, this study found significantly increased all cause mortality in snus users compared with never tobacco users, largely from elevated cardiovascular mortality. The RR for lung cancer among snus users compared with never tobacco users was 0.8 among men aged 55–65, whereas the RR was 30.6 (95% CI 14.6 to 64.1) for smokers of at least 15 cigarettes per day (again compared with never tobacco users).

Overall, the results of the five large studies examining snus in relation to cancer are consistent in finding no increased cancer risk among snus users. All of the Swedish studies of the relation between snus and cancer were robust enough to detect significant effects for tobacco smoking (often involving very large effect sizes), and the studies of oral cancer were also able to detect significant relations with alcohol use. The lack of relation with snus is therefore unlikely to be caused by methodological problems such as low statistical power.

Cardiovascular disease

Bolinder and colleagues conducted a series of epidemiological and clinical studies^{34–39} examining the effects of long term snus use on health, focusing on cardiovascular risk factors and myocardial infarction. Their first report³⁵ focused on a cross sectional study of almost 98 000 Swedish construction workers undergoing health examinations in 1971–4, including over 5000 exclusive snus users. This study found an increased prevalence of circulatory and respiratory symptoms among snus users and heavy smokers as compared to non-tobacco users, and an increased prevalence of hypertension in snus users compared to non-tobacco users. Surprisingly this study found the lowest prevalence of hypertension among smokers of at least 15 cigarettes per day. The results were based on univariate analyses, and did not control for potential confounders other than age.³⁵

Bolinder's second study³⁴ examined the relation between tobacco use and cardiovascular mortality in a larger sample ($n = 135\ 036$) of Swedish male construction workers recruited at a health examination in 1971–4 and followed up 12 years later.

This study found that snus users had a significantly higher risk of dying from a cardiovascular event than never tobacco users (RR 1.4, 95% CI 1.2 to 1.6). This excess risk was comparable to that of ex-smokers who had quit in the past five years, but smaller than heavy smokers (RR 1.9 compared with never tobacco users). The analyses in this study adjusted for age and region of origin, and (for at least some analyses, although it was not always stated) also adjusted for body mass index, blood pressure, diabetes, and heart problems at the time of entering the study. Alcohol consumption and cholesterol were not measured and so could not be controlled for.

Subsequent studies focused on a smaller sample of Swedish firemen (around 140, split approximately equally between snus users, smokers, and non-tobacco users). These

studies found that snus use did not influence exercise capacity,³⁶ or play a major role in the atherosclerotic process^{37,38} (both of which were adversely affected by smoking). However, they replicated the previous finding of higher daytime (but not night time) heart rate and blood pressure among both snus users and smokers as compared to non-tobacco users.³⁹ Overall, these studies by Bolinder and colleagues are suggestive of an increased cardiovascular risk from snus use, that is probably mediated by nicotine's sympathetic stimulant effects, and is of a smaller magnitude than the excess cardiovascular risks caused by smoking. It was suggested that snus' effects on blood pressure may be related to its sodium content (1.3–3.5% sodium chloride and 1.5–3.5% sodium bicarbonate).

However, two subsequent case-control studies by Huhtasaari and colleagues^{40,41} did not find a significantly increased risk of myocardial infarction among snus users as compared to non-tobacco users. Both of these studies were based on data collected in northern Sweden as part of the World Health Organization MONICA (multinational monitoring of trends and determinants in cardiovascular diseases) project. In both reports, the cases and controls were identified in the 1990s.

Huhtasaari and colleagues⁴⁰ found an age adjusted OR for myocardial infarction (MI) of 0.89 (95% CI 0.62 to 1.29) for snus use versus no tobacco use, whereas smoking significantly increased risk of an MI (OR 1.87, 95% CI 1.40 to 2.48). In multivariate analyses smoking remained significantly associated with MI, whereas snus use was not.

Huhtasaari subsequently conducted a larger study than the one reported in 1992, and included more detailed tobacco use histories and closer matching of cases and controls (matched for sex, date of birth, and area of residence).⁴¹ This study found (after adjustment for multiple cardiovascular risk factors) that cigarette smoking significantly increased risk of an MI (OR 3.53, 95% CI 2.48 to 5.03), whereas snus use significantly reduced the risk (OR 0.58, 95% CI 0.35 to 0.94) compared with men who never became regular tobacco users. When the analysis focused only on fatal cases, there was a tendency towards increased risk in snus users, but this was not significant (OR 1.5, 95% CI 0.45 to 5.03).

There is no clear explanation for the difference in results between the Bolinder³⁴ and Huhtasaari^{40,41} studies, although the different study populations, time periods covered, and outcomes measured (sudden death versus non-fatal MI) may have contributed. The similar magnitude of effect for fatal cardiovascular events found in these studies is suggestive of a slightly increased risk overall. On the other hand it remains possible that the effect of snus in the Bolinder study was caused by some unmeasured (and therefore uncontrolled) confounding factor, with dietary habits and alcohol consumption being examples of baseline variables not measured in that study. This possibility is supported by a recent report of the effects of smokeless tobacco in the USA, based on analyses of the First National Health and Nutrition Examination Survey epidemiologic followup study (NHANES-1) data.⁴² This study had 96% follow up of the original 14 407 participants and 98% identification of death certificates for the 4604 decedents by 1992. Male smokeless tobacco users were found to have moderately increased risks of some disorders, but all of these excess risks disappeared when variables such as race and poverty were controlled for. For example, the crude hazard ratios for male smokeless users versus non-tobacco users were 1.5 and 2.1 for circulatory and respiratory diseases before adjustment, but after adjustment for confounders these hazard ratios became 1.0 and 0.9. One potentially serious flaw with this study⁴² is that pipe and cigar users were included in the "non-tobacco user" comparison group, seriously undermining confidence

in their conclusion that US smokeless tobacco users have similar mortality outcomes to non-tobacco users. We cite this paper as an example of the changes in outcomes that can result from controlling for baseline variables, rather than as evidence of the safety of US smokeless tobacco.

Bolinder *et al's* first study³⁵ found snus users to be at excess risk of a number of respiratory symptoms. For example, the OR for "cough in the morning" for snus users versus never tobacco users was 2.1 (95% CI 1.8 to 2.4), as compared with an OR of 7.9 for smokers versus never tobacco users. It is not easy to think of a plausible mechanism whereby exclusive snus use might cause respiratory symptoms. This study excluded all those who reported mixed use of snus and cigarettes or reported being an ex-smoker (n = 59, 864 excluded). However, the increased respiratory symptoms suggest the possibility that some of those reporting exclusive snus use were actually occasional or ex-smokers. Passive smoke exposure is another possible confounding factor that could potentially contribute to these findings. This study was initially funded by a health insurance group with the purpose of examining factors affecting sick leave and disability pensions. Some participants may have under-reported their recent or ex-smoking due to their belief that it either was not worth mentioning, or out of a concern that it may somehow affect their future benefits.

In reviewing the evidence from a range of clinical and experimental studies, Benowitz⁴³ concluded: "Overall, the epidemiologic and experimental data suggest that nicotine absorbed from smokeless tobacco, nicotine gum or transdermal nicotine is not a significant risk factor for accelerating coronary artery disease or causing acute cardiovascular events." This conclusion is supported by a recent case-control study that examined risk factors for stroke among Swedish men.⁴⁴ In multivariate analyses, controlling for other risk factors, smoking was related to increased risk of stroke (OR 1.74) whereas snus use was not (OR 0.87, 95% CI 0.41 to 1.83).

Given the inconsistencies in the results of these studies, it remains possible that snus users have a slightly increased cardiovascular risk as compared to never tobacco users, even after controlling for other confounding factors. However, all of the large studies of the effects of tobacco use on cardiovascular disease in Sweden are in agreement that "the use of smokeless tobacco (with snuff being the most studied variant) involves a much lower risk for adverse cardiovascular effects than smoking does".⁴⁵

Respiratory diseases

A Pubmed search did not identify any studies that specifically examined the effect of snus on respiratory diseases; similarly the IOM report did not address the effects of smokeless tobacco on respiratory illnesses.³ The reason for this is presumably that there is no plausible causal mechanism whereby smokeless tobacco could cause respiratory disease. A recent study of mortality in US smokeless users reported no increased risk of respiratory diseases in smokeless users.⁴² This contrasts heavily with the effect of continued smoking on chronic obstructive pulmonary disease, with 50% of elderly Swedish smokers developing the condition as compared with less than 20% of never smokers.⁴⁶

Diabetes

Bolinder³⁷ found that smokers had significantly higher fasting blood glucose values than never tobacco users whereas snus users were not significantly different from never users. Eliasson and colleagues⁴⁷ found that neither smoking nor snus use was associated with changed glucose tolerance or insulin concentrations. However, a more recent study by Persson⁴⁸ found an increased risk of (asymptomatic)

type 2 diabetes among both heavy smokers (25+ cigarettes per day) and heavy snus users (3+ cans per week), with significant odds ratios of 2.7 and 2.6, respectively, for these two groups as compared with non-tobacco users. It should be noted that this study specifically recruited men over 35 years old, 50% of whom had a family history of diabetes. The effects of snus on risks for diabetes are unclear and it may be that any effects are restricted to heavy users and/or those with a family history of diabetes.

Pregnancy

A Pubmed search did not identify any studies that had specifically examined the effects of snus use during pregnancy. However, given that animal studies have implicated nicotine as a cause of some of the widely known adverse effects of tobacco exposure during pregnancy (on both the health of the mother and healthy development of the fetus), it follows that snus use during pregnancy is likely to incur some of the risks associated with smoking during pregnancy.⁴⁹ The preliminary results of one study (as yet unpublished) have been presented at a conference earlier this year.⁵⁰ The study examined data from the Swedish Birth Register for women who delivered babies during 1999–2000. The study compared 789 snus users to 11 242 cigarette smokers and 11 500 women not using any tobacco. Smokers gave birth to babies weighing an average of 206 g (7.3 ounces) less than non-tobacco users. Snus users gave birth to babies weighing an average of 40 g (1.4 ounces) less than non-tobacco users. Snus users were also about twice as likely as non-tobacco users to deliver prematurely (perhaps partially explaining the slightly lower birth weight), and were more likely than both smokers and non-tobacco users to suffer pre-eclampsia. Clearly, the full results of this study and additional studies on this topic are required before coming to conclusions, particularly given the possibilities for confounding variables to cause small sized effects. However, given the known risks of nicotine in pregnancy, and the preliminary results of this unpublished study, it seems likely that snus use can cause adverse health effects in pregnancy and should not be promoted as safe for use in pregnancy. It would be a particular cause for concern were there to be evidence of increased snus use among women of reproductive age, without an equal or greater reduction in smoking in that group. Given that smoking during early pregnancy in Sweden has already declined from 31% in 1983 to 12% in 2000,³¹ it could be argued that the potential for snus to have a "positive" impact on smoking in pregnancy has similarly shrunk. It would seem as though Swedish women are on a positive trend towards tobacco-free pregnancies without snus, and that it would be best kept that way.

THE PATTERN OF NICOTINE USE IN SWEDEN OVER THE PAST CENTURY

Total consumption of snus and cigarettes in Sweden have changed dramatically over the past century, with the most pronounced changes occurring over the past 20 years when cigarette consumption has reduced significantly and at the same time snus consumption has risen significantly. Figure 2 provides only a crude snapshot of overall sales, that hides sex-specific changes and changes in the size of the population. Adult (over 14) cigarette consumption went from approximately 0.2 kg/person in the 1920s to 1.1 kg/person in 1970 and then down to 0.6 kg/person at the end of the 20th century. Across the same time points Snus consumption fell from 1.4 kg/person to 0.4 kg/person and then has increased again to 0.9 kg/person by 2000. Figure 2 also serves as a reminder of some of the other factors affecting cigarette consumption; the large drop in cigarette sales in 1997 was probably related to an 18% price increase in January of that

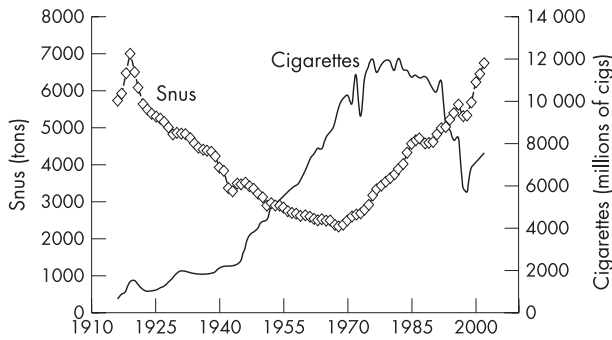


Figure 2 Sales of snus and cigarettes in Sweden 1916–2002 (source: Swedish Match 2003). Note that cigarette sales may not precisely reflect true domestic consumption in the same year, particularly during periods with price changes (for example, after 1996). Other discrepancies between consumption and registered sales have occurred, especially in the period after 1998, because of increasing sales in Sweden to consumers in neighbouring countries and large changes in the “market share” for cigarettes imported by organised illegal trade. Note also that the population in Sweden has increased by approximately 60% from 1916 to 2000.

year, and the rebound in 1999 was probably caused by a 24% price decrease in August of 1998.

Chewing tobacco is also available in Sweden, but the total amount sold is less than 1% of the quantity of snus sold. Similarly, in addition to cigarettes, cigars, cigarillos, pipe tobacco and “roll-your-own” (RYO) tobacco are available in Sweden. These represent a relatively small and diminishing segment of the smoking market. For example, 125 million cigars/cigarillos were sold in 1983, as compared with 58 million in 1999 (less than 1% of the number of cigarettes sold); 1510 metric tons of pipe/RYO tobacco were sold in 1983, compared with 906 tons in 1999 (and 4479 tons of cigarettes sold in 1999).

A more detailed picture of recent trends can be seen by examining prevalence of daily smoking and daily snus use by sex (fig 3). This shows a much larger drop in male smoking (from 40% in 1976 to 15% in 2002) compared with the fall in female daily smoking (34% in 1976 to 20% in 2002) coinciding with an increase in male daily snus use from around 10% in 1976 to 23% in 2002. Other surveys of tobacco use in Sweden such as those carried out by the Swedish government, or as part of the WHO MONICA project (discussed below), similarly show a greater reduction in male smoking prevalence than female smoking prevalence in Sweden from the 1980s (when more men than women smoked) to the late 1990s (when more women than men smoked).^{52–53}

One recent study has specifically examined whether snus use appears to have directly influenced smoking rates in northern Sweden.⁵³ This study used the dataset developed for the northern Sweden component of the WHO MONICA study. This involved collection of data from four representative population based surveys conducted in 1986, 1990, 1994, and 1999, including detailed questions on tobacco use among approximately 1500 adults at each time point. This study found stable prevalence of “all tobacco use” among men (at around 40%) over the 13 year period, but with male smoking decreasing from 23% to 14% and snus use increasing from 22% to 30%, as the proportion of snus using ex-smokers increased from 9% to 14%. In women, smoking prevalence remained stable from 1986 to 1994 at 27% then dropped to 22% in 1999 when snus use rose from 2% to 6% (fig 4).

A more detailed picture of the likely role of snus in smoking cessation in Sweden can be gained by examining the prevalence of ex-smoking among ever smokers by history

of snus use and by sex in the Rodu study.⁵³ As shown in fig 5, a higher proportion of male than female ever smokers had quit, and most of these had also used snus. The data from this study provide strong support for the role of snus in promoting smoking cessation among Swedish men (fig 5).

The same research group has recently published a prospective follow up study of over 70% of the participants in 1986, 1990, and 1994 who were successfully followed up in 1999 (n = 1651).⁵⁶ This study found a continuing trend away from smoking among men in northern Sweden, moving to a smoking prevalence around 10% in those followed up in 1999. Of those men who were smokers (no snus use) in the 1986–94 surveys, 39% had quit smoking by 1999, one third of whom had switched to snus use. Among women who were smokers at the baseline surveys, 30% had quit by 1999, only 10% of whom had switched to snus. This study concluded: “use of snus played a major role in the decline of smoking rates amongst men in northern Sweden. The evolution from smoking to snus use occurred in the absence of a specific public health policy encouraging such a transition.”

It should be noted that fig 4 (consistent with fig 3) shows that while cigarette smoking has fallen dramatically among Swedish men, overall tobacco use has not. Some may view this as a failure of tobacco control (compared with some other countries). We view changes in tobacco caused disease as the decisive factor when evaluating the effects of tobacco control, and as discussed below, these changes have been very positive for Swedish men. It could also be argued that this reduction in male smoking may have occurred without snus. Here we regard the comparison with Swedish women (little snus use, smaller smoking reduction, smaller health improvement) and the characteristics of male ex-smokers (large proportion switching to snus when quitting smoking) as strongly suggestive of snus having a direct effect on the changes in male smoking and health.

WHAT HAVE BEEN THE NET EFFECTS OF SNUS ON PUBLIC HEALTH IN SWEDEN

The reductions in male smoking prevalence that have occurred in Sweden over the past 25 years have been the largest of any developed nation in the world. At the same time, Swedish men have also experienced a notable reduction in the incidence of the major smoking caused diseases. To exemplify this, fig 6 shows the pattern of changes in lung cancer incidence in Sweden and its near neighbour, Norway, from 1960 to 1999. Since the mid 1970s there has been a

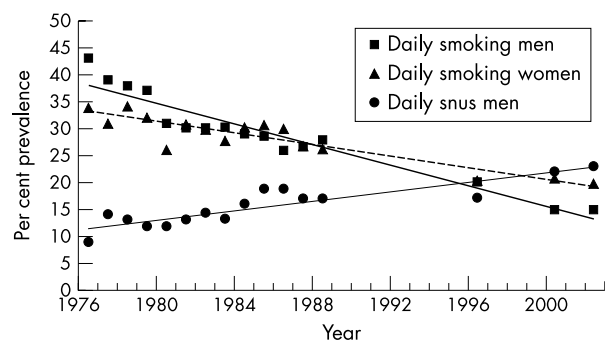


Figure 3 Prevalence of daily smoking for men and women (ages 18–70 years) in Sweden 1976–2002 and prevalence of daily snus use for men (age 18–70 years) in Sweden 1976–2002 with observation points (markers) and least square regression lines. 1976–1983 data were obtained from National Smoking and Health Association (NTS)⁵⁴ and 1988, 1996, 2000, and 2002 data were obtained from surveys performed as collaborative research projects by the Institute for Tobacco Studies and Research Group for Information and Societal Studies (ITS/FSI).⁵⁵

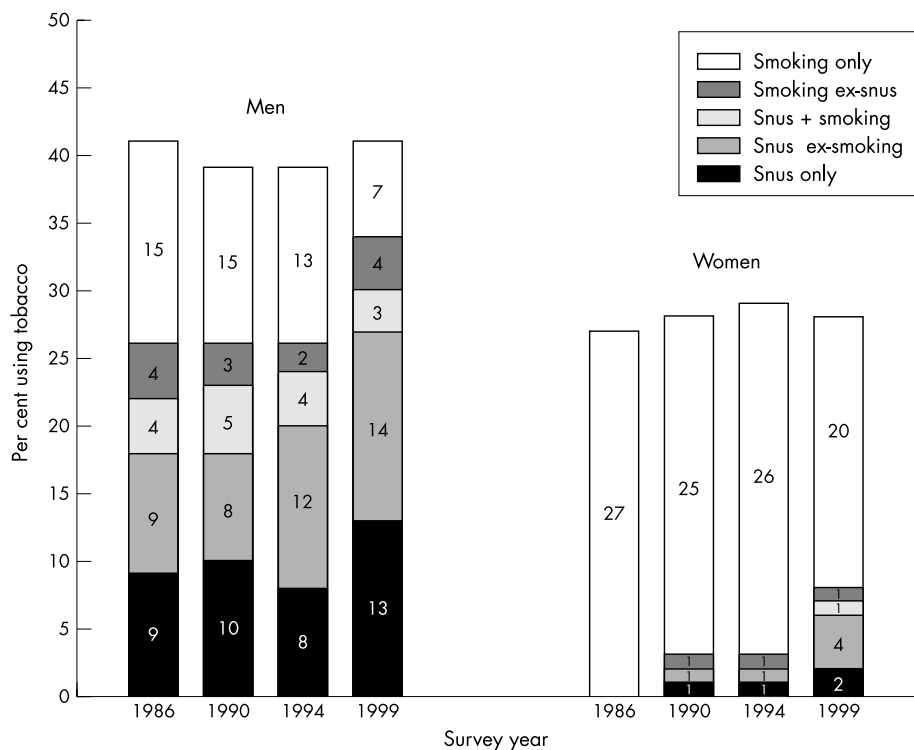


Figure 4 Prevalence of current tobacco use (mutually exclusive categories) among men and women aged 25–64 in two Swedish counties 1986–1999. Based on an original figure by Rodu *et al.*⁵³ Reproduced from the *Journal of Internal Medicine*, with permission.

pronounced reduction in the incidence of lung cancer in Swedish men, as compared with Swedish women, and both men and women in Norway.

As of 2000, Sweden has a lower standardised rate of male lung cancer incidence than any comparable developed nation

in the world. Sweden also has a low rate of oral cancer by international standards and this low rate has been falling over the past 20 years while snus use has increased. Sweden’s low rates of both lung and oral cancer are shown in fig 7.

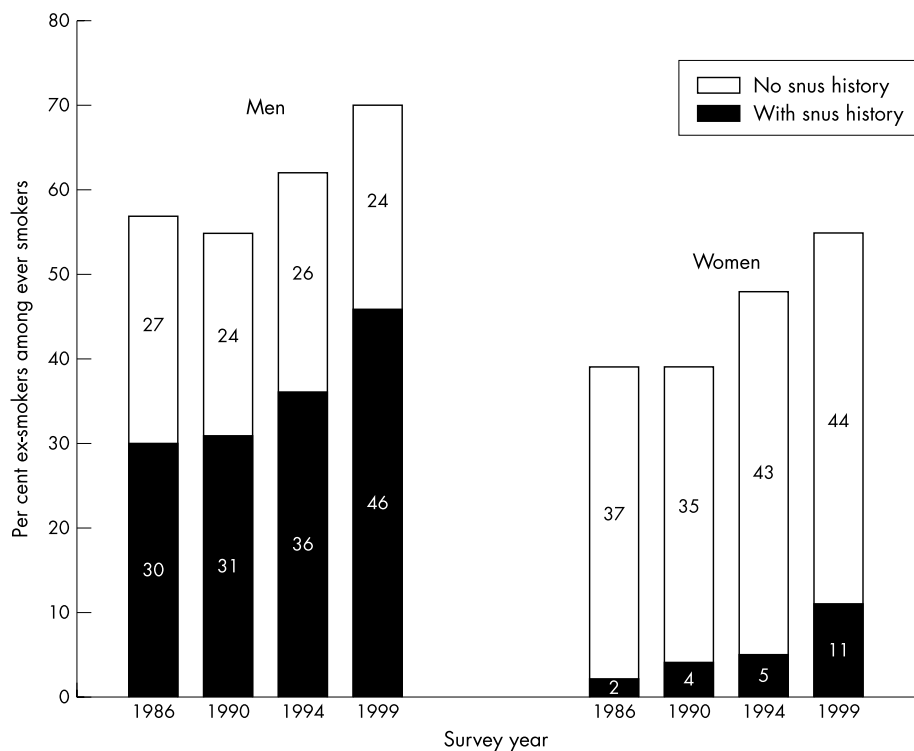


Figure 5 Per cent ex-smokers among ever smokers by snus use history among men and women aged 25–64 in two Swedish counties 1986–1999. Based on an original figure by Rodu *et al.*⁵³ Reproduced from the *Journal of Internal Medicine*, with permission.

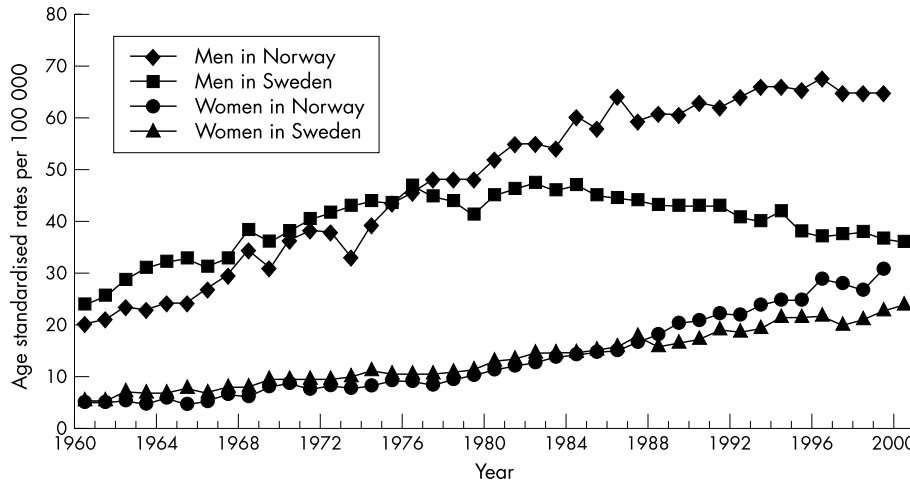


Figure 6 Lung cancer incidence for men and women in Sweden and Norway from 1960–1999 for age standardised rates per 100 000 inhabitants based upon census population in each country. Based upon an original figure from cancer registry sources compiled by Wicklin.⁵⁷

Interestingly Swedish men have also had a significant improvement in cardiovascular health over the same period. For example, Rosen and colleagues studied trends in heart attacks in Sweden over the years 1987 to 1995 (amounting to 360 000 separate heart attacks in total).⁵⁹ They found a 22% drop in heart attacks in men aged 30–64 years during that period, roughly double the decline among same aged women over the same period (fig 8).

It is noteworthy that these improvements in tobacco caused illnesses have occurred primarily in men, despite a stable consumption of tobacco among men during that time period. The main factor that has changed is that many Swedish men have switched from smoked tobacco to snus. Of course one cannot state with absolute certainty that if snus had not been available in Sweden that just as many men would have quit smoking either without assistance or perhaps by switching to nicotine replacement therapy. However, the pattern of sex differences in smoking cessation and snus use within Sweden, together with the between-country differences in smoking prevalence changes and health changes (comparing Sweden with other similar countries that have lower snus use, such as Norway),

strongly suggests that a significant portion of the health improvement among Swedish men over the past 20 years has been due to a large proportion quitting smoking or never starting to smoke, but using snus instead.

IS SNUS A “GATEWAY” TO SMOKING OR A PATHWAY FROM SMOKING IN SWEDEN?

It has been argued that smokeless tobacco could become a “gateway” product, hooking young people on nicotine from a cheaper and more easily concealed product, before they more easily move on to yet more addictive and harmful products such as cigarettes. For many reasons, the evidence from Sweden is not supportive of such a view. Firstly, if snus was acting to attract young people towards smoking one might expect the only country in Europe with a sizable snus market to have had the worst record for reducing smoking prevalence rather than the best. Secondly, when one examines the sex differences in tobacco use patterns, if snus was attracting young men towards smoking, one would expect the change in smoking prevalence to have been worse for men than for women, whereas it has been significantly better (that is, smoking prevalence has fallen more for men

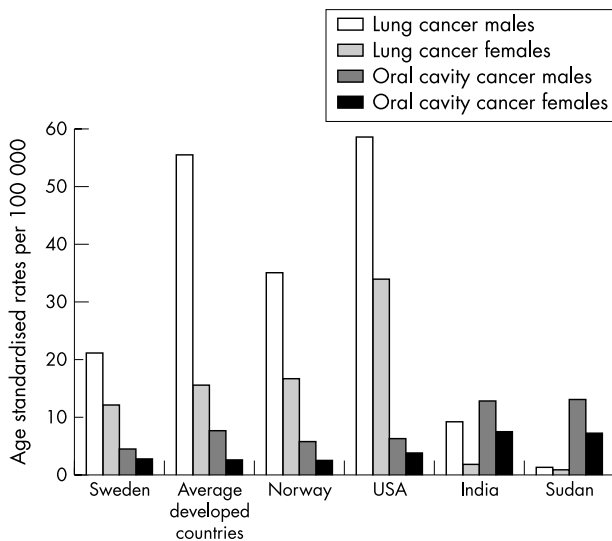


Figure 7 Age standardised rate of lung cancer and oral cavity cancer for males and females in selected countries and a global average for more developed countries based upon age standardised rates for 100 000 based upon world population census.⁵⁸

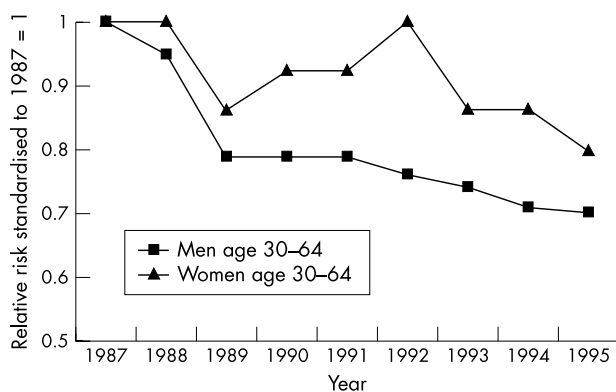


Figure 8 Incidence of myocardial infarction for men and women aged 30–64 years in Sweden 1987–1995. Age standardised index with relative risk of 1 at 1987. Derived from original figure from Rosen.⁵⁹ Reproduced from the *Journal of Internal Medicine*, with permission.

than for women in Sweden). Looking only at daily smoking prevalence among 16 year olds in Sweden, this has remained remarkably stable at around 11% for boys and 16% for girls for the past 20 years. Again this is not consistent with the idea that snus is acting as a gateway to smoking among boys. Thirdly, when one looks at the pattern of changes in tobacco use among Swedish men, the proportion of current smokers who are ex snus users is consistently smaller than the proportion of current snus users who are ex smokers (4% v 14% of the adult male population in 1999, with only 3% current users of both snus and smoked tobacco, in the Rodu *et al* 2002 study⁵³).

A study recently presented by Ramstrom⁶⁰ examined smoking status in Sweden by snus use, using data from a representative sample ($n = 6700$) of the Swedish population aged 16–79 years collected in 2001–2. In the sample of men, 15% were daily smokers and 20% were daily snus users (19% v 2% among women). Among 2879 men, 468 (16%) were primary daily snus users (that is, they started daily snus without having previously started smoking). Twenty per cent of this group subsequently became daily smokers, compared with 45% of men who were not primary snus users. This suggests that snus use is protective against smoking rather than a gateway towards it. It is possible that this pattern of results could be caused by a combination of age and cohort effects. However, when we examined this issue we found lower rates of smoking onset among primary snus users in both older (born 1922–56) and younger (born 1957–1985) cohorts. Among those men who ever became daily smokers, 71% with a history of snus use quit smoking completely, compared with 54% of those with no snus history. Of those men who have quit smoking completely after having used snus as a cessation aid, 75% are currently daily snus users and 25% have quit snus use as well. Of all those men who quit smoking and mentioned the use of a single smoking cessation aid, 62% stated that they used snus as a cessation aid, compared with 38% who mentioned using nicotine replacement therapy. Again this is more consistent with snus being a pathway from smoking.

A study recently reported by Gilljam and Galanti⁶¹ also suggests that snus has primarily been a pathway from smoking among Swedish men. Their study consisted of a survey of approximately 1000 current smokers and 1000 ex-smokers (all men aged 25–55 years). Twenty nine per cent of the ex-smokers had used snus to quit, and smoking cessation was significantly more likely among men who had used snus as compared with men who had not. Among those who used snus, 28% gave “health concerns” as their primary reason for

snus use (for example, to help quit smoking or because it was less dangerous than smoking).

A recent study of tobacco use among young people in Sweden reported a larger prevalence of combined snus and cigarette use⁶² than reported in adult studies. This study was based on a 1998 survey targeting all 15–16 year old children in Stockholm (the capital city). Only 1.3% of girls reported snus use so this paper focused on boys ($n = 6287$): 14.3% were cigarette users, 5.7% were snus users, and 13.8% used both. Thus the majority (71%) of male snus users at that age were also smoking tobacco, although it should be noted that these percentages include people using these tobacco products less than daily. This study also highlighted the fact that at this age the young people had not yet established a stable profile of tobacco use, and that tobacco use, and particularly combined smoking and snus use, was linked with a number of other problem behaviours. Thus the likelihood of being a current snus user was several times higher among boys who reported having been drunk (OR 9.6), or used illicit drugs (OR 2.4) compared with those who did not. The authors of this study concluded: “smokeless tobacco use in adolescence does not substitute cigarette smoking and can be an indicator of a drug- and risk-seeking lifestyle.” It therefore seems unlikely that either form of tobacco use is a “gateway” to the other, but rather that both are markers of risk taking behaviour in adolescent males in Sweden. Unless there is a more recent cohort effect, or a sustained difference in use patterns between Stockholm and northern Sweden, the data on tobacco use among Swedish men suggest that many of these combined non-daily users at age 15 will subsequently quit smoking and will transfer to exclusive snus use. However, given the high frequency of combined snus and cigarette use in this study, it is clear that the pattern of transitional and combined use of different tobacco products among young people should continue to be closely monitored. One study in Finland examined the effect on youth snuff use of legislation banning the sale of snuff in 1995.⁶³ It reported very little effect on snuff use (1% reduction in prevalence) and some negative consequences, including 12% of existing snuff users switching to smoking.

A recent report on smokeless tobacco use in the USA and Sweden concluded that at least 77% of US smokeless users and 83% of Swedish snus users appear to be “non-gateway” users in that their snuff use did not lead to smoking or their smoking preceded their snuff use.⁶⁴

Overall, the patterns of tobacco use in Sweden suggest that those who start using snus are less likely to become smokers, and that among people who become smokers, their chances of quitting smoking are higher if they use snus.

WHAT ARE THE LESSONS FROM THE SWEDISH EXPERIENCE?

None of the studies reviewed in this paper were randomised controlled trials and so no specific causal relations can be inferred from any individual study. Both within and outside Sweden, smoking is primarily influenced by factors other than availability of smokeless tobacco (for example, real price of cigarettes, health education, smoke-free air policies, industry marketing, etc). That having been said, we feel that the analysis of the change in patterns of tobacco use and health outcomes over time described here, including the comparison between countries and between sexes within Sweden, is suggestive of a positive rather than a negative net effect of snus use on tobacco smoking and hence on public health in Sweden. A key component of the evidence on this is the differential smoking quit rate between men and women. Most of the other important background factors affecting cigarette consumption (for example, price) would be expected to have similar effects on men and women and so

What this paper adds

There is considerable debate over the role of alternative non-smoked tobacco products in reducing the harm to health caused by tobacco. The widespread use of a specific type of smokeless tobacco (snus) in Sweden has been cited as an example where this may have had an overall positive effect on health.

This review suggests that snus is notably less harmful to health than cigarettes, and that in Sweden snus has served as a pathway from smoking, rather than a gateway to smoking among Swedish men. A proportion of the reduction in illness caused by tobacco among Swedish men may be attributable to their shift from smoking to snus use. Policy and regulations on nicotine delivery should be designed to effectively discourage use of the most harmful products (that is, cigarettes) rather than products that are much less harmful.

they are unlikely to account for the sex differences in quitting. One important reason for male smoking cessation rates being higher is that many more Swedish men than women use snus.

We do not assume that these same benefits would automatically transfer to other countries, or even that they will remain constant in Sweden. Most countries of the world have very limited (or no) regulation of tobacco ingredients, or marketing. There may be little to stop a company from introducing a product that delivers significantly higher quantities of toxins than snus, and directing the marketing at young people, or even young non-smoking women of childbearing age. In such a scenario it is perfectly possible that snus or other smokeless products would have a negative effect on public health. However, in Sweden we have a concrete example in which availability of a less harmful tobacco product has probably worked to produce a net improvement in health in that country.

The main conclusions that can be drawn from the Swedish Experience are as follows:

- Implementation of stronger, evidence based regulation of tobacco products is necessary to avoid unintended public health consequences from both tobacco availability and tobacco bans in Sweden and worldwide.^{7 65}
- Significant proportions of smokers are capable of transferring their nicotine dependence from an ultra-fast nicotine delivery product (a cigarette) to a medium rate nicotine delivery product (snus) so long as it delivers comparable amounts of nicotine, and so long as it is competitive on price, accessibility, and long term availability. This suggests that were a comparable non-tobacco pharmaceutical product (for example, a high dose nicotine gum) to become available and be able to compete on an even (or advantageous) basis, it may also have similar effects in helping a significant proportion of the smoking population transfer to a safer product. Unfortunately pharmaceutical nicotine replacement therapy (NRT) is currently regulated as part of a different regulatory system (along with medicines) that puts it at a competitive disadvantage as compared with tobacco products.⁶⁶ The total elimination of most of the toxins in the nicotine delivery product (as in NRT) is clearly preferable to the marginal or unverified reductions in toxin delivery that are typically achieved by tobacco products.
- It appears to be extremely unlikely that nicotine is capable of stimulating cancer under normal use conditions. The media regularly issues scare stories about nicotine replacement products potentially causing cancer, usually

stemming from media coverage of laboratory studies in animals or test tubes that interpret their findings as implying that nicotine may cause cancer in humans. In Sweden large numbers of snus users are consuming large quantities of nicotine, absorbed at a single part of the body (the mouth), along with significant concentrations of other carcinogens, for most of their adult life without evidence of increased cancer risk. The epidemiology of snus and cancer in Sweden does not support the view that nicotine itself is a risk factor for cancer.²⁷⁻³³

- Snus is certainly not harmless. It can cause reversible lesions in the mouth, it most likely causes harmful effects to the unborn fetus when used by a pregnant woman, and long term use may contribute to cardiovascular disease (although most of the available evidence suggests that cardiovascular risks are not increased by snus).
- Snus is clearly less harmful to the individual user than smoked tobacco, and also less harmful than the types of smokeless tobacco used in some other parts of the world, notably Sudan and India.²⁹ The manufacturers of snus have voluntarily set fairly sensible toxicity standards for their product in order to reduce health risks as much as technologically possible. These or more thorough standards should now be applied across the industry and across countries. It could be argued that these same standards should also be applied to the other tobacco products (chewing tobacco, cigars, and pipe tobacco) that Swedish Match also produces and sells, and that a similar set of standards should apply to all nicotine delivery products.

In accepting that we now have smokeless tobacco products available that are less harmful than the dominant products (cigarettes), public health professionals and policymakers need to decide whether to focus effort on restricting access to the most harmful products (smoked tobacco products), or focus much time, energy, and legislation on restricting access to the least harmful products, that under some circumstances can produce a net public health benefit.

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REFERENCES

- 1 Slade J. Innovative nicotine delivery devices from tobacco companies. In: Ferrence R, Slade J, Room R, Pope M, eds. *Nicotine and public health*. Washington DC: American Public Health Association, 2000;209-28.
- 2 Shiffman S, Gitchell JG, Warner KE, et al. Tobacco harm reduction: conceptual structure and nomenclature for analysis and research. *Nicotine and Tobacco Research* 2002;4(suppl 2):S133-29.

- 3 **Stratton K**, Shetty P, Wallace R, *et al*, eds. *Clearing the smoke: assessing the science base for tobacco harm reduction*. Institute of Medicine, National Academy of Sciences. Washington DC: National Academy Press, 2001.
- 4 **Bates C**. Clearing the smoke or muddying the water? *Tobacco Control* 2001;**10**:87–8.
- 5 **Hirshhorn N**. Clearing the smoke – or spreading the fog? *Nicotine and Tobacco Research* 2002;**4**(suppl 2):S191–3.
- 6 **Burns DM**, Benowitz NL. Public health implications of changes in cigarette design and marketing. In: National Cancer Institute. *Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine*. *Smoking and Tobacco Control Monograph No 13*. Bethesda, Maryland: US Department of Health and Human Services, 2001.
- 7 **Bates C**, Fagerstrom K, Jarvis M, *et al*. European Union policy on smokeless tobacco: a statement in favour of evidence based regulation for public health. *Tobacco Control* 2003;**12**:360–7.
- 8 **Wahlberg I**, Wiernik A, Christakopoulos A, *et al*. Tobacco-specific nitrosamines. A multidisciplinary research area. *Agro-Food-Industry Hi-Tech* 1999;**8**:23–8.
- 9 **Osterdahl BG**, Sloarach SA. Volatile N-nitrosamines in snuff and chewing tobacco on the Swedish market. *Food Chem Toxicol* 1983;**21**:759–762.
- 10 **Nilsson R**. A qualitative and quantitative risk assessment of snuff dipping. *Regul Toxicol Pharmacol* 1998;**28**:1–16.
- 11 **Djordjevic MV**, Fan J, Bush LP, *et al*. Effects of storage conditions on levels of tobacco specific N-nitrosamines and N-nitrosamino acids in U.S. moist snuff. *J Agr Food Chem* 1993;**41**:1790–4.
- 12 **Andersson G**, Bjornberg G, Curvall M. Oral mucosal changes and nicotine disposition in users of Swedish smokeless tobacco products: a comparative study. *J Oral Pathol Med* 1994;**23**:161–7.
- 13 **Brunnemann KD**, Qi J, Hoffmann D. Aging of oral moist snuff and the yields of tobacco specific n-nitrosamines (TSNA). Progress report prepared for the Massachusetts Tobacco Control Program. Department of Public Health, Boston Massachusetts, 2001. <http://www.tobacco.org/News/010622BostonRe.html>.
- 14 **Brunnemann KD**, Qi J, Hoffmann D. Chemical profile of two types of oral snuff tobacco. *Food Chem Toxicol* 2002;**40**:1699–703.
- 15 **Brunnemann KD**, Hoffmann D. Chemical composition of smokeless tobacco products. In: *Smoking and Tobacco Control Monograph 2: smokeless tobacco or health: an international perspective*. Bethesda, Maryland; Department of Health and Human Services. 1993:96–106.
- 16 **Idris AM**, Nair J, Oshima H, *et al*. Unusually high levels of carcinogenic nitrosamines in Sudan snuff (Toombak). *Carcinogenesis* 1991;**12**:1115–8.
- 17 **Idris AM**, Ibrahim SO, Vassstrand EN, *et al*. The Swedish Snus and the Sudanese Toombak: are they different? *Oral Oncology* 1998;**34**:558–66.
- 18 **Hoffmann D**, Djordjevic MV, Fan J, *et al*. Five leading U.S. commercial brands of moist snuff in 1994: assessment of carcinogenic N-nitrosamines. *J Natl Cancer Inst* 1995;**87**:1862–9.
- 19 **Gothiatek Standard**. www.gothiatek.com
- 20 **Curvall M**, Romert L, Norlen E, *et al*. Mutagen levels in urine from snuff users, cigarette smokers and non tobacco users – a comparison. *Mutation Research* 1987;**188**:105–10.
- 21 **Holm H**, Jarvis MJ, Russel AH, *et al*. Nicotine intake and dependence in Swedish snuff takers. *Psychopharmacology* 1992;**108**:507–11.
- 22 **Larsson I**, Curvall M, Enzell CR. Disposition of nicotine and cotinine in plasma, saliva and urine of snuff users. Poster presented at the Third European Congress of Biopharmaceutics and Pharmacokinetics, Freiburg, 1987.
- 23 **Henningfield JE**, Kennan RM. Nicotine delivery kinetics and abuse liability. *J Consult Clin Psychol* 1993;**61**:743–50.
- 24 **Russell MAH**, Jarvis MJ, Feyerabend C, *et al*. Nasal nicotine solution: a potential aid to giving up smoking? *BMJ* 1983;**286**:683–4.
- 25 **West R**, Hajek P, Foulds J, *et al*. A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology* 2000;**149**:198–202.
- 26 **Fant RV**, Henningfield JE, Nelson RA, *et al*. Pharmacokinetics and pharmacodynamics of moist snuff in humans. *Tobacco Control* 1999;**8**:387–92.
- 27 **Schildt E-B**, Eriksson M, Hardell L, *et al*. Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. *J Cancer* 1998;**77**:341–6.
- 28 **Lewin F**, Norell SE, Johansson H, *et al*. Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck. *Cancer* 1998;**82**:1367–74.
- 29 **Critchley JA**, Unal B. Health effects associated with smokeless tobacco: a systematic review. *Thorax* 2003;**58**:435–43.
- 30 **Ahlbom A**, Olsson U, Parshagen G. *Health hazards of moist snuff*. Report of the National Board of Health and Welfare, Sweden, 1997.
- 31 **Hirsch JM**, Livian G, Edward S, *et al*. Tobacco habits among teenagers in the city of Goteborg, Sweden, and possible association with dental caries. *Swed Dent J* 1991;**15**(3):117–23.
- 32 **Ye W**, Ekstrom AM, Hansson LE, *et al*. Tobacco, alcohol and the risk of gastric cancer by sub-site and histologic type. *Int J Cancer* 1999;**83**:223–9.
- 33 **Lagergren J**, Bergstrom, Lindgren A, *et al*. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. *J Cancer* 2000;**85**:340–6.
- 34 **Bolinder G**, Alfredsson L, Englund A, *et al*. Smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers. *Am J Public Health* 1994;**84**:399–404.
- 35 **Bolinder G**, Ahlberg BO, Lindell JH. Use of smokeless tobacco: blood pressure elevation and other health hazards found in a large-scale population survey. *J Intern Med* 1992;**232**:327–34.
- 36 **Bolinder G**, Norén A, Wahren J, *et al*. Long-term use of smokeless tobacco and physical performance in middle-aged men. *Eur J Clin Invest* 1997;**27**:427–33.
- 37 **Bolinder G**, de Faire U, Alfredsson L. Effects of long term smokeless tobacco use on metabolic cardiovascular risk factors and hemostatic function. MD thesis. Stockholm, 1997.
- 38 **Bolinder G**, Norén A, de Faire U, *et al*. Smokeless tobacco use and atherosclerosis: an ultrasonographic investigation of carotid intima media thickness in healthy middle-aged men. *Atherosclerosis* 1997;**132**:95–103.
- 39 **Bolinder G**, de Faire U. Ambulatory 24-h blood pressure monitoring in healthy, middle-aged smokeless tobacco users, smokers, and non tobacco users. *Am J Hypertens* 1998;**11**:1153–63.
- 40 **Huhtasaari F**, Asplund K, Lundberg V, *et al*. Tobacco and myocardial infarction: is snuff less dangerous than cigarettes? *BMJ* 1992;**41**:1252–6.
- 41 **Huhtasaari F**, Lundberg V, Eliasson M, *et al*. Smokeless tobacco as a possible risk factor for myocardial infarction: a population-based study in middle-aged men. *J Am Coll Cardiol* 1999;**34**:1784–90.
- 42 **Accortt NA**, Waterbor JW, Beall C, *et al*. Chronic disease mortality in a cohort of smokeless tobacco users. *Am J Epidemiol* 2002;**156**:730–7.
- 43 **Benowitz NL**. Snuff, nicotine and cardiovascular disease: implications for tobacco control. *J Am Coll Cardiol* 1999;**34**:1791–3.
- 44 **Asplund K**, Nasic S, Janler U, *et al*. Smokeless tobacco as a possible risk factor for stroke in men. A nested case-control study. *Stroke* 2003;**34**:1754–9.
- 45 **Asplund K**. Smokeless tobacco and cardiovascular disease. *Prog Cardiovasc Dis* 2003;**45**:383–94.
- 46 **Lundback B**, Lindberg A, Lindstrom M, *et al*. Not 15 but 50% of smokers develop COPD? – report from the obstructive lung disease in northern Sweden studies. *Resp Med* 2003;**97**:115–22.
- 47 **Eliasson M**, Asplund K, Evrin PE. Relationship of cigarette smoking and snuff dipping to plasma fibrinogen, fibrinolytic variables and serum insulin. The Northern Sweden MONICA Study. *Atherosclerosis* 1995;**113**:41–53.
- 48 **Persson P-G**, Carlsson S, Svanström L, *et al*. Cigarette smoking, oral moist snuff use and glucose intolerance. *J Intern Med* 2002;**248**:103–10.
- 49 **Ernst M**, Moolchan ET, Robinson ML. Behavioral and neural consequences of prenatal exposure to nicotine. *J Am Acad Child Adolesc Psychiatry* 2001;**40**:630–41.
- 50 **England L**, Klebanoff M. The effect of snuff and smoking on the developing fetus. Paper presented at the Annual Meeting of the Society for Maternal-Fetal Medicine, San Francisco, 7 February 2003.
- 51 **Wallskar H**, Sylwan L. *Smoke-free children-a report: the first 10 years*. Swedish Cancer Society, Swedish Heart-Lung Foundation and the Swedish Institute for Public Health, 2002.
- 52 **Henningfield JE**, Fagerstrom KO. Swedish match company, Swedish snus and public health; a harm reduction experiment in progress? *Tobacco Control* 2001;**10**:253–7.
- 53 **Rodu B**, Stegmayr B, Nasic S, *et al*. Impact of smokeless tobacco use on smoking in northern Sweden. *J Intern Med* 2002;**252**:398–404.
- 54 **Osterman T**. Tobaksvanor i Sverige (Tobacco Habits in Sweden) Socialstyrelsen redovisar 1986:9. National Board of Health and Welfare, Stockholm, 1986:152.
- 55 **Ramström L**, Osterman T. Survey sponsored by the Swedish National Institute of Public Health, Stockholm, Sweden.
- 56 **Rodu B**, Stegmayr B, Nasic S, *et al*. Evolving patterns of tobacco use in northern Sweden. *J Intern Med* 2003;**253**:660–5.
- 57 **Wicklin B**. Differences in smoking habits and lung cancer incidence between Sweden and Norway. Poster presented at the 3rd International Conference on Smokeless Tobacco. Stockholm, September 2002.
- 58 **Ferlay J**, Bray P, Pisani P, *et al*. GLOBOSCAN 2000: Cancer incidence, mortality and prevalence worldwide, Version 1.0 IARC CancerBase No. 5 Lyon, IARC Press, 2001.
- 59 **Rosen M**, Alfredsson L, Hammar N, *et al*. Attack rate, mortality and case fatality for acute myocardial infarction in Sweden during 1987–95. Results from the National AML register in Sweden. *J Intern Med* 2000;**248**:159–64.
- 60 **Ramstrom L**. Patterns of use of Swedish smoke-free tobacco, snus: A gate leading to smoking, or a way to give it up? Abstract from 4th SRNT European Conference, Santandar, October 2002. *Nicotine & Tobacco Research* 2003;**5**:268.
- 61 **Gilljam H**, Galanti MR. Role of snus (oral moist snuff) in smoking cessation and smoking reduction among Swedish men. Paper presented at 9th annual meeting of the Society for Research on Nicotine and Tobacco, New Orleans, 2003.
- 62 **Galanti R**, Wickholm S, Gilljam H. Between harm and dangers oral snuff use, cigarette smoking and problem behaviours in a survey of Swedish male adolescents. *Eur J Public Health* 2001;**11**:340–5.
- 63 **Merne ME**, Tieskos JT, Syrjanen SM. Snuff use and smoking among senior high school students: effects of a snuff sales ban. *Oral Dis* 1998;**4**:207–12.
- 64 **Kozlowski LT**, O'Connor RJ, Edwards BQ, *et al*. Most smokeless tobacco use is not a casual gateway to cigarettes: using order of product use to evaluate causation in a national US sample. *Addiction* 2003;**98**:1077–85.
- 65 **Slade J**, Bickel W, Crowley T, *et al*. The role of managing nicotine in controlling the tobacco epidemic. In: Ferrence R, Slade J, Room R, Pope M, eds. *Nicotine and Public Health*. Washington DC: American Public Health Association, 2000:483–501.
- 66 **McNeill A**, Foulds J, Bates C. Regulation of nicotine replacement therapies (NRT): a critique of current practice. *Addiction* 2001;**96**:1757–68.