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**Is Swedish snus a preventive
substitute for cigarettes?**

Diploma thesis



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Written Declaration

I declare that I completed the submitted work individually and only used the mentioned sources and literature. Concurrently, I give my permission for this diploma/bachelor thesis to be used for study purposes.

Prague 15.03.2010

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List of Abbreviations:

MI:	Myocardial Infarction
TNSAs:	Tobacco specific nitrosamines
FTND-ST:	Fagerstrøms Test for Nicotine Dependence-smokeless Tobacco
HONC:	Hooked on Nicotine Checklist
BP:	Blood Pressure
RR:	Relative Risk
CI:	Confidence Interval
OR:	Odds ratio
HR:	Hazard ratio
WHO:	World Health Organization
HOMA:	Homeostatic model assessment

Introduction

This is a review paper on the usage of smokeless tobacco, snus. A narrative view of published papers and other data sources (for example, internet-base information) on snus use, use of other tobacco products, and changes in health status in Sweden and Norway.

The snus consumption have increased substantially during the recent decades and today more than every fifth male adult uses snus daily in Norway and Sweden. Some of the publications made from snus are written in Scandinavia, and therefore some of the papers are directly translated from Scandinavian into English. It must be emphasized that this is not a study on snus, rather a review paper.

This text will shortly be about the dramatic increase in snus usage among adults in Scandinavia, mainly Sweden and Norway the last decade and their short and long-term effects. In the 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. 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. 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 the fact is no less deadly than standard cigarettes. The introduction and marketing of these new 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 products switching that may have had a positive effect on smoking and public health. This review paper aims to get a better view and knowledge about smokeless tobacco usage in Scandinavia and its likely effects on tobacco smoking and public health in Sweden and Norway respectively.

1. What is Snus?

“Snus” is the name given to the form of smokeless snuff tobacco commonly used in Sweden and Norway. 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 discharged.

In most countries smokeless tobacco constitutes only a small proportion of the total tobacco market, except in Sweden and Norway where snus constitutes approximately 20 to 50% of the total tobacco sold.

In Norway and Sweden usage of snus has increased in recent decade whereas smokeless tobacco is prohibited in European Union since 1992(1). The rationale behind the ban was to protect public health by preventing people from starting to use

new tobacco products and to ensure proper functioning of the European market. Sweden, where the use of snus has been widespread, was granted derogation from the ban on its entry to the EU in 1995 due to a long tradition of the use of snus in this country. Finland Entered the EU at the same time as Sweden, but did not ask for derogation. Norway, which is not member of the EU but a member of the European Economic Areas, the marketing of moist snus is allowed.

1.1. Manufacturing

There is a choice of 60 tobacco plants, *Nicotiana* species that can be used to prepare Swedish snus. However, the majority of the commercial tobacco produced and sold in Scandinavia is manufactured from the *Nicotina Tobaccum* plant.

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 (2). 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% flavoring, table 1. It is claimed that the heating process kills bacteria, producing a relatively sterile product. The product is then packaged in cans.

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 (3). 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 manufacturing may itself have prevented microbial activation of nitrites (4).

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 TSNAs. 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 (5).

Although different products vary in their pH levels, snus typically has a pH in the range 7.8–8.5. 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 (6). 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 (7).

1.2. Chemical composition of Swedish snus

Table 1. Content In Swedish snus, according to Bollinder (8)

Since 2005 the tobacco industry is forced by law to declare the constituent in their products. The chemical composition and the nicotine content in snus depend on the tobacco as well as the cultivation, harvest, production process and storage.

Chemical substance	Percent (%)
Tobacco	40-50 %
Water	45-60%
Sodium	1.5-3.5 %
Bicarbonate	1.5-3.5 %
Moisturizing agents (glycerol and propylene glycol)	1.5-3.5 %
Aroma additives	<1%
Nicotine	0,5-1.3%
TSNA	4-5 µg/g
PAH	< 5 µg/g

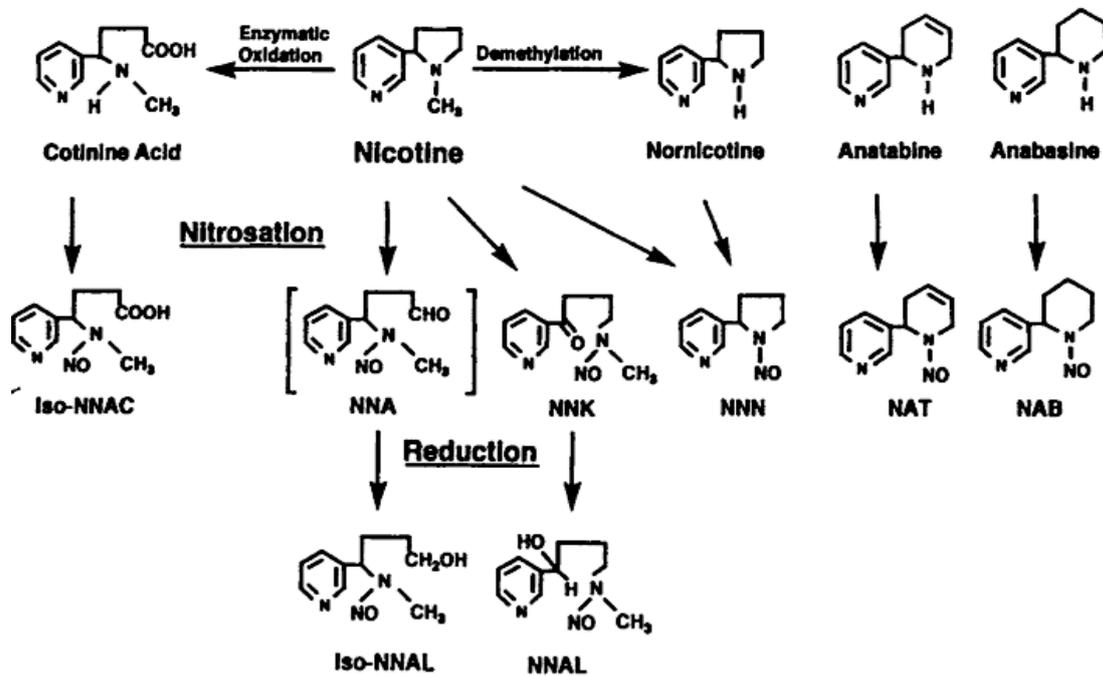
More than 3000 chemical substances are found in snus such as amino acids, carbohydrates, lignin, fatty acids, chlorophyll and their breakdown products as well as heavy metals, such as lead and cadmium. Secondary metabolites include alkaloids, nicotine being the predominant (85-95% of total alkaloids) but also TSNAs, flavors, polyphenols and aromatic substances.

Nicotine is the most important addictive substance in smokeless tobacco and their nicotine content varies between 0.5-1.3% nicotine depending on the type of snus.

About 30 carcinogens have been identified in chewing tobacco.

Among these, the major contributors to the carcinogenic activity are the tobacco specific N-nitroamines (TSNA), figure 1. These agents are formed exclusively from nicotine and from minor tobacco alkaloids, primary during the processing, fermentation, and aging of tobacco. The TNSA are organ specific carcinogens, I.e., independent of the route of their application, they induce mainly tumors in specific tissues and organs.

Figure 1. Formation of TSNA . Taken from Hoffmann and Djordjevic (9).



The level of TSNA varies between different types of smokeless tobacco and levels have declined in snus used in Sweden and USA since 1980s, table 2. Possible as a result of the difference in manufacturing and storing procedures, snus had been claimed to lower the levels of some harmful substances that many of the brands available in North American and notable lower levels than exist in the smokeless tobacco used in Africa and India.

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 ($\mu\text{g/g}$)	NNN ($\mu\text{g/g}$)	Total TSNA ($\mu\text{g/g}$)
Sweden					
Three brands* (1990–91) ¹⁵	Swed Match		1.4–2.1	5.2–5.7	9.2–11.2
Eltan 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)
Skoal, 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)
Skoal Bandts 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	Canwood	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	Canwood	3.2 (3.4–3.0)	0.2 (.24–.16)	3.1 (3.4–2.8)	4.1 (4.5–3.7)
Skoal (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.

Table 2. Levels of TSNA (NNK and NNN), nicotine and manufacturer of different types of chewing tobacco. Taken from tobaccoprogram.org, used sources for their table (6 and 7).

Snus also contains antioxidants and nitrates, which could partly neutralize the hazardous effects from nicotine and TSNA, these effects are yet to be discovered in the future.

1.3. Nicotine

The absorption of nicotine from snus through the oral mucosa is slower than when the tobacco is smoked, can be seen at figure 2.

Free nicotine or unionized nicotine can cross the cell membranes and bind to receptors at the autonomic ganglia, the adrenal medulla and the central cholinergic synapses. Exposure to nicotine results in effects that work through the activation of several nervous system pathways, the cardiovascular effects are mainly due to stimulation of the sympathetic ganglia and the adrenal medulla whereas parasympathetic stimulation leads to gastrointestinal effects (13).

The level of unionized nicotine increases with higher pH, which facilitates the absorption of nicotine (10). The tobacco industry is perfectly aware of this and is continuously increasing pH in their products. This makes the consumer gradually more dependent on their product. In Sweden there is a huge debate about this topic in 2009, because the tobacco producer intentionally doesn't inform about these changes, and consequently more addicted consumers. Small changes in the pH create a substantially greater amount of free nicotine, table 4. Previous studies on smokeless tobacco report that the pH ranges from 5.39 to 7.99 and the proportion of unionized nicotine varied between 0.23%-48.3% (11) where moist snus had the highest mean pH.

Brand	Nicotine (mg/g)	pH	Unionized nicotine %
General (loose)	7.0	8.55	77.149
General Maxi Portion	8.5	8.70	82.242
General Portion	7.0	8.75	83.764
General White Portion	7.5	8.40	73.335
Grov snus (loose)	7.0	8.30	66.608

Table 3 (12), a small overview of the most commonly sold types of snus in Scandinavia and their nicotine, pH and unionized nicotine (free nicotine).

1.4. Nicotine delivery

Snus contains 0.5-1.3% nicotine. An average consumer daily dose is 19 g. This adds up to around 150 mg of nicotine, where around half is absorbed (50-75 mg).

Compared with a person that smokes 20 cigarettes daily, 40-50 mg will be absorbed, a regular snus user will get the same amount of nicotine as a person that smokes 30 cigarettes daily (19 g snus = 30 cigarettes) (1).

As shown in fig 2, 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. These nicotine levels are very similar to those found in cigarette smokers, 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 about twice as high as the nicotine concentrations typically obtained from nicotine replacement therapy. The nicotine levels shown in fig 2 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.

Cigarette smokers will have a peak of nicotine in their blood circulatory system after 5-10 minutes, then dropping fairly quick when stopped. At the other hand, snus consumers will have a peak after 15-20 minutes and it can be substantially elevated for a prolonged period of time (1).

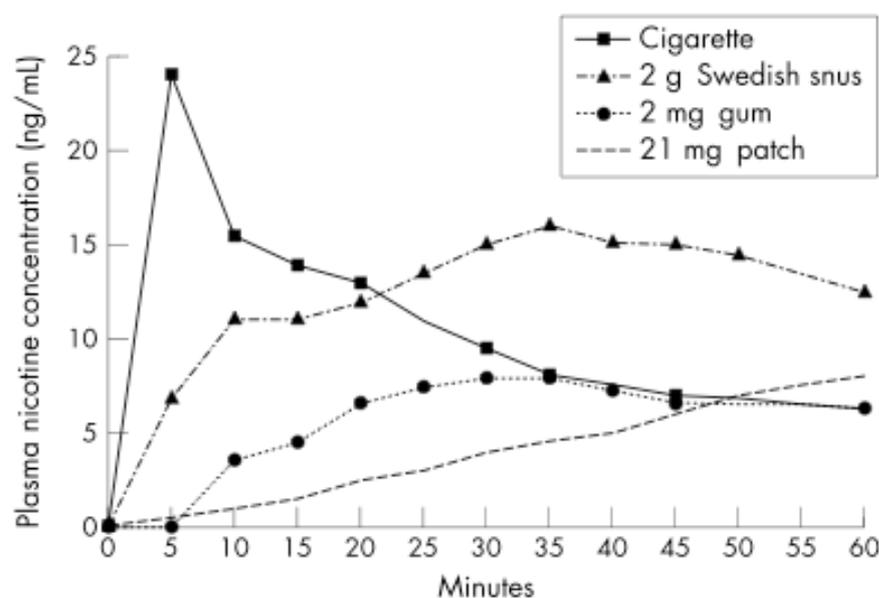


Figure 2. Venous blood concentration in nanograms of nicotine per milliliter (ng/ml) of plasma as a function for various nicotine delivery systems; all plasma nicotine concentrations have been made reconfigured such that the pre-absorption levels starts at 0 ng/ml (that is, take out the baseline difference). Swedish snus plasma nicotine concentration in 10 Swedish users from a single 2 g pinch of loose snus adapted from Holm et al. (14). Cigarette and 2 mg nicotine gum, adapted from Russel et al. (16). 21 mg patch adopted from Stratton et al. (17).

1.5. Different types of snus

- Portion snus is a prepackaged powder in small bags made of the same material as teabags. It comes in smaller quantities than the loose powder but is considered easier to handle and exploration than the loose powder. Moreover there are two sub types of portion snus:
 Type A: Original Portion is the first form of portion snus. The sachets are sprayed with water during the manufacturing process, resulting in a brown pouch
 Type B: White portion is a drier form of portion snus. It does not undergo a process of being sprayed with water during the manufacturing process, so the

pouch material appears white. It also contains various flavors like mint, eucalyptus etc.

- Loos snus is a moist powder, which can be portioned and packed into a cylindrical or spherical shape with the fingertips.

1.6. Price

Loose snus is sold in a tin weighing 45 g.

Portion is most commonly sold in three different variants, mainly mini, normal/large and maxi. The weights may vary, but the most sold snus labels share their weight.

Mini portion weight is 0.5 g, with 20 pieces per tin. Standard portions weigh is 1 g, with 24 portions per tin, and maxi portions weight is 1.7 g, with 17 pieces per tin.

Despite weight, the price for both 24 g and 45 g tins are approximately 3-5 Euro in Sweden and 8-10 euro in Norway, as Norwegian consumption taxes are considerably higher, per April 2010.

2. Health risks

2.1. Nicotine dependence

Given the pattern of nicotine absorption describes above there can be no doubt that snus is dependence forming in much the same way as other forms of tobacco consumption. There are clear evidence that users of products with snus like delivery profiles develop cravings and nicotine withdrawal symptoms when attempting to abstain, and find it difficult to quit as will be written below.

In a cohort study from Stockholm written by the medical journal Addiction in 2009 (18), the question asked was whether symptoms of nicotine dependence, addiction, and withdrawal symptoms differ between exclusive smokers, exclusive snus users or dual users.

The survey instrument was a self-completed questionnaire. The questionnaire included questions on health behaviors, psychosocial characteristics and the use of tobacco and alcohol. There were participants of 3 different groups for both genders. The mean age was 17.6 years.

- Current exclusive smokers (n=466)
- Exclusive snus users (n= 209)
- Dual users (n= 144)

In order to measure addiction the, researchers used various measure tools:

- **Fagerstrøms Test for Nicotine Dependence-Smokeless Tobacco (FTND-ST).** The Fagerstrøms, table 4, nicotine dependence test is a well-developed and validated questionnaire for smokers, while few nicotine dependence measures have been evaluated and researched for smokeless tobacco, in this case snus. In 2005 J. Ebbert, Patten and Schroeder (19) made the FTND-ST with the following scoring system for snus users.

Question	Answers	Points
1. How soon after your wake up do you place your first dip?	Within 5 min	3
	6-30 min	2
	31-60 min	1
	After 60 min	0
2. How often do you intentionally swallow tobacco juice?	Always	2
	Sometimes	1
	Never	0
3. Which chew would you hate to give up the most?	The first one in the morning	1
	Any other	0
4. How many cans/pouches per week do you use?	More than 3	2
	2-3	1
	1	0
5. Do you chew more frequently during the first hours after awakening than during the rest of the day?	Yes	1
	No	0

Table 4. FTND-ST. A score of 5 or more indicated a significant dependence, while a score of 4 or less shows a low to moderate dependence

- **Hooked on Nicotine Checklist (HONC)** is a test to describe short-term patterns of smoking acquisition exhibited by smoker, table 5. The HONC performs equally well when used with smokers of any age, gender, racial or ethnical background, and level of experience with smoking.

Table 5. HONC

Questions	NO	YES
1. Have you ever tried to quit, but couldn't?		
2. Do you smoke <u>now</u> because it is really hard to quit?		
3. Have you ever felt like you were addicted to tobacco?		
4. Do you ever have strong cravings to smoke?		

5. Have you ever felt like you really needed a cigarette?		
6. Is it hard to keep from smoking in places where you are not supposed to?		
7. Did you find it hard to concentrate because you couldn't smoke?		
8. Did you feel more irritable because you couldn't smoke?		
9. Did you feel a strong need or urge to smoke?		
10. Did you feel nervous, restless or anxious because you couldn't smoke?		

Result: The analysis was significantly different by gender. Dual users reported the highest addiction and withdrawal symptoms. The analysis also proved that dual users characterized by earlier age at onset of tobacco use compared to smokers and exclusive snus users. Median age of initiation of each product in dual users different significantly, yet no significant differences appeared between age at initiation of either cigarette or snus compared to the corresponding age in the groups of exclusive users. There will be written more about this topic in section 7.

As expected all three groups of users reported some symptoms of nicotine dependence. Exclusive snus users scored higher at the FNDT-ST compared with exclusive cigarette smokers and even higher addiction rate amongst dual users. Also in HONC, they found slightly higher addiction to tobacco among exclusive snus users and dual snus users compared to smokers.

Withdrawal symptoms were divided into two groups:

1. Nine symptoms of psychological nature: craving, upset and tension, impaired concentration, depressed mood, irritability and anger, restlessness, increased appetite/weight, anxiety and sleep disturbances.
2. Three symptoms of physical nature: muscular pain, nausea and heart palpitations.

When comparing the three groups of tobacco users, the conclusion was that the highest score were recorded for psychological symptoms among dual users and the lowest score among exclusive snus users compared to the mean score of the whole group. Physical factors did not differ between the three groups. It must be noted that snus users reported a lower frequency of quit attempts. This typology might be linked with topography of snus use. A snus dip is held in in between the lips and the gum, this makes it easy to conceal and therefore forbidden (e.g., in schools) as well as not putting someone else health at risk. Therefore, the low perceived health risk might be the possible explanation for the low frequency of quilt among exclusive snus users

compared to smokers.

Dual users and exclusive snus users reported back higher frequent nicotine dependence symptoms compared to exclusive smokers as well as reporting feeling addicted to tobacco more often than smokers, with dual users reporting fivefold higher prevalence compared to exclusive smokers.

3.0. Snus and the risk of cardiovascular diseases

Bolinder and colleagues conducted a series of epidemiological and clinical studies focusing on cardiovascular risk factors and myocardial infarction already back 1990s. The newest study in cardiovascular disease and snus exposure was published in 2007 by m. Hergens, Bolinder et al. (20) looked at the following topics.

- Assessing the risk of fatal and non-fatal myocardial infarction among men who use snus but have never smoked.
- Compare the probability of all deaths and cardiovascular death among snus users and none snus users among subjects who suffered from a myocardial or ischemic stroke.
- To study whether snus use affects the risk of fatal and non-fatal stroke among never smoking men.
- To investigate if there is a difference in risk from snus use between subtypes of stroke, such as ischemic, hemorrhagic and unspecified stroke.
- To compare the prevalence of high blood pressure among snus users and none snus users among never smoking men.

3.1. Myocardium infarction

The study was designed as a case-control study. In a case-control study, it's used exposure data collected in a retrospective form, from questionnaires in a population based case control-study. Patients, who recently were diagnosed with the disease under the study, were compared with individuals without the disease, so called controls.

In all, the total of 1432 cases of MI, aged 54-70, who had suffered either a fatal or a non-fatal MI (1173 nonfatal and 259 cases of fatal outcome), and 1810 controls who never suffered from MI.

Result: Age groups and hospital catchment area was adjusted and it proved no increased risk of MI among former and current snus users. On the other hand, increased risk was observed for fatal MI, both among former and current snus users, table 6.

Snuff use	Controls		All Cases		Non –fatal cases		Fatal cases	
	N	N	OR* (95% CI)	N	OR* (95% CI)	N	OR* (95% CI)	
Never	598	293	1.0§	248	1.0§	45	1.0§	
Former†	12	7	1.2 (0.46–3.1)	6	1.2 (0.43–3.2)	1	1.7 (0.21–13.6)	
Current	28	10	0.73 (0.35–1.5)	7	0.59 (0.25–1.4)	3	1.7 (0.48–5.5)	

Table 6. Association between snus use and MI among never smoking men. The association are expressed as OR with 95% CI. Taken from Hergens and Bollinder(20).

3.2. Myocardial infarction and stroke

Hergens and Bolinder also studied all employees within the construction industry in Sweden between 1963-1993, total of 118 395 participants that never smoked with no prior myocardial infarction, followed in a cohort study. A cohort study can be simplified as a group of individuals, which are followed over time regarding disease incidence occurrence. A cohort member must be at risk (alive and free of the disease under the study) when the follow up starts. In the study, the participants where excluded with disease like MI, stoke or hypertension prior investigation.

In total, 3651 (2810 non fatal, 841 fatal) cases of MI and 3249 (2968 non fatal, 281 fatal) cases of stroke were identified during follow up. There are three different types of cerebral stroke, ischemic, hemorrhagic and unspecified. 70% of the cases were ischemic, 17% hemorrhagic and 13% unspecified. The average age at diagnosis was 66,1, 59, 4, 65,6 years among patients with ischemic, hemorrhagic and unspecified stroke, respectively,

Result: Compared to non-tobacco users, no overall increased risk of acute MI or stroke was observed among snus users. There was an increased risk of fatal MI 1.3 RR 95% CI 1.1-1.6. All subtypes of stroke were increased, especially the ischemic part with RR 1.6 CI 95% 1.0-2.6, figure 3.

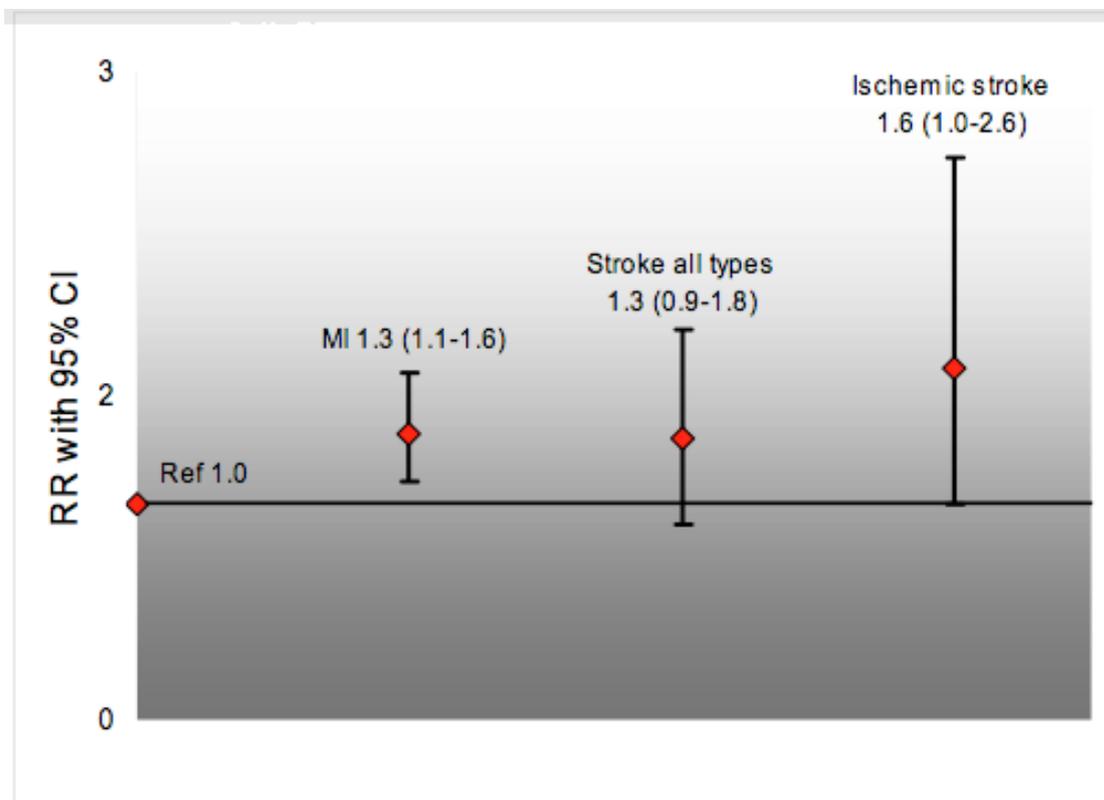


Figure 3. Adjusted RR with 95 % CI for fatal MI, ischemic stroke and all types of

stroke among snus users. Taken from Hergens and Bollinder (20).

3.3. Hypertension

In this study, Hergens and Bollinder (20) the definition of high blood pressure was systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg at baseline. Among the participants 120 926 never smoking men was in the analysis, with approximately 4400 cases of hypertension were identified in the register. Among those with normal blood pressure at baseline, 751 cases with high blood pressure or hypertension were observed during follow up.

Result: There was a clear trend toward hypertension among the snus users compared toward never snus users. When taking age into consideration, it was observed slightly increased BP among snus users in the older age compared to the younger groups. Also during follow up an increased risk of hypertension and high blood pressure was present among the snus users.

4. Cancer

Smokeless tobacco and the risk of cancer have been evaluated thoroughly in several reports. Both the International Agency for Research on Cancer and the Scientific Committee on Emerging and Newly Identified Health Risks concluded that smokeless tobacco is associated with an increased risk for several types of cancer, such as oral cancer and pancreatic cancer. On the other hand the risk of cancer from use of Swedish moist snus is not as strong, but can not be ruled out. The main scientific research done on Swedish snus is done on oral and pancreatic cancer. Even though, there are various results from the studies and at moment its hard to evaluate the real health risk of cancer from usage of snus. The tobacco-industry has used the uncertainty of the various researches and today there are no cancer warnings at Swedish snus, rather the vague “this product may be harmful for your health”. This change was adjusted from the previous warning, “this product may cause cancer” for approximately 5 years ago.

4.1. 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 on the mouth, head and neck.

Practically every regular snus user will in the beginning have some damages at the mucosa. In the start it's a reddish change as a sign of irritation. After a time the mucosa becomes with and thicker and it might develop leukoplakia. This is thought to be a pre stadium of oral cancer (21).

Snus cause a number of non-malignant oral diseased, including oral lesions and dental caries (21) however it appears as thought the lesions produced by snus are reversible and disappear of snus is cease (22).

Two large case-control studies in Sweden showing no increased risk of cancer on the head, neck or mouth among snus users (23 and 24).

A panel of Norwegian scientist had a critical review on the two Swedish publications and found some misleading and weak points, and concluded that it was impossible to draw any conclusions from the publications (25).

Lewin and colleagues (26) conducted a similar designed study, identifying cases of head and neck cancer in two regions in Sweden between 1988 and 1991 and matched controls. This study on the found 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 was 1.0 (95% CI 0.6 to 1.6.) Similar there were no significant relations between duration of snus use or lifetime consumption and head/neck cancer.

In 2007 there was a publication in Lancet by Lou and Colleagues (27) studies once the risks for cancer of the oral cavity (and lung and pancreas) among Swedish snus users. Detailed information about tobacco smoking and snus use was obtained from 279 897 male Swedish construction workers in 1978-92, as written before. Complete follow up until the end of 2004 was accomplished through links with population and health registers. Just like Bollinger did her studies, they focused on the group or workers who reported to be never smokers.

Result. They found 60 cases of oral cancer of the non-smokers. Snus was unrelated to incidence of oral cancer (0.8, 95% CI 0.4-1.7) and concluded that they were unable to confirm any excess of oral or lung cancer in snus user.

The newest publication found on PubMed dating from 2008 by Roosaar (28) Shows a slightly different a new picture of snus and oral cancer. In a cohort study comprised of 9967 men who participated in a population based survey back in 1973-74 that was follow up until the end of 2002.

Result: Statistically significant increase in the incidence of the combined category of oral and pharyngeal cancer among daily users (snus) an IR of 3.1, 95% CI 1.5-6.6 was found. Although the combined previous literature on snus and oral cancer weigh toward no association, this population based prospective study provide suggestion evidence of snus related risk that cannot be ignored.

4.2. Esophagus and stomach cancer

With so many carcinogenic factors as mentioned above (in the chemical composition of snus), there are without doubt increased risks of cancers in various organs. Among these the gastrointestinal track seems like it has the largest predisposition for developing neoplasia. These include esophagus, stomach, anal canal and pancreas.

Lasergen and colleagues (29) conducted a case control study designed to test the association between smoking, snus and alcohol use, and cancer of the esophagus and stomach in Sweden.

Result. Combined smoking and alcohol use was strongly associated with esophageal squamous cell carcinoma for heavy users compared with newer users. OR 23.1 for heavy users compared with newer users. Snus use on the other hand was not significantly associated with any of the cancer site under the study in a variety of analyses. There was a possible link, in a relatively small size of sub samples (n= 14 cases) of snus use and esophageal squamous cell carcinoma. The OR was 2.0 for use over 25 years versus never snus use, and the authors concluded no significant risk associated between snus usage and the risk of the studies tumors.

4.3. Colon, rectal and anal cancer

In mars 2010 there was published an article about cancer in colon, rectal and anal region from tobacco users, snus users and combined in International Journal of Cancer. It was the same construction workers that had been followed in so many previous studies, as written previously in this review-paper. The study was completed by Nordenvall and colleagues (30). Hazard Ratio (HZ) can be considered to be an estimate of relative risk.

Result: After 37 years of follow up, smoke had some rather derogatory numbers. For colon cancer the increased risk was marginally elevated (HR 1.08, 95% CI 0.99-1.99), On the other hand, a modest elevation risk was seen in rectal cancer (HR 1.16, 95 % CI 1.04-1.30) and a substantially excess risk of anal cancer (HR 2.41, 95% CI 1.06-5.48). Snus use was not significantly associated with an increased risk of colorectal or anal cancer, although the point estimate for colon cancer was similar to that observed among smokers. The between link between rectal and anal cancer was declined.

4.4. Pancreas cancer

Two rather new studies concerning snus and pancreas cancers have taken place in 2007 and 2010. Both conclude that snus is linked with relative increased risk of pancreas cancer, The newest article posted mars 2010 by Song and colleagues (31) had a focus on the carcinogenic effects of cigarette smoke and snus on pancreas, using a transgenic

Pancreatic cancer is the forth leading cause of death among both men and women, Comprising 6% of all cancer-realted deaths. The incidence of pancreatic cancer has risen slowly over the years. The disease is know for its notoriously difficult diagnosis in its early stages. At the time of diagnosis, 52% of all patiens have distant disease at 26% have regional spread. The relative 1-year survival is only 24% and the overall 5-year survival rate for the disease is less than 5%. Overall the incidence of pancreatic cancer has been relatively stable for decades, the incidence of pancreatic cancer in males has been slowly dropping over the past 2 decades, while the incidence in females has increases slightly. These trends probably represents the effect of changing smoking rates for men and women. (32)

mouse model. These findings provide a throughout insight into the mechanism by which tobacco products are likely to promote carcinogenesis both, which was little known before the investigation. The study examined the carcinogenic effects of an aqueous extract of cigarette smoke and snus in mouse models of chronic pancreatitis and a wild type mouse (control mouse).

Result: Mice with the injected tobacco extract developed significant pancreatic ductile epithelial flattening and severe glandular atrophy compared with untreated transgenic mice. The epithelial cells of the ducts had a high proliferative index, minimal apoptosis and chronic inflammation. There was also shown an up regulation of TNF-alpha and increased expression of IL-6, TGF-beta and SDF-1. Simplified this proved the snus carcinogenic effects on pancreatic tissue.

Lancet concluded in 2 studies published in May 2007 that it appears to increase the risk for pancreatic cancer.

One of them is an article by Lou and Colleagues (27), the same publication as written about under the oral cancer topic in this review.

Result: Snus use was independently associated with increased risk of pancreatic cancer. RR risk for regular users of snus 2.0 95% CI 1.2-3.3, compared with never users of any tobacco. Also in this paper, there was the question or not if snus was linked with lung cancer, but they were unable to confirm any excess of lung cancer among the users, table 7.

	Lung	Pancreas
Never users	73	37
Current smokers	700	124
Current snus users	51	84

Table 7. Mortality rate for cancer in lung and pancreas male construction workers, according to tobacco use (27).

5. Diabetes

There is evidence that smokers are at increased risk of developing type 2 diabetes, as well as the condition underlying diabetes, I.e., insulin resistance and impaired glucose tolerance. This finding has stimulated to research the relationship between snus use and diabetes type 2. Five epidemiological studies have examined the relationship between use of Swedish snus and diabetes or metabolic syndromes incidence or prevalence. Three studies found an elevated risk for heavy snus user, but two studies found no association.

The classification of impaired glucose tolerance and diabetes according to WHO 1985 criteria, I.e. 2 h plasma glucose levels between 7.8 and 11.0 mmol L⁻¹ for impaired glucose tolerance (n=172) and 11.1 mmol L⁻¹ or higher for diabetes (n=55). HOMA(the homeostatic model assessment) is a method used to calculate insulin resistance and

Karolinska hospital in Stockholm with Persson and colleagues (33) investigated the association between cigarette smoking and use or snus, and impaired glucose tolerance and type 2 diabetes. It was performed a population based cross sectional study of glucose intolerance and tobacco use in Stockholm 1992-1994. 3120 men in the age 35-56 years, of whom 52% had a family history of diabetes. Oral glucose tolerance test was performed, and 55 men detected with type 2 diabetes and 172 with impaired glucose tolerance.

Insulin resistance was based on HOMA. All the men had to fill out a questionnaire about snus usage and cigarette smoking, for snus they asked for weekly number of cans(50 g each) consumed.

Results: It was previously proved that smoking caused insulin resistance (34). This effect could be due to a stimulation of the sympathetic nervous system by nicotine.

The risk of developing diabetes type 2 is higher among snus users than smokers. Smokers have 1.3 OR 95% CI, while OR 1,5 95% CI among intermittened snus users, compared with control group. Even worse outcome for snus users using 3 cans a week, the OR was 2,7 95 % CI for catching diabetes 2. Just for an understanding, the research proved that smokers inhaling over 25 cigarettes daily had OR 2,6 95% CI. Table 8

Tobacco use	Normal glucose tolerance (n ^a)	Impaired glucose tolerance			Type 2 diabetes		
		n ^a	OR ^b	95% CI	n ^a	OR ^b	95% CI
Cigarettes							
Never	1072	62	1.0		14	1.0	
Former	995	61	0.9	0.6–1.3	21	1.3	0.7–2.7
Current	714	43	1.0	0.7–1.6	17	1.3	0.6–2.7
No. of cigarettes day⁻¹							
Never	1072	62	1.0		14	1.0	
1–24	1494	81	0.9	0.6–1.3	25	1.1	0.5–2.1
25+	204	22	1.3	0.7–2.2	13	2.6	1.1–5.8
Duration of smoking							
Never	1072	62	1.0		14	1.0	
≤ 19 years	678	39	0.9	0.6–1.4	11	1.3	0.6–2.9
20+ years	1026	65	1.0	0.7–1.4	27	1.3	0.7–2.6
Moist snuff							
Never	1915	121	1.0		34	1.0	
Former	376	19	0.7	0.4–1.2	5	0.8	0.3–2.0
Current	492	26	0.8	0.5–1.3	13	1.5	0.8–3.0
No. of boxes of snuff week⁻¹ in current snuffers							
Never	1915	121	1.0		34	1.0	
≤ 2	235	10	0.7	0.4–1.4	1	0.2	0.0–2.0
3+	256	15	0.8	0.4–1.4	12	2.7	1.3–5.5
Current consumption of cigarettes or snuff							
Never	895	55	1.0		9	1.0	
Moist snuff only	121	6	0.9	0.4–2.1	4	3.9	1.1–14.3
Cigarettes only	517	31	1.0	0.6–1.6	14	1.8	0.7–4.5

^aThe numbers differ as a result of missing data.

^bMultiple logistic regression estimated odds ratios, adjusted for age (35–40, 41–46, 47–51 and 52–56 years), body mass index (≤ 24.9, 25.0–27.9, 28.0–29.9 and 30.0+ kg m⁻²), family history of diabetes (yes/no), physical activity (high/low) and alcohol consumption (low, medium and high).

Table 8. Diabetes type 2 among cigarette smokers and snus users. Taken from Persson et al.(33)

Another cross-sectional study by Wandell and colleagues (34) found no association between snus usage and metabolic syndrome or newly diagnosed diabetes. They evaluated current and former snus users as well as dosage level among men 1859, aged 60 years, in Stockholm, Sweden,

A well-conducted cohort study concluded that the use of snus was not associated with increased risk of diabetes by Eliasson in 2004 (35). These investigations studies the effects of snus use on the risk of Diabetes type 2, as well as its underlying conditions, among a large number of Swedish men. Snus users did not have increased risk of developing any of these conditions.

6. Musculoskeletal system

Only one article was published about the topic injuries at the musculoskeletal system and snus, dating back to 1997 by the Norwegians Heir and Eide (36).

480 people attending compulsory military service in Norway under a period of hard physical activity was examined to find attributing factors for sports injuries. Under a period of 10 weeks, 25 % of the attending got some sort of injury either to muscles or the skeleton. 50 % smoked cigarettes and 15% was regular snus users. Smokers with at least 10 cigarettes daily got easily stress injuries. At the regular snus users, the stress injuries were twice as often than in smokers. A hypothesis for this could be the effect of snus on vasoconstrictor, cause local blood flow dysfunction and nerve conductance dysfunction.

7. Occurrence of snus in Norway

The average consumption of snus in Norway was 500 tons in the 1950's and then decreased substantially toward 250 and 290 tons during 1973-1993. From 1997-2000 it had increased back up to 368 tons. Average 103 g for each Norwegian and 3 kg for each snus users. Statens tobakkskaderåd /National Council on Smoking and Health(37) started their measuring of snus usage in 1985, so its we have to assume and look at similar numbers from Sweden. Most of the Swedes started using snus in the 1970s at 25 years of age and above. Looking into the 1980's the trend was gradually younger snus users and less cigarette smokers.

Already in 1985 12% of the Norwegian male population used snus regularly in the age group 65-74 years, while men at 16-24 years, only 9% used it regularly. The 1990s was a decade of gradually more snus users, among the younger population, aged 16-continued to get fans. The other side of the parameter, the elderly, it was a gradually decrease among users . Women were holding back at the snus and only 2-3% used the smokeless tobacco products in the 1990s.

In recent decades the sale increased dramatically.

Among adolescents and teenagers between 16-24 years of age, the total of 14% used snus daily and 11% sometimes. There are substantially differences between male and female. 21% of all men in the age group 16-24 used snus daily vs. 6% of the female group. The increase has been dramatically large since 2000. Among females under 25 years, there has been a 300% increase the last years. Table 9

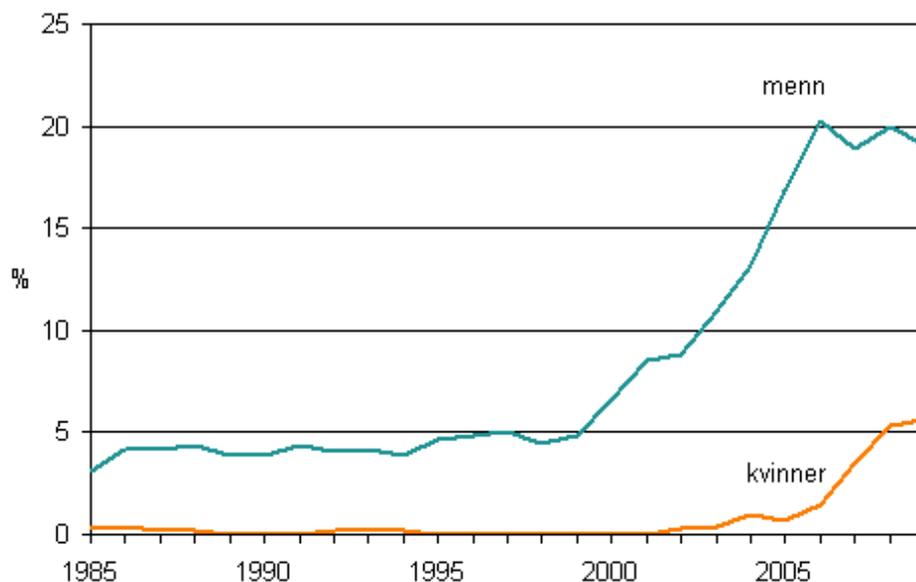


Table 9(21) Menn=Male Kvinner=Female.
 Taken from the Norwegian National Council on Smoking and Health (37).

Large increase is observed among young male that snuses.

The highest amount of snus consumers are in male aged 16-44 years. The total number of snusers in this group have increased greatly, especially during 1995 until 2005. The incline is seen in both regular and intermitted use. Table 9

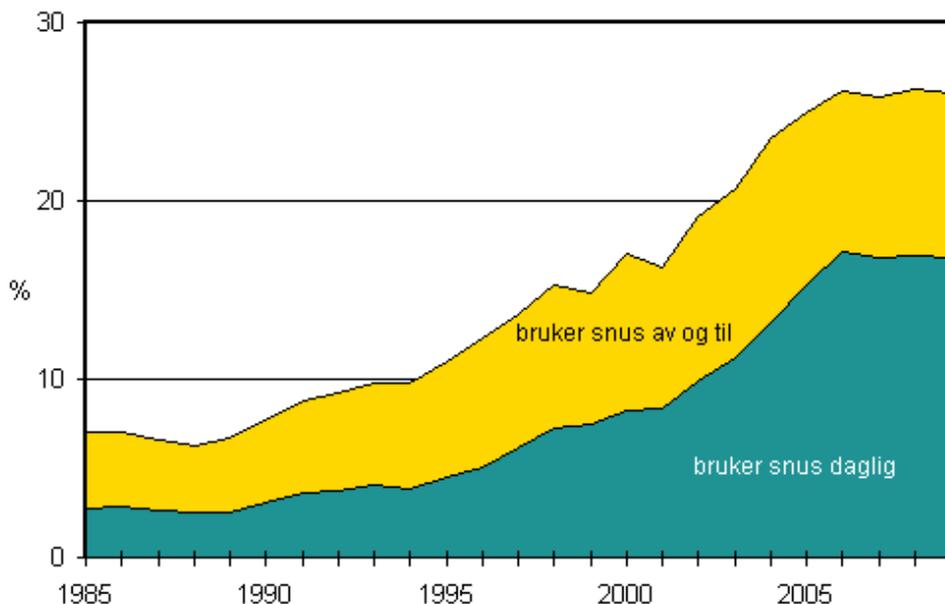


Table 10 (21) Snus av og til=intermitted use of snus. Bruker snus daglig=daily use
 Taken from the Norwegian National Council on Smoking and Health (37).

Less smokers, increasing snus users

Among the youngest men(16-24 years) its now more common to use snus than smoking cigarettes. Its in this group that smoking has its most prominent loss of users. Among females. Table 11

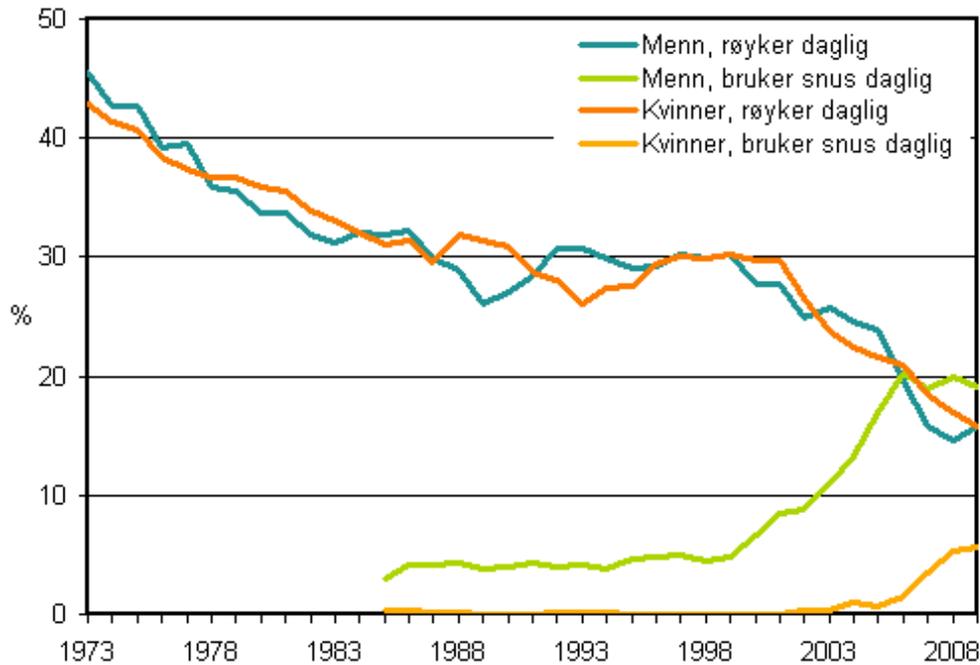


Table 11. Men, røyker daglig= male, daily smokers Menn, bruker snus daglig= male, daily snus users Kvinner, røyker daglig= females, smoking daily Kvinner, bruker snus daglig= females, daily snus users.

Taken from the Norwegian National Council on Smoking and Health (37).

8. Conclusion

None of the studies reviewed in this paper was randomized controlled trails and so no specific relations can be inferred from any individual study.

- Snus is certainly not harmless. There is not such a thing as harmless tobacco.
- Usage of snus gives higher nicotine dependence than smoking. So trying to implicate that snus is a good substitute for quitting smoking is misleading.
- Snus gives hypertension and increased risk of fatal MI. What needs to be emphasized is the need for further investigation, before making a definite conclusion.
- Snus is a great provoker of ischemic cerebral stroke as well as other types of stroke.
- Snus is a direct link between cancer. The highest probability is pancreatic and oral cancer. There are some studies that can not prove the direct link between oral cancer and snus usage, but there is also here much more studies that needs to me made.
- There is a increased chance of developing Diabetes type 2 from regular snus usage.
- Snus is clearly less harmful to individuals use than smoked tobacco. The manufacturers of snus have voluntarily set fairly sensible toxicity standards for their products in order to reduce health risks as much as possible.
- Public health professionals and policymakers need to decide whether to focus on restricting access to the most harmful products (smokes tobacco products),

or focus much time, energy, and legislation on restricting access to the least harmful products.

- 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 Norway, Sweden and worldwide.

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