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Summary of the epidemiological evidence relating snus to health

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ABSTRACT

Interest in snus (Swedish-type moist snuff) as a smoking alternative has increased. This wide-ranging review summarizes evidence relating snus to health and to initiation and cessation of smoking. Meta-analyses are included. After smoking adjustment, snus is unassociated with cancer of the oropharynx (meta-analysis RR 0.97, 95% CI 0.68–1.37), oesophagus (1.10, 0.92–1.33), stomach (0.98, 0.82–1.17), pancreas (1.20, 0.66–2.20), lung (0.71, 0.66–0.76) or other sites, or with heart disease (1.01, 0.91–1.12) or stroke (1.05, 0.95–1.15). No clear associations are evident in never smokers, any possible risk from snus being much less than from smoking. "Snuff-dipper's lesion" does not predict oral cancer. Snus users have increased weight, but diabetes and chronic hypertension seem unaffected. Notwithstanding unconfirmed reports of associations with reduced birthweight, and some other conditions, the evidence provides scant support for any major adverse health effect of snus. Although some claims that snus reduces initiation or encourages quitting are unsoundly based, snus seems not to increase initiation, as indicated by few smokers using snus before starting and current snus use being unassociated with smoking in adults (the association in children probably being due to uncontrolled confounding), and there are no reports that snus discourages quitting.

1. Introduction

Smokeless tobacco is used worldwide, but the products vary considerably. In parts of North Africa and Central and South-East Asia the tobacco is sometimes heavily roasted, often used with other products, such as betel nut, slaked lime and areca nuts (Critchley and Unal, 2003; International Agency for Research on Cancer, 2007a; Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), 2008), and may contain high levels of carcinogenic nitrosamines (Idris et al., 1991; Stepanov et al., 2005) and other carcinogenic impurities, including significant quantities of polycyclic aromatic hydrocarbons (International Agency for Research on Cancer, 1985). The product used also varies between the USA and Sweden, the only North American and European countries where smokeless tobacco is commonly used (International Agency for Research on Cancer, 2007a). In the USA chewing tobacco is common, and moist and dry snuff are also used, but in Sweden a type of moist snuff known as snus is the dominant product (Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), 2008). This review concentrates on the rapidly accumulating epidemiological evidence relating snus to health.

Swedish-type moist snuff ("snus") consists of finely ground air- or sun-cured tobacco, salt (sodium chloride), water, humidifying agents, chemical buffering agents (sodium carbonate), and food-grade flavourings. In former years a pinch (or dip) was placed between the gum and upper lip, often for 11–14 h daily (International Agency for Research on Cancer, 2007a), but more recently the most common method of application by far is by portion-packed tobacco in small sachets. This change follows studies showing that use of pack products greatly reduces the risk of tobacco-related oral pathological changes (Andersson and Axéll, 1989; Axéll, 1993). Use of snus involves nicotine exposure similar to, and perhaps somewhat greater than, that from smoking (Agewall et al., 2002; Bolinder et al., 1997a,b; Bolinder and de Faire, 1998; Eliasson et al., 1991; Holm et al., 1992; Wennmalm et al., 1991).

The potential carcinogenicity of smokeless tobacco products used in western countries is practically wholly associated with the presence of the tobacco specific nitrosamines (TSNA) NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) and NNN (N′-nitrosonornicotine) (International Agency for Research on Cancer, 2007a; Nilsson, 1998). It should be noted that snus has, for several decades, been based on a low-nitrate tobacco that is neither fermented nor fire cured, giving very low levels of TSNA as well as of carcinogenic polycyclic aromatic hydrocarbons. Also, Swedish retailers refrigerate packages to prevent formation of

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index; CI, confidence interval; CID, circulatory disease; IHD, ischaemic heart disease; MONICA, Multinational Monitoring of trends and determinants in Cardiovascular disease; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, (N′-nitrosonornicotine); OR, odds ratio; RR, relative risk; SCENIHR, Scientific Committee on Emerging and Newly Identified Health Risks; TSNA, tobacco specific nitrosamines.

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TSNA during storage (International Agency for Research on Cancer, 2007a; Nilsson, 1998). Current levels of TSNA is snus are below 2 μg/g dry weight (Osterdahl et al., 2004).

Although selling snus is banned in other EU countries, Sweden has a special derogation due to its long history of use. In Sweden, the proportion of tobacco sold as snus (by weight) fell from 67% in 1925 to 19% in 1965, when use was concentrated in older men, but then rose, to 54% in 2005 (Forey et al., 2006–2009), with usage spreading to younger people (Nordgren and Ramström, 1990). Recent surveys report regular use by about 20% of males and 3% of females aged 15+ (Forey et al., 2006–2009). Compared with other West European countries, manufactured cigarette smoking in males is less common in Sweden (Table 1). Also, Sweden has a relatively low rate of major smoking-related diseases (Table 2), although it should be noted that inter-country comparisons are affected by other factors (e.g. alcohol consumption) and that Table 2 only considers an illustrative selection of countries. Foulds et al. (2003) have commented on the strikingly favourable lung cancer trend among Swedish (compared to Norwegian) men, accompanied by their increased use of snus and decreased smoking.

Recently, interest in snus as a possible safer alternative to smoking has risen, various reviews being published (Broadstock, 2007; Colilla, 2010; Critchley and Unal, 2003; Nilsson, 1998; Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), 2008). These are often limited by not including meta-analyses, considering few health effects, failing clearly to separate effects of snus and other types of smokeless tobacco, omission of some recent relevant studies, and/or (as demonstrated later) inappropriately evaluating evidence on smoking initiation or cessation. Recently, my colleagues and myself have reviewed the evidence relating smokeless tobacco use in Europe and North America to cancer (Lee and Hamling, 2009a), oropharyngeal cancer (Weitkunat et al., 2007), pancreatic cancer (Sponsiello-Wang et al., 2008), circulatory disease (CID) (Lee, 2007) and oral disease (Kallischnigg et al., 2008). The current epidemiological evidence for these and other possible effects of snus is summarized in Sections 3.1–3.14, with data on the interrelationship of snus with smoking considered in Sections 3.15–3.17. Attention is limited to evidence from Sweden and on occasion its neighbours. The intent is to provide an up-to-date, comprehensive summary of the main evidence relating to snus use as a possible alternative to smoking.

Table 1
Age-adjusted[a] prevalence (%) of manufactured cigarette smoking in males aged 15+ in selected West European countries[b].

Country	1991–1995	1996–2000	2001–2005
Austria	37	36	39
Denmark	29	29	28
France	33	25	31
Germany	35	34	33
Ireland	28		
Italy	36		
Portugal	34		
Spain	47		
Sweden	23	19	17
Switzerland[c]	39	37	36
UK	27	21	22

Data not yet available for some countries for 1996–2005.
[a] Age-adjusted to the European standard population (Waterhouse et al., 1976).
[b] *Source:* International mortality and smoking statistics (Forey et al., 2010).
[c] Data are for smoking of any product. Cigarettes form the great majority of the market in Switzerland.

Table 2
Age-standardized mortality rates[a] from smoking-related diseases in men in selected countries relative to Sweden (100)[b].

	Sweden	USA	UK	Hungary	France	Japan
Ischaemic heart disease	100	108	109	210	43	30
Stroke	100	72	113	284	70	128
COPD	100	204	205	226	75	69
Oral cancer	100	116	123	853	337	141
Oesophageal cancer	100	137	249	202	179	201
Stomach cancer	100	64	127	274	115	481
Liver cancer	100	106	88	181	231	398
Pancreatic cancer	100	102	86	151	104	122
Larynx cancer	100	237	200	1089	461	118
Lung cancer	100	209	175	369	206	155
Bladder cancer	100	97	135	184	151	67
Kidney cancer	100	82	90	127	96	63

[a] Rates for men aged 35+ in 2004 standardized to the European standard population (Waterhouse et al., 1976).
[b] Estimated from WHO mortality database (<http://www.who.int/healthinfo/morttables/en/>).

2. Materials and methods

For cancer and CID methods are as described previously (Lee, 2007; Lee and Hamling, 2009a), with searches updated to September 2010. Studies in Sweden, Norway, Denmark and Finland are considered. Random-effects meta-analyses (Fleiss and Gross, 1991) are restricted to relative risk (RR) or odds ratio (OR) estimates for snus use (ever vs. never or current vs. never) which are controlled for smoking, based either on whole population data adjusted for smoking, or data for never smokers. Meta-analyses use either whole population estimates if available and never smoker estimates otherwise (maximising power but allowing possible bias from incomplete smoking adjustment), or estimates for never smokers (avoiding bias, but using far fewer cases). The main focus is on effect estimates for ever snus use for cancer, and for current snus use for CID. Results by duration and extent of snus use are also discussed, but meta-analyses are not conducted.

For non-neoplastic oral disease and CID risk factors, meta-analyses are not conducted, methods being as described previously (Kallischnigg et al., 2008; Lee, 2007), with searches updated to September 2010.

For other diseases, MEDLINE searches were conducted of "snuff OR snus OR smokeless tobacco" alone, or along with terms for diseases. These were supplemented by citations in recent reviews and in papers obtained. As the data are so limited for any single endpoint, control for smoking was not a requirement to consider the paper.

Searches were also conducted in conjunction with "smoking", "smoking initiation" or "smoking cessation". Papers selected, as well as studies cited in International Smoking Statistics (Forey et al., 2010), provided data relating current snus use to current smoking and ever snus use to ever smoking, and relating snus use to initiation in never smokers and to cessation in current smokers.

For cross-sectional studies relating snus to smoking, numbers of subjects in four groups (both products, snus only, smoking only, neither) are used to derive the OR with its 95% confidence interval (CI) (Gardner and Altman, 1989). For predicting initiation and cessation, cohort study data on numbers of users and non-users at baseline and numbers starting smoking or quitting by the end are used to estimate the RR with 95% CI (Gardner and Altman, 1989). Where data for a study are available from several publications, those presenting results consistently for several survey waves, those including occasional smokers/users, and those presenting sex- or age-specific results are generally preferred. Results based on very few subjects are omitted, so often only male results are presented. Publications on smoking initiation and cessation based on retrospective studies are also considered, and their propensity for bias discussed.

While discussion of the results is mainly limited to Section 4, discussion of issues specific to particular endpoints is, on occasion, included in the relevant part of Section 3 to assist understanding.

3. Results

3.1. Cancer

Three cohort studies report relevant results; the construction workers study (Bolinder et al., 1994; Fernberg et al., 2006, 2007; Luo et al., 2007; Odenbro et al., 2005; Zendehdel et al., 2008), the Norway cohorts study (Boffetta et al., 2005) and the Uppsala county study (Roosaar et al., 2008). Eight publications (Blomqvist et al., 1991; Hansson et al., 1994; Lagergren et al., 2000; Lewin et al., 1998; Lindquist et al., 1987; Rosenquist et al., 2005; Schildt et al., 1998; Ye et al., 1999) describe case-control studies for one or more cancer types. Apart from the Norway cohorts study (Boffetta et al., 2005) all studies were conducted in Sweden. Table 3 presents results for ever use by cancer type.

Control for confounding variables is limited. Of the 16 publications cited in Table 3, two (Blomqvist et al., 1991; Hansson et al., 1994) provide completely unadjusted estimates, while four (Boffetta et al., 2005; Bolinder et al., 1994; Lindquist et al., 1987; Odenbro et al., 2005) provide estimates adjusted only for age, sex (when relevant) and, in two cases, area of residence. Other variables adjusted for include only body mass index in four publications (Fernberg et al., 2006, 2007; Luo et al., 2007; Zendehdel et al., 2008) and only alcohol in another four (Lewin et al., 1998; Roosaar et al., 2008; Rosenquist et al., 2005; Schildt et al., 1998). Only two publications provide estimates adjusted for multiple potential confounding variables other than age, sex and area of residence. One (Ye et al., 1999) adjusted for body mass index and alcohol, while the other (Lagergren et al., 2000) adjusted for these factors and also diet, education, exercise and reflux symptoms.

No overall association is seen for oropharyngeal cancer, the most studied cancer type. For the whole population, an increase (RR 3.1, 95% CI 1.5–6.6) seen in the Uppsala county study (Roosaar et al., 2008), based on 11 cases, contrasts with six studies showing no increase, the overall estimate being 0.97 (0.68–1.37). The never smoker estimate, 1.01 (0.71–1.45), based on four studies, is also null. These results are supported by long-term follow-up of 1115 individuals with "snuff-dippers lesion" (Axéll et al., 1976), which observed no oral cancers at the sites of lesions seen initially (Roosaar et al., 2006).

For oesophageal cancer, overall population estimates from four studies provide a non-significant combined estimate (1.10, 0.92–1.33). In contrast, a single estimate for never smokers from the construction workers study (Zendehdel et al., 2008) of 1.92 (1.00–3.68), based on 11 exposed cases, adjusted for age and body mass index but not alcohol consumption, is marginally significant. Derived from widely differing separate estimates of 3.5 (1.6–7.6) for squamous cell carcinoma and 0.2 (0.0–1.9) for adenocarcinoma, this estimate of 1.92 (1.00–3.68) for never smokers can be compared with a whole population estimate of 1.00 (0.79–1.27), based on 77 cases, itself derived from estimates of 1.0 (0.8–1.4) for squamous cell carcinoma and 1.0 (0.6–1.5) for adenocarcinoma. The evidence for oesophageal cancer is at most suggestive of a possible relationship, requiring confirmation in further studies.

The evidence for stomach cancer is similar to oesophageal cancer, whole population estimates from five studies showing no association (0.98, 0.82–1.17), but the construction workers study (Zendehdel et al., 2008) showing some increase for never smokers (1.33, 1.03–1.72). Here another study (Ye et al., 1999) shows no association (0.5, 0.2–1.2) for never smokers, the overall data suggesting no relationship.

The evidence for pancreatic cancer, discussed fully elsewhere (Sponsiello-Wang et al., 2008), is difficult to interpret. The Norway cohorts study (Boffetta et al., 2005) reported an increase for the whole population (1.67, 1.12–2.50) but not for never smokers (0.85, 0.24–3.07). In contrast, the construction workers study (Luo et al., 2007) reported an increase for never smokers (2.0, 1.2–3.3) but not for the whole population (0.9, 0.7–1.2). Neither combined estimate, for the whole population (1.20, 0.66–2.20) or never smokers (1.61, 0.77–3.34), indicates any clear effect. Overall, these studies, neither of which controlled for alcohol or diabetes, provide an inconclusive suggestion of a possible association. One should note that the smokeless tobacco consumed in the Norway cohorts study was not Swedish snus, but a poorly defined snuff probably characterized by a higher content of TSNA than comparable Swedish products. Although probably not representative for the snuff consumed, two samples of Norwegian oral snuff analyzed in 1983 (Osterdahl et al., 1984) exhibited rather high levels of NNK (5.4 and 7.8 μg/g) and NNN (26 and 58 μg/g).

Table 3 presents limited results for various other cancers, with no individual estimate increased. Not included in Table 3 is a RR estimate of 4.7 (1.6–13.8) from one study (Lewin et al., 1998), associated with ever snus use in never smokers for the combined incidence of cancer of the oropharynx, oesophagus and larynx. Bearing in mind the lack of association seen in the whole population estimates for the individual sites (see Table 3) this increase provides unconvincing evidence of a true effect.

The construction workers study (Bolinder et al., 1994) and the Uppsala county study (Roosaar et al., 2008) present results for overall cancer, with the combined estimates 1.03 (0.91–1.16) for the whole population and 1.10 (0.94–1.29) for never smokers. One study (Roosaar et al., 2008) reported an increase for smoking-related cancers combined in never smokers (1.6, 1.1–2.5), though not for the whole population.

Estimates in Table 3 relate to ever (vs. never) snus use except where indicated. As described elsewhere (Lee and Hamling, 2009a), some studies provide results for current use but these do not affect the conclusion that no clear effect on cancer risk has been demonstrated.

Of the 16 publications cited in Table 3, eight (Fernberg et al., 2006; Lagergren et al., 2000; Lewin et al., 1998; Luo et al., 2007; Odenbro et al., 2005; Rosenquist et al., 2005; Schildt et al., 1998; Ye et al., 1999) reported results by duration or amount of snus use. One study (Fernberg et al., 2006) reported an increased risk of Hodgkin's disease in users of snuff for over 30 years (RR 3.78, 95% CI 1.23–11.60), based on four exposed cases, but no corresponding increase for Non-Hodgkin's lymphoma (0.69, 0.41–1.15). However, no other study reported any significant tendency for risk of any cancer to increase with increasing duration or amount of use (results not shown), and the overall dose–response results do not affect the interpretation of the data for snus use and cancer.

3.2. Non-neoplastic oral disease

Three experimental studies (Andersson et al., 1995; Andersson and Warfvinge, 2003; Larsson et al., 1991), one cohort study (Roosaar et al., 2006), one case-control study (Rosenquist, 2005), and nine cross-sectional studies (Andersson and Axéll, 1989; Andersson et al., 1994; Axéll et al., 1976; Frithiof et al., 1983; Hirsch et al., 1982; Jungell and Malmström, 1985; Pindborg and Renstrup, 1963; Roed-Petersen and Pindborg, 1973; Rolandsson et al., 2005; Salonen et al., 1990) relate snus to "snuff-dipper's lesion", as defined by Axéll et al. (1976) or similarly. Generally current users have 100% incidence, with severity clearly associated with daily time used and amount consumed (Andersson and Axéll, 1989; Axéll et al., 1976; Rolandsson et al., 2005; Rosenquist, 2005).

Table 3
Summary of evidence comparing risk of cancer in ever and never snus users based on studies conducted (or other Scandinavian countries[a]).

Cancer	Source	Study type[b]	Sex	Whole population		Never smokers		Adjustment factors[d]
				N[c]	RR/OR (95% CI)	*N*[c]	RR/OR (95% CI)	
Oropharynx	Boffetta et al. (2005)	PC	M	9	1.10 (0.50–2.41)			Age
	Luo et al. (2007)	PC	M	NA	0.70 (0.50–0.90)	10	0.80 (0.40–1.70)	Age, BMI
	Roosaar et al. (2008)	PC	M	11	3.10 (1.50–6.60)	5	2.30 (0.70–8.30)	Age, alc, res, time
	Blomqvist et al. (1991)	CC	M + F			2	0.67 (0.08–5.75)[e]	None
	Lewin et al. (1998)	CC	M	63	0.98 (0.63–1.50)			Age, alc, res
	Schildt et al. (1998)	CC	M + F	67	0.80 (0.50–1.30)	28	1.01 (0.64–1.57)[e]	Age, alc[f] sex, res
	Rosenquist et al. (2005)	CC	M + F	20	0.70 (0.30–1.30)			Alc
	Total			7	0.97 (0.68–1.37) [g,h]	4	1.01 (0.71–1.45)	
Oesophagus	Boffetta et al. (2005)	PC	M	9	1.40 (0.61–3.24)			Age
	Zendehdel et al. (2008)	PC	M	77	1.00 (0.79–1.27)[e]	11	1.92 (1.00–3.68)	Age, BMI
	Lewin et al. (1998)	CC	M	19	1.20 (0.70–2.20)			Age, alc, res
	Lagergren et al. (2000)	CC	M + F	68	1.31 (0.89–1.92)[e]			Age, alc, BMI, diet, edu, exe, rflx, sex
	Total			4	1.10 (0.92–1.33)	1	1.92 (1.00–3.68)	
Stomach	Boffetta et al. (2005)	PC	M	74	1.11 (0.83–1.48)			Age
	Zendehdel et al. (2008)	PC	M	311	1.08 (0.96–1.22)[e]	76	1.33 (1.03–1.72)[e]	Age, BMI
	Hansson et al. (1994)	CC	M + F	NA	0.70 (0.47–1.06)[i]			
	Ye et al. (1999)	CC	M	83	0.77 (0.56–1.06)[e]	11	0.50 (0.20–1.20)	Age, alc, BMI, res, ses
	Lagergren et al. (2000)	CC	M + F	53	1.20 (0.80–1.80)			Age, alc, BMI, diet, edu, exe, rflx, sex
	Total			5	0.98 (0.82–1.17)	2	0.90 (0.35–2.30)[h]	
Pancreas	Boffetta et al. (2005)	PC	M	45	1.67 (1.12–2.50)	3	0.85 (0.24–3.07)	Age
	Luo et al. (2007)	PC	M	NA	0.90 (0.70–1.20)	20	2.00 (1.20–3.30)	Age, BMI
	Total			2	1.20 (0.66–2.20)	2	1.61 (0.77–3.34)	
Lung	Boffetta et al. (2005)	PC	M	72	0.80 (0.61–1.05)	3	0.96 (0.26–3.56)	Age
	Luo et al. (2007)	PC	M	NA	0.70 (0.60–0.70)	18	0.80 (0.50–1.30)	Age, BMI
	Total			2	0.71 (0.66–0.76)	2	0.82 (0.52–1.28)	
Larynx	Lewin et al. (1998)	CC	M	24	0.90 (0.50–1.50)			Age, alc, res
Bladder	Boffetta et al. (2005)	PC	M	69	0.83 (0.62–1.11)			Age
Kidney	Boffetta et al. (2005)	PC	M	22	0.72 (0.44–1.18)			Age
Cutaneous squamous cell carcinoma	Odenbro et al. (2005)	PC	M	29	0.64 (0.44–0.95)			Age
Leukaemia	Fernberg et al. (2007)	PC	M			NA	No increased risk	Age, BMI
	Lindquist et al. (1987)	CC	M + F	18	0.94 (0.47–1.89)[e]			Age, res, sex
Multiple myeloma	Fernberg et al. (2007)	PC	M			NA	No increased risk	Age, BMI
Non-Hodgkin's Lymphoma	Fernberg et al. (2006)	PC	M			66	0.77 (0.59–1.01)	Age, BMI
Hodgkin's disease	Fernberg et al. (2006)	PC	M			15	0.88 (0.49–1.58)	Age, BMI
All smoking-related	Roosaar et al. (2008)	PC	M	71	1.10 (0.80–1.40)	39	1.60 (1.10–2.50)	Age, alc, res, time
Any cancer	Bolinder et al. (1994)	PC	M			96	1.10 (0.90–1.40)[j]	Age, res
	Roosaar et al. (2008)	PC	M	237	1.00 (0.87–1.15)	138	1.10 (0.90–1.40)	Age, alc, res, time
	Total			2	1.03 (0.91–1.16) [g]	2	1.10 (0.94–1.29)	

[a] All studies conducted in Sweden except for the Norway cohorts study (Boffetta et al., 2005).
[b] PC = prospective cohort, CC = case-control.
[c] For a study the number of cases exposed to snus. For totals the number of estimates combined. NA = not available.
[d] Abbreviations used: alc = alcohol, BMI = body mass index, edu = education, exe = exercise, res = area of residence, rflx = reflux symptoms, ses = socioeconomic status. All whole population estimates are also adjusted for smoking.
[e] RR/OR and/or 95% CI estimated from data provided in the source.
[f] Alcohol only adjusted for in whole population estimate.
[g] Includes estimates for never smokers for studies where whole population estimates are not available.
[h] Significant heterogeneity at $p < 0.05$.
[i] Estimates are for snus users, with timing undefined.
[j] Estimates are for current snuff users.

Short-term quitting reduces severity (Frithiof et al., 1983), longer-term quitting eliminating the lesion (Jungell and Malmström, 1985; Larsson et al., 1991; Roosaar et al., 2006). Switching to lower nicotine, lower pH or portion-bag snuff also reduces severity (Andersson et al., 1995; Andersson and Warfvinge, 2003; Larsson et al., 1991; Roosaar et al., 2006). As noted earlier, a cohort study (Roosaar et al., 2006) observed no subsequent cancers at sites where lesions were identified initially.

Some studies relate snus to periodontal and gingival diseases (Bergström et al., 2006; Modéer et al., 1980; Montén et al., 2006; Rolandsson et al., 2005; Wickholm et al., 2004). No relationship is seen with plaque or calculus (Montén et al., 2006; Wickholm et al., 2004), pocket depth (Bergström et al., 2006; Montén et al., 2006; Wickholm et al., 2004), attachment loss (Montén et al., 2006), alveolar bone level (Montén et al., 2006), bone height (Bergström et al., 2006) or periodontal disease, defined as three or more teeth with pocket depth $\geqslant 5$ mm (Wickholm et al., 2004). One study (Modéer et al., 1980) reported an increased ($p < 0.001$) gingival index in snus users, others (Bergström et al., 2006; Montén et al., 2006; Rolandsson et al., 2005; Wickholm et al., 2004) finding no relationship with gingivitis, gingival index or gingival bleeding. One study (Montén et al., 2006) reported increased gingival recession in snus users, and one (Wickholm et al., 2004) did not. A relationship of snus to periodontal and gingival diseases is not clearly established.

Snus is unrelated to number of teeth present (Bergström et al., 2006; Rolandsson et al., 2005) or number filled (Rolandsson et al., 2005). A reported increase in dental caries in 14–19 year old users (Hirsch et al., 1991) is questionable, analyses not being age-adjusted, and users being markedly older than non-users. A possible relationship of snus use with tooth loss and dental caries is not established.

A recent nationwide study in Finland (Rintakoski et al., 2010) reports an increased risk (OR 2.06, 95% CI 1.19–3.56) of weekly bruxism (teeth grinding) in regular users of snuff, after adjustment for covariates.

3.3. CID

Five cohort studies report relevant results; the construction workers study (Bolinder et al., 1994, 1992; Hergens et al., 2007, 2008a), the Swedish living conditions survey (Haglund et al., 2007; Johansson et al., 2005), the Uppsala county study (Roosaar et al., 2008), the Malmö study (Janzon and Hedblad, 2009) and the Swedish twin registry study (Hansson et al., 2009). There are also case-control studies, some nested within cohort studies (Ahmed et al., 2000; Asplund et al., 2003; Wennberg et al., 2007), and some not (Hergens et al., 2005; Huhtasaari et al., 1992, 1999). All the studies were conducted in Sweden. Table 4 presents results for current use by disease type. All these data are for men, and fatal/non-fatal cases combined. Reasons for excluding some studies are given in Table 4. Although an attempt was made to avoid CID cases being included more than once, some overlap is likely, e.g. for reports based on the Multinational Monitoring of trends and determinants in Cardiovascular disease (MONICA) study (Asplund et al., 2003; Huhtasaari et al., 1992, 1999; Wennberg et al., 2007). This seems unavoidable without unacceptable power loss.

As for cancer, control for confounding variables is somewhat limited. Of the 12 publications cited in Table 4, one (Huhtasaari et al., 1999) provides completely unadjusted estimates, while three (Bolinder et al., 1994; Hergens et al., 2005; Huhtasaari et al., 1992) provide estimates adjusted only for age and, in two cases, area of residence. Other variables adjusted for include only body mass index in two publications (Hergens et al., 2007, 2008a) and only alcohol in one (Roosaar et al., 2008). Although the other studies (Asplund et al., 2003; Haglund et al., 2007; Hansson et al., 2009; Janzon and Hedblad, 2009; Wennberg et al., 2007) adjust for multiple confounders, none consider all of such classical risk factors as blood pressure, cholesterol level, obesity, diabetes and exercise.

The results for ischaemic heart disease (IHD) and acute myocardial infarction (AMI) suggest no relationship with current use, an early report from the construction workers study (Bolinder et al., 1994) of an increase in never smokers being outweighed by numerous studies showing no relationship. The overall estimates are close to 1.00 both for the whole population (1.01, 0.91–1.12) and never smokers (0.99, 0.85–1.14). RRs for current (rather than ever) use are presented, since the risk from smoking declines rapidly following quitting (International Agency for Research on Cancer, 2007b). Using estimates for ever use does not affect the conclusion that snus is unassociated with AMI/IHD (data not shown).

The results are for fatal and non-fatal cases combined, partly to allow greater power. Also, publication bias is an issue, some studies not reporting results separately. Anyway, an association for fatal cases but not for all cases seems unlikely unless implausibly snus protects against non-fatal cases. The construction workers study (Hergens et al., 2007) shows an increase in fatal AMI (RR 1.32, 1.08–1.61) for current use among never smokers, but no increase in non-fatal AMI (0.94, 0.83–1.02). Four other small studies (Haglund et al., 2007; Hergens et al., 2005; Huhtasaari et al., 1999; Wennberg et al., 2007) show no significantly increased risk of fatal AMI/IHD.

The results for stroke also suggest little association with current use. No estimate is significant, with the combined estimates, 1.05 (0.95–1.15) for the whole population and 1.06 (0.96–1.17) for never smokers. Conclusions are unaffected by considering ever use (data not shown). Two studies (Haglund et al., 2007; Hergens et al., 2008a) report results for fatal stroke, neither showing a significant increase in risk of stroke.

The results for any CID are similar to IHD/AMI, with an increase only in the early construction workers study report (Bolinder et al., 1994). The overall estimates are 1.08 (0.92–1.27) for the whole population and 1.08 (0.87–1.33) for never smokers.

Of the 12 publications cited in Table 4, only four (Hansson et al., 2009; Hergens et al., 2007, 2008a; Huhtasaari et al., 1992) reported results by duration or amount of snus use, but none showed any significant trends by level of exposure for IHD/AMI, stroke or any CID (results not shown).

Although a small effect of snus on the incidence of CID cannot be excluded, this has not been demonstrated by the available epidemiological data.

3.4. Diabetes

Some publications (Attvall et al., 1993; Eliasson et al., 1996, 1991, 1995, 2004; Hergens et al., 2005; Johansson et al., 2005; Norberg et al., 2006; Persson et al., 2000; Wallenfeldt et al., 2001; Wändell et al., 2008) report results for diabetes or related endpoints. One study of diabetes (Persson et al., 2000) reported a notable association, with ORs of 3.9 (1.1–14.3) comparing current exclusive snus users and never tobacco users, and 2.7 (1.3–5.5) in current heavy snus users, regardless of tobacco consumption. Other studies (Eliasson et al., 2004; Hergens et al., 2005; Johansson et al., 2005; Norberg et al., 2006; Wändell et al., 2008) report no clear relationship. No clear association is reported with glucose intolerance (Eliasson et al., 2004; Norberg et al., 2006; Persson et al., 2000), fasting glucose levels (Eliasson et al., 1991, 1995; Wallenfeldt et al., 2001) or fasting insulin levels (Attvall et al., 1993; Eliasson et al., 1991, 1995; Wallenfeldt et al., 2001). An association of metabolic syndrome with high consumption (OR 1.6, 1.26–2.15 for >4 cans/week) in one study (Norberg et al., 2006) was not seen

Table 4
Summary of evidence comparing risk of CID in current and never snus users based on studies conducted in Sweden[a].

Disease	Source	Study type[b]	Whole population		Never smokers		Adjustment factors[d]
			N[c]	RR/OR (95% CI)	*N*[c]	RR/OR (95% CI)	
IHD/AMI[e]	Bolinder et al. (1994)	PC			172	1.35 (1.13–1.62)[f]	Age, res
	Hergens et al. (2007)	PC			416	1.02 (0.92–1.14)	Age, BMI, res
	Haglund et al. (2007)	PC	43	0.83 (0.60–1.15)[f,g]	28	0.77 (0.51–1.15)[g,h]	Age, exe, hea, ill, res, ses
	Wennberg et al. (2007)	NCC	88	0.90 (0.67–1.22)[f,g]	21	0.82 (0.46–1.43)	Age, BMI, cho, edu, lei, phy
	Huhtasaari et al. (1992)	CC	91	1.01 (0.66–1.55)[f,g]	59	0.89 (0.62–1.29)[g,h]	Age
	Huhtasaari et al. (1999)	CC	79	0.89 (0.64–1.23)[f,g]	59	0.93 (0.65–1.34)[h]	None
	Hergens et al. (2005)	CC	147	0.99 (0.78–1.25)[f]	10	0.73 (0.35–1.50)	Age, res
	Janzon and Hedblad (2009)	PC	33	1.05 (0.80–1.40)[g]	4	0.75 (0.30–1.80)[g]	Age, BMI, bp, dia, mar, occ, phy
	Hansson et al. (2009)	PC	70	0.86 (0.66–1.14)	18	0.85 (0.51–1.41)	Age, bp, chol, dia
	Total[i]		9	1.01 (0.91–1.12)	9	0.99 (0.85–1.14)	
Stroke	Bolinder et al. (1994)	PC			30	1.29 (0.83–1.99)[f]	Age, res
	Hergens et al. (2008a)	PC			412	1.05 (0.95–1.17)	Age, BMI, res
	Haglund et al. (2007)	PC	28	1.18 (0.78–1.77)[f,g]	19	1.07 (0.65–1.77)[g,h]	Age, exe, hea, ill, res, ses
	Asplund et al. (2003)	NCC			30	0.87 (0.41–1.83)[g]	Age, bp, cho, coh, dia, edu, mar, per, res
	Janzon and Hedblad (2009)	PC	35	0.97 (0.70–1.40)[g]	4	0.59 (0.20–1.50)[g]	Age, BMI, bp, dia, mar, occ, phy
	Hansson et al. (2009)	PC	36	0.91 (0.64–1.31)	14	1.18 (0.67–2.08)	Age, bp, chol, dia
	Total[i]		6	1.05 (0.95–1.15)	6	1.06 (0.96–1.17)	
Any CID[k]	Bolinder et al. (1994)	PC			220	1.40 (1.20–1.60)	Age, res
	Haglund et al. (2007)	PC	71	0.94 (0.72–1.21)[f,g]	24	0.87 (0.64–1.18)[f,g,h]	Age, exe, hea, ill, res, ses
	Roosaar et al. (2008)	PC	NA	1.11 (0.96–1.25)[l]	NA	1.15 (0.97–1.37)[l]	Age, alc, per, res
	Janzon and Hedblad (2009)	PC	68	1.02 (0.82–1.26)[f,g]	8	0.67 (0.35–1.30)[f,g]	Age, BMI, bp, dia, mar, occ, phy
	Hansson et al. (2009)	PC	104	0.91 (0.73–1.13)	32	1.00 (0.69–1.46)	Age, bp, chol, dia
	Total[i]		5	1.08 (0.92–1.27)[j]	5	1.08 (0.87–1.33)[j]	

[a] All results are for males and include fatal and non-fatal cases, where relevant. No evidence was found for countries other than Sweden. Excluded are a study of subarachnoid haemorrhage (Koskinen and Blomstedt, 2006), with no valid controls or smoking adjustment; a stroke study (Ahmed et al., 2000) with no smoking adjustment; an early publication from the living conditions survey (Johansson et al., 2005) superseded by a later one (Haglund et al., 2007); and the first construction workers study publication (Bolinder et al., 1992) superseded by the second (Bolinder et al., 1994). Results from this second publication (Bolinder et al., 1994) are retained, later publications (Hergens et al., 2007, 2008a) involving different workers receiving medical checks at different times.

[b] PC = prospective cohort, NCC = nested case-control, CC = case-control.

[c] For individual estimates the number of cases exposed to ST. For total estimates the number of individual estimates combined. NA = not available.

[d] Abbreviations used: alc = alcohol consumption, BMI = body mass index, bp = blood pressure, cho = cholesterol level, coh = cohort, dia = diabetes, edu = education, exe = exercise, fhi = family history of early MI, hea = self reported health, ill = longstanding illness, lei = leisure time, mar = marital status, per = period, phy = physical activity, res = area of residence, ses = socioeconomic status. All whole population estimates are also adjusted for smoking.

[e] IHD/AMI = ischaemic heart disease or acute myocardial infarction.

[f] Estimated from data in source article.

[g] Estimate is for current vs. non-current snus users.

[h] Estimate is for non-current smokers.

[i] Includes estimates for never smokers for studies where whole population estimates are not available.

[j] Significant heterogeneity at $p < 0.05$.

[k] CID = circulatory disease.

[l] Estimate is for ever vs. never snus users.

in another (Wändell et al., 2008). An association of snus use with diabetes is not clearly established.

3.5. Blood pressure

Two crossover studies (Hirsch et al., 1992; Rohani and Agewall, 2004) investigating acute effects of snus both reported significantly increased blood pressure during rest, though only one (Rohani and Agewall, 2004) found an effect during exercise. However, cross-sectional studies (Ahlbom et al., 1997; Ångman and Eliasson, 2008; Bolinder and de Faire, 1998; Bolinder et al., 1992; Eliasson et al., 1991; 1995; Hergens et al., 2005, 2008b; Janzon and Hedblad, 2009; Johansson et al., 2005; Wallenfeldt et al., 2001; Wennmalm et al., 1991) have generally not found higher blood pressure in snus users, exceptions being two publications from the construction workers study (Bolinder et al., 1992; Hergens et al., 2008b). One of these (Hergens et al., 2008b) also found that, among never smokers with normal blood pressure initially, ever snus users had a significantly increased age- and body mass index (BMI)-adjusted risk of hypertension (1.36, 1.07–1.72) occurring during follow up. The results for blood pressure and CID are similar in that an association with snus use was seen only in the construction workers study. The overall evidence does not demonstrate a chronic effect of snus on blood pressure.

3.6. Other risk factors for CID

Numerous publications (Ahlbom et al., 1997; Berggren et al., 2007; Bolinder et al., 1997a,b, 1992; Ekenvall and Lindblad, 1985; Eliasson et al., 1991, 1995; Ellingsen et al., 2009; Hergens et al., 2005; Janzon and Hedblad, 2009; Nafziger et al., 2007; Norberg et al., 2006; Rohani and Agewall, 2004; Stegmayr et al., 1993; Sundbeck et al., 2009; Wallenfeldt et al., 2001; Wennmalm et al., 1991) provide information on snus and CID-related endpoints. No relationship is reported with atherosclerosis (Bolinder et al., 1997a; Wallenfeldt et al., 2001), response to exercise (Bolinder et al., 1997b; Wennmalm et al., 1991), cholesterol levels (Ahlbom et al., 1997; Bolinder et al., 1997a; Eliasson et al., 1991, 1995; Hergens et al., 2005; Norberg et al., 2006; Wallenfeldt et al., 2001), fibrinogen (Ahlbom et al., 1997; Bolinder et al., 1997a; Eliasson et al., 1991, 1995), platelet activity (Berggren et al., 2007; Wennmalm et al., 1991) or antioxidant and vitamin levels (Ellingsen et al., 2009; Stegmayr et al., 1993). However, consistent reports (Hergens et al., 2005; Janzon and Hedblad, 2009; Nafziger et al., 2007; Norberg et al., 2006; Sundbeck et al., 2009) show users have increased obesity. There are two reports (Bolinder et al., 1992; Ekenvall and Lindblad, 1985) of an increase in Raynaud-type symptoms and one (Rohani and Agewall, 2004) of impaired endothelial function in snus users. For triglycerides two studies (Norberg et al., 2006; Wallenfeldt et al., 2001) found

an increase in users, but three (Ahlbom et al., 1997; Bolinder et al., 1997a; Eliasson et al., 1991) found no relationship.

3.7. Respiratory system diseases

The Uppsala county study (Roosaar et al., 2008) reported increased respiratory mortality among male users aged 80+ (1.8, 1.2–2.7), after adjustment for age, residence and smoking, but not at age <80 (RR 0.8, 0.4–1.6). Similar relationships were seen in never smokers. The construction workers study has not reported mortality results, but did report (Bolinder et al., 1992) that, in never smokers, users had an increased age-adjusted risk of morning cough (2.1, 1.8–2.4), >3 months' cough/year (1.4, 1.1–1.7), and breathlessness on effort (1.4, 1.3–1.6). It is unclear whether these associations are due to confounding by other factors or are relevant to snus as currently used.

3.8. Digestive system diseases

No study reports overall mortality results for digestive system diseases. In the construction workers study (Bolinder et al., 1992) no positive association was reported in never smokers with age-adjusted risk of heartburn (0.9, 0.8–0.9) or peptic ulcer (1.1, 0.9–1.2). No association between snus and gallstone disease was seen in a prospective study of twins (Katsika et al., 2007). After adjustment for sex, age, zygosity, BMI, alcohol and smoking, an OR of 1.05 (0.49–2.23) was reported when comparing diseased twins with all other twins in the study, with no relationship also seen in twin pairs with one having the disease. A case-control study of inflammatory bowel disease (Persson et al., 1993) reported an increased risk in snus users of both Crohn's disease (2.1, 1.0–4.6) and ulcerative colitis (2.2, 1.1–4.6), after adjustment for age and smoking, in current and former cigarette smokers. The increased risk of ulcerative colitis in current smokers using snus seems surprising, as it contrasts with the often reported reduced risk in current smokers (Mahid et al., 2006). It also contrasts with a recent report from the construction workers study (Carlens et al., 2010) that ever snus use was not associated with the onset of either Crohn's disease (RR 0.9, 0.8–1.1) or ulcerative colitis (1.1, 0.9–1.2), after adjustment for smoking, during follow-up of over 20 years.

3.9. All-cause mortality

In never smoking construction workers (Bolinder et al., 1994), age-adjusted all-cause mortality was increased in users (1.4, 1.3–1.8), more clearly at age 35–54 (1.9, 1.6–2.4) than at age 55–65 (1.2, 1.0–1.3). The excess corresponds largely to the CID increase in this study. An increased all-cause mortality was also reported in the Uppsala county study (Roosaar et al., 2008) in analyses adjusted for age, area of residence, alcohol and smoking (1.10, 1.01–1.21), and in never smokers (1.23, 1.09–1.40). While the combined estimate for never smokers from the two studies (1.30, 1.15–1.47) suggests an association, more evidence is clearly needed.

3.10. Pregnancy and reproductive effects

One study of singleton live births in Sweden in 1999–2000 (England et al., 2003) compared pregnancy outcomes in snus users, smokers and non-tobacco users. Compared to non-users, adjusted mean birthweight was reduced in users by 39 g (6–72 g) and in smokers by 190 g (178–202 g). Preterm delivery was increased in both snus users (OR 1.98, 1.46–2.68) and in smokers (1.57, 1.38–1.80). Preeclampsia was reduced in smokers (0.63, 0.53–0.75), as often reported (Conde-Agudelo et al., 1999), but was increased in users (1.58, 1.09–2.27). Adjustment factors included maternal age, parity, BMI and infant sex, but not alcohol or illicit drug use.

Recently Wikström and her colleagues have reported extended results from the Swedish Medical Birth Register based on births in 1999–2006. In one publication (Wikström et al., 2010b) exclusive snus users, compared to non-users of tobacco, were found to have no increased risk of preeclampsia (OR 1.11, 0.97–1.28), after adjustment for early pregnancy BMI, maternal age, parity and years of education, conflicting with the substantial increase reported earlier (England et al., 2003). There was also no increased risk of gestational hypertension (0.89, 0.68–1.15). In another publication (Wikström et al., 2010a) exclusive snus users were found to have an increased adjusted risk of very preterm birth (1.38, 1.04–1.83), and moderately preterm birth (1.25, 1.12–1.40), associations being weaker than reported earlier (England et al., 2003). These publications (Wikström et al., 2010a,b) confirmed the reduced incidence of preeclampsia and increased risk of preterm delivery in smokers.

In a study of military conscripts (Richthoff et al., 2008), average age 18 years, 51 reported using snus. Smokers had a lower sperm count, sperm concentration and follicle-stimulating hormone level than non-smokers, but snus was unassociated with any reproductive parameter. Analyses adjusted for alcohol and length of abstinence.

Recent reviews (Rogers, 2008; Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), 2008) criticize the limited data, too sparse to allow conclusions.

3.11. Psychiatric disorders

In never smoking construction workers (Bolinder et al., 1992), users had an increased age-adjusted risk of sleeping disturbances (1.2, 1.1–1.4) and nervous problems (1.2, 1.1–1.4).

In a study of patients with risperidone-treated schizophrenia or schizophrenia-related disorders (Levander et al., 2007), snus use in men and smoking in both sexes was more frequent than nationally reported. Nicotine users and non-users did not differ in diagnosis, symptoms, side effects, weight, cognitive functions, personality or outcome. The authors suggested that patients with psychosis fail to desist from nicotine rather than experience positive effects of usage. Snus users were not considered separately.

In a study of students (Lund et al., 2008), smoking and snus were both associated with increased alcohol, drug taking and gambling. Physical activity was negatively associated with smoking and positively with snus. After adjustment for these and other variables, poor mental health was associated with smoking but not with snus use.

There is no reliable indication that snus use affects the onset of psychiatric disorders.

3.12. Neurodegenerative disorders

A 20 year follow-up of the construction workers (Fang et al., 2006) investigated the relationship of smoking and snus use to amyotrophic lateral sclerosis. Compared to never tobacco users, no tobacco-related increases were seen, with RRs 0.6 (0.3–1.5) for pure snus users and 0.9 (0.6–1.4) for smokers using snus.

In a case-control study of multiple sclerosis (Hedström et al., 2009), an increased risk was evident in smokers in both sexes. In never smokers, no increase was seen for current snus use (0.8, 0.4–1.3) or for long-term snus use before disease onset (0.3, 0.1–0.8). Similar results were reported based on the construction workers study (Carlens et al., 2010) with multiple sclerosis increased in smokers, but not (1.0, 0.9–1.2) in ever snus users, after adjustment for smoking.

These results provide no suggestion that snus use increases the incidence of neuro-degenerative disease.

3.13. Musculoskeletal disorders and other conditions

In never smoking construction workers (Bolinder et al., 1992), users had increased recent low back pain (OR 1.1, 1.0–1.2). In military conscripts (Mattila et al., 2008), low back pain was associated with smokeless tobacco, with the OR 1.4 (1.2–1.7), adjusted for age, health status and diseases in the last year. The authors suggested this association may arise because snus is popular in sportsmen, the sport causing the low back pain. In a 12 year study (Holmberg and Thelin, 2006), snus was unassociated with primary care or sick leave due to neck and/or low back pain, but was associated with an increased OR (3.46, 1.35–8.84) of disability pension for such pain. This is difficult to interpret, being adjusted for current neck and/or low back pain and for back diagnosis during follow-up. In people with chronic pain (Jakobsson, 2008), pain intensity was higher in smokers, but not snus users, after age and sex adjustment. The endpoint here was any pain for at least three months, though this would often be musculoskeletal.

Some studies investigated other endpoints. A study of military conscripts (Heir and Eide, 1997) found that snus was associated with proneness to musculoskeletal injuries during training, with the OR 2.31 (1.34–3.99) after adjustment for age and fitness. A study of men operated on for knee deformity (W-Dahl and Toksvig-Larsen, 2007) found no effect of snus on bone healing or post-operative complications, though effects were seen in smokers. In never smoking construction workers (Bolinder et al., 1992) the risk of disability pension for musculoskeletal diagnoses was increased in snus users, with ORs increased at both age 46–55 years (2.8, 1.6–4.8) and 56–65 years (1.5, 1.2–1.8).

Recently, the construction workers study reported (Carlens et al., 2010) that ever snus use, adjusted for smoking, was unassociated with onset of rheumatoid arthritis (RR 1.0, 0.9–1.2) during the follow-up period. The same publication also noted no relationship of ever snus use with onset of sarcoidosis (RR 1.1, 0.8–1.5).

A case-control study (Wolk et al., 2009) reported finding no association between current snus use and the onset of plaque psoriasis (OR 1.0, 0.6–1.9).

A study of pain and post-operative nausea and vomiting following three common surgical procedures (Brattwall et al., 2010) reported a significantly reduced incidence in regular users of tobacco, both smokers and snus users, during the early post-operative period. However, the results were mainly presented for combined nicotine users, and specific effects of snus could not be clearly identified.

3.14. General health

In never smoking construction workers (Bolinder et al., 1992) the age-adjusted RR for snus use was 1.1 (1.0–1.2) for frequent sick leave ($\geqslant$1 day four times yearly) and 1.2 (1.1–1.2) for long leave ($\geqslant$30 days yearly). Among those aged 46–55 years, snus was associated with an increase (2.5, 1.7–3.5) of having a disability pension. No RR for age 55–64 years was given.

In a cross-sectional study (Halling et al., 2007), having "best general health", assessed by five indicators, was unassociated with either daily snus or daily smoking, with ORs adjusted for age and demographic variables of, respectively, 0.94 (0.79–1.12) and 0.90 (0.79–1.02) compared to never tobacco users. Past snus (OR 0.74, 0.61–0.90) and past smoking (0.82, 0.74–0.90) were associated with lower risk. Whether giving up snus causes, or results from, poorer health is unassessable in a cross-sectional study.

3.15. Interrelationship of snus use and smoking

Snus use might in theory encourage initiation or discourage quitting. Before considering evidence on smoking changes, evidence on joint smoking and snus use is considered.

Table 5 presents prevalence ORs from eleven publications in adults (Christensen, 2004; Lundqvist et al., 2009; Novo et al., 2000; Persson et al., 2004; Ramström, 1986; Ramström and Tibblin, 1987, 1988; Ramström and Foulds, 2006; Rodu et al., 2002; Stegmayr et al., 2005; Wadman, 2009) and eight in adolescents (Danielson, 2003; Galanti et al., 2001b; Grotvedt et al., 2008; Hedman et al., 2007; Hvitfeldt and Nyström, 2009; Nilsson et al., 2009; Rosendahl et al., 2005; Wiium et al., 2009) relating current snus and current smoking. In adolescents ORs range from about 4 to over 10, with one exception (Wiium et al., 2009). In adults there is no clear association, with 28 ORs greater than 1.0, and 25 less than 1.0, and no consistent tendency for the OR to vary by sex, age or time of survey.

Table 6 presents prevalence ORs relating ever snus use to ever smoking from six publications in adults (Furberg et al., 2005, 2008b; Hergens et al., 2005; Ramström and Tibblin, 1988; Ramström and Foulds, 2006; Rodu et al., 2002) and four in adolescents (Galanti et al., 2001a,b; Haukkala et al., 2006; Rosendahl et al., 2005). A strong relationship is consistently seen, with ORs typically over 10 for children, though lower in adults.

These results could be explained by some people avoiding tobacco, many of the rest trying both products and ultimately settling for one. The percentage currently using both (Table 5) is quite low, rarely exceeding 10%, but the percentage ever using both (Table 6), is higher, especially for men.

3.16. Does snus use affect smoking initiation?

This question can be investigated in cohort studies following up never smokers. Table 7 presents data from three publications (Galanti et al., 2001a, 2008; Lundqvist et al., 2009), the unadjusted RRs consistently showing a positive relationship. While one study (Galanti et al., 2008) reported an adjusted OR (1.95, 0.96–3.80) similar to the unadjusted OR (1.81, 0.92–3.56), the adjustment was only for age and sex and not for factors predictive of initiation, e.g. propensity for risk taking. Table 7 also presents results from some studies (Haukkala et al., 2006; Lundqvist et al., 2009; Stenbeck et al., 2009; Tillgren et al., 1996) where smoking at the end of follow-up was related to snus use in non-smokers, not never smokers, at the start, so some people smoking at the end might have been ex-smokers initially. These also show a positive relationship. One study (Haukkala et al., 2006) reported that adjustment for school, sport participation, and school achievement substantially reduced the association. However, the range of adjustment factors was far less than those considered in US studies of smokeless tobacco use which reported that adjustment substantially reduced (Severson et al., 2007) or even eliminated (Timberlake et al., 2009) the observed association of smokeless tobacco with initiation.

Two studies of Swedish adults (Furberg et al., 2005; Ramström and Foulds, 2006) used retrospective data to study effects on initiation. Ramström and Foulds (Ramström and Foulds, 2006) divided 3125 men into five groups (snus only, $n = 402$; snus first, then smoking, $n = 100$; smoking only, $n = 888$; smoking first, then snus, $n = 338$; never tobacco, $n = 1397$). The authors noted that the percentage subsequently smoking among those who started on snus (100/502 = 20%) was substantially lower than among those who had not started on snus (1226/2623 = 47%, OR 0.28, 0.22–0.36). Furberg et al. (2005) compared any lifetime smoking between men using snus before smoking and men who had never used snus. Lifetime smoking was negatively related to both regular snus use (OR 0.2, 95% CI 0.2–0.3) and occasional snus use (OR 0.5, 95% CI 0.3–0.7). Though both authors (Furberg et al., 2005; Ramström and Foulds, 2006) concluded that snus use is associated with reduced initiation, neither of the tests used are valid. Although the ORs calculated were both substantially less than 1.0 this does not

Table 5
Relationship between current snus use[a] and current smoking[b] in Sweden (or other Scandinavian countries)[c].

Study[e]	Year (s)	Source	Age	Sex	Number of subjects[d]				OR (95% CI)
					Snus and smoking	Snus only	Smoking only	Neither	
Studies in adults									
SSLC survey[f]	1980–81	Persson et al. (2004)	16–24	M	79 (7.0%)	215	208	620	1.09 (0.81–1.48)
			25–44	M	164 (6.6%)	847	303	1181	0.75 (0.61–0.93)
			45–64	M	73 (4.1%)	574	106	1037	1.24 (0.91–1.70)
			65–84	M	63 (3.7%)	451	200	971	0.68 (0.50–0.92)
	1988–89		16–24	M	79 (7.9%)	87	229	607	2.41 (1.72–3.39)
			25–44	M	174 (8.1%)	483	405	1097	0.98 (0.79–1.20)
			45–64	M	68 (4.1%)	439	147	1011	1.07 (0.79–1.46)
			65–84	M	34 (2.6%)	249	138	861	0.85 (0.57–1.26)
			16–84	F	42 (0.7%)	1650	45	4683	2.62 (1.72–4.01)
	1996–97		16–24	M	21 (7.0%)	38	107	128	0.65 (0.36–1.17)
			25–44	M	83 (6.5%)	194	417	595	0.61 (0.46–0.82)
			45–64	M	85 (4.6%)	343	260	1159	1.11 (0.84–1.45)
			65–84	M	35 (2.3%)	177	103	1231	2.40 (1.59–3.62)
			16–84	F	27 (1.1%)	781	46	1701	1.28 (0.79–2.07)
	2004		16–24	M	20 (5.4%)	19	104	224	2.22 (1.13–4.33)
			25–44	M	50 (5.3%)	66	296	528	1.33 (0.90–1.98)
			45–64	M	41 (4.5%)	167	181	527	0.71 (0.49–1.04)
			65–84	M	1 (0.2%)	38	36	384	0.22 (0.02–2.10)
			16–84	F	36 (1.3%)	453	90	2228	1.97 (1.32–2.94)
MONICA survey[g] (Norrbotten and Västerbotten)	1986	Rodu et al. (2002)	25–64	M	32 (4.0%)	145	153	476	0.69 (0.45–1.05)
	1990		25–64	M	38 (5.0%)	138	138	452	0.90 (0.60–1.35)
			25–64	F	8 (1.0%)	16	199	572	1.44 (0.61–3.41)
	1994		25–74	M	30 (4.0%)	149	112	455	0.82 (0.53–1.27)
			25–74	F	8 (1.0%)	16	204	557	1.37 (0.58–3.24)
	1999		25–74	M	20 (3.0%)	183	74	399	0.59 (0.35–1.00)
			25–74	F	7 (0.9%)	44	155	532	0.55 (0.24–1.24)
	2004	Stegmayr et al. (2005)	25–74	M	19 (2.0%)	252	84	580	0.52 (0.31–0.88)
			25–74	F	19 (2.0%)	84	149	682	1.04 (0.61–1.76)
NTS survey	1985	Ramström (1986)	18–34	M	82 (19.7%)	79	92	164	1.85 (1.24–2.76)
			35–70	M	50 (7.7%)	62	207	329	1.28 (0.85–1.93)
	1986	Ramström and Tibblin (1987)	18–34	M	58 (15.8%)	78	96	135	1.05 (0.68–1.61)
			35–70	M	46 (7.1%)	76	185	343	1.12 (0.75–1.69)
	1987	Ramström and Tibblin (1988)	18–34	M	86 (19.2%)	87	81	193	2.36 (1.59–3.50)
			35–70	M	47 (6.7%)	33	219	406	2.64 (1.64–4.24)
VIP study[h] (Västerbotten)	1990–94	Lundqvist et al. (2009)	30, 40, 50, 60	M	314 (4.1%)	1573	1104	4695	0.85 (0.74–0.97)
			30, 40, 50, 60	F	43 (0.5%)	227	1914	6616	0.65 (0.47–0.91)
	2000–04		40, 50, 60, 70	M	252 (3.3%)	1767	726	4942	0.97 (0.83–1.13)
			40, 50, 60, 70	F	69 (0.8%)	453	1305	6973	0.81 (0.63–1.06)
Your country and your life survey[i]	2001–02	Ramström and Foulds (2006)	16–24	M	12 (3.0%)	83	32	269	1.22 (0.60–2.47)
			25–44	M	22 (2.0%)	319	121	648	0.37 (0.23–0.59)
			45–64	M	24 (2.0%)	200	200	755	0.45 (0.29–0.71)
			65–79	M	6 (1.1%)	39	68	451	1.02 (0.42–2.50)
Survey in industrial town[g] (Northern Sweden)	1986	Novo et al. (2000)	21	M	33 (5.9%)	118	111	298	0.75 (0.48–1.17)
	1994		21	M	35 (8.3%)	83	41	262	2.69 (1.61–4.51)
Health on equal terms survey[i,j]	2004	Wadman (2009)	16–29	M	26 (3.0%)	191	61	591	1.32 (0.81–2.15)
			30–44	M	42 (3.0%)	363	153	837	0.63 (0.44–0.91)
			45–64	M	60 (3.0%)	358	318	1252	0.66 (0.49–0.89)
			65–84	M	12 (1.0%)	84	120	982	1.17 (0.62–2.20)
	2009		16–29	M	20 (2.9%)	130	48	484	1.55 (0.89–2.71)
			30–44	M	9 (1.0%)	183	64	660	0.51 (0.25–1.04)
			45–64	M	50 (3.0%)	285	218	1125	0.91 (0.65–1.26)
			65–84	M	13 (1.0%)	114	114	1025	1.03 (0.56–1.88)

(*continued on next page*)

Table 5 (*continued*)

Study[e]	Year (s)	Source	Age	Sex	Number of subjects[d]				OR (95% CI)
					Snus and smoking	Snus only	Smoking only	Neither	
Eurobarometer[k]	2002	Christensen (2004)	15+	M	18	68	77	327	1.12 (0.63–2.00)
Studies in adolescents									
BROMS cohort[l] (Stockholm)	2001–02	Rosendahl et al. (2005)	15–16	M	42 (3.9%)	32	249	755	3.98 (2.46–6.44)
OLIN cohort (Norrbotten)	2002	Hedman et al. (2007)	14–15	M	28 (1.7%)	231	18	1386	9.33 (5.08–17.1)
			14–15	F	18 (1.1%)	52	130	1464	3.90 (2.22–6.86)
Postal surveys	1994	Nilsson et al. (2009)	13, 15, 17	M	72 (4.0%)	126	144	1456	5.78 (4.13–8.09)
	2003		13, 15, 17	M	42 (3.0%)	84	42	1230	14.6 (9.05–23.7)
CAN school surveys[m]	1984	Hvitfeldt and Nyström (2009)	15–16	M	1178 (7.1%)	2525	1347	11, 614	4.02 (3.68–4.40)
	1994		15–16	M	204 (7.2%)	350	263	2014	4.46 (3.60–5.54)
	2004		15–16	M	296 (11.2%)	242	188	1908	12.4 (9.90–15.6)
			17–18	M	427 (19.4%)	270	270	1235	7.23 (5.91–8.85)
Stockholm schools	1998	Galanti et al. (2001b)	15–16	M	869 (13.8%)	359	898	4161	11.2 (9.73–12.9)
HBSC school survey[n]	2001–02	Danielson (2003)	15	M	37 (6.1%)	91	30	451	6.11 (3.59–10.4)
Norway school survey (six counties)	2000–04	Grotveldt et al. (2008)	15–16	M	987 (12.7%)	683	1064	5038	6.84 (6.08–7.70)
			15–16	F	218 (2.8%)	54	2408	5088	8.53 (6.31–11.5)
Norway telephone survey[n]	2004	Wiium et al. (2009)	16–20	M+F	60 (3.0%)	152	365	1427	1.54 (1.12–2.13)

[a] Definition includes regular and occasional use except where stated.
[b] Definition includes regular and occasional smoking of any product except where stated.
[c] Nationwide surveys in Sweden except where stated.
[d] Estimated where necessary from data provided. Note that for some studies (MONICA, your country your life, health on equal terms, postal surveys, CAN, HBSC) numbers were estimated from small percentages given only to whole numbers, increasing the variability of the estimates.
[e] Abbreviations used: SSLC = Swedish Survey of Living Conditions (Swedish acronym ULF), MONICA = Multinational Monitoring of trends and determinants in Cardiovascular disease, NTS = Swedish National Smoking and Health Association, VIP = Västerbotten Intervention Program, BROMS = Children's Smoking and Environment in Stockholm County, OLIN = Obstructive Lung disease in Northern Sweden, CAN = Central Alliance for Alcohol and Drug Information, HBSC = Health Behaviour in School-aged Children.
[f] Current snus = daily for surveys from 1988–89; current smoking = daily. Data provided by Högstrup.
[g] Current snus = daily; current smoking = one cigarette or more per day.
[h] Current snus = regular; current smoking = one cigarette or more per day.
[i] Current snus = daily; current smoking = daily.
[j] Surveys conducted annually 2004–09 but only selected years shown.
[k] Current snus = chew tobacco or take snuff. Regular surveys which occasionally included relevant data, only selected year shown. Only Sweden shown, as other types of smokeless tobacco are more likely to be included in other countries.
[l] Current snus use and smoking = at least monthly; smoking is of cigarettes specifically.
[m] Nationwide surveys conducted annually since 1971, relevant data available for age 15–16 from 1984 and for age 17–18 from 2004, but only selected years shown. The precise definitions of smoking and snus use changed in 1997. Before then, ORs for 15–16 year old males ranged from about 4 to 6, and afterwards typically greater than 9.
[n] Current snus and smoking = at least weekly.

Table 6
Relationship between ever snus[a] and ever smoking[b] in Sweden (or other Scandinavian countries)[c].

Study[e]	Year(s)	Source	Age	Sex	Number of subjects[d]				OR (95% CI)
					Snus and smoking	Snus only	Smoking only	Neither	
Studies in adults									
SALT twin cohort born 1935–58	1999–2002	Furberg et al. (2005)	41–67	M	3083 (22.3%)	1036	5466	4237	2.31 (2.13–2.50)
STAGE twin cohort born 1959–85[f]	2005–06	Furberg et al. (2008b)	20–47	M	3763 (44.0%)	1360	1424	2006	3.90 (3.56–4.27)
			20–47	F	2251 (21.4%)	422	4406	3441	4.17 (3.72–4.66)
MONICA surveys[g] (Norrbotten and Västerbotten)	1986	Rodu et al. (2002)	25–64	M	191 (23.7%)	97	237	282	2.34 (1.74–3.16)
	1990		25–64	M	176 (23.0%)	130	207	253	1.65 (1.24–2.22)
			25–64	F	23 (2.9%)	16	318	437	1.98 (1.03–3.80)
	1994		25–74	M	185 (24.8%)	97	196	269	2.62 (1.93–3.56)
			25–74	F	33 (4.2%)	16	383	353	1.90 (1.03–3.51)
	1999		25–74	M	194 (28.7%)	122	124	237	3.04 (2.22–4.16)
			25–74	F	55 (7.4%)	15	307	362	4.32 (2.39–7.81)
NTS survey[g]	1987	Ramström and Tibblin (1988)	18–34	M	111 (25.4%)	79	89	158	2.49 (1.69–3.68)
			35–70	M	111 (15.7%)	8	363	223	8.52 (4.08–17.8)
Your country and your life survey[g]	2001–02	Ramström and Foulds (2006)	16–79	M	438 (14.0%)	402	888	1397	1.71 (1.46–2.01)
AMI study controls (Stockholm and Västernorrland)	1992–94	Hergens et al. (2005)	45–70	M	232 (12.8%)	40	940	598	3.69 (2.60–5.24)
Studies in adolescents									
BROMS cohort[h] (Stockholm)	1997–98	Galanti et al. (2001a)	11	M	91 (5.9%)	35	241	1170	12.6 (8.35–19.1)
			11	F	27 (1.8%)	19	197	1239	8.94 (4.88–16.4)
			12	M	220 (15.0%)	40	314	893	15.6 (10.9–22.4)
			12	F	74 (5.2%)	25	344	973	8.37 (5.23–13.4)
	2001–02	Rosendahl et al. (2005)	15–16	M	172 (17.0%)	100	75	666	15.3 (10.8–21.5)
			15–16	F	81 (8.3%)	111	64	715	8.15 (5.55–12.0)
Stockholm schools	1998	Galanti et al. (2001b)	15–16	M	2868 (45.6%)	199	1468	1752	17.2 (14.7–20.2)
ESFA cohort [i] (Helsinki, Finland)	1998–2001	Haukkala et al. (2006)	14	M	92 (6.6%)	11	461	833	15.1 (8.00–28.5)
			15	M	269 (21.6%)	29	387	563	13.5 (9.01–20.2)
			16	M	453 (38.8%)	44	308	363	12.1 (8.60–17.1)

[a] Definition includes regular and occasional use except where stated.
[b] Definition includes regular and occasional smoking of any product except where stated.
[c] Nationwide surveys in Sweden except where stated.
[d] Estimated where necessary from data provided. Note that for the MONICA study numbers were estimated from small percentages given only to whole numbers, increasing the variability of the estimates.
[e] Abbreviations used: SALT = Screening Across Lifespan Twin study, STAGE = Screening Twin Adults Genes and Environment study, MONICA = Multinational Monitoring of trends and determinants in Cardiovascular disease, NTS = Swedish National Smoking and Health Association, AMI = acute myocardial infarction, BROMS = Children's Smoking and Environment in Stockholm County, ESFA = European Smoking Prevention Framework Approach,
[f] Smoking is of cigarettes specifically.
[g] Ever snus = daily; ever smoking = daily.
[h] For 1997–98, ever snus = ever tried; ever smoked = ever smoked cigarettes, even a single cigarette puff. For 2001–02, ever relates to weekly use for at least 3 months.
[i] Ever smokers includes triers; ages are approximate relating to 7th, 8th and 9th grades.

Table 7
Smoking initiation (or resumption) during follow-up by initial snus use[a] based on cohort studies in Sweden (or other Scandinavian countries)[b].

Study/start date[c]	Source	Age (years, at start)	Follow up (years)[d]	Sex	No snus		Snus[f]		RR (95% CI)
					N[d]	n[e]	N[e]	n[e]	
Never smoked at start									
VIP cohort 1990–94	Lundqvist et al. (2009)	30, 40, 50, 60	10	M	3596	51	965	40	2.92 (1.94–4.39)
		30, 40, 50, 60	10	F	5210	121	131	4	1.31 (0.49–3.51)
BROMS cohort 1997–98	Galanti et al. (2001a)	11	1	M	1114	201	34	14	2.28 (1.50–3.48)
		11	1	F	1185	200	18	5	1.65 (0.77–3.50)
	Galanti et al. (2008)	11	7	M + F	1960	424	39	13	1.54 (0.98–2.42)[g]
Never smoked or ex-smoker at start									
VIP cohort 1990–94	Lundqvist et al. (2009)	30, 40, 50, 60	10	M	4695	109	1573	70	1.92 (1.43–2.57)
		30, 40, 50, 60	10	F	6616	224	227	11	1.43 (0.79–2.58)
SSLC cohort 1980–81	Tillgren et al. (1996)	16–84	8	M	1334	80	286	29	1.69 (1.13–2.54)
SSLC cohort 1988–89	Stenbeck et al. (2009)[h]	16–44	8	M	503	20	200	11	1.38 (0.68–2.83)
		45–84	8	M	789	16	120	6	2.47 (0.98–6.18)
ESFA cohort 1998	Haukkala et al. (2006)	13	1	M	833	–	11	–	6.21 (3.20–12.1)[i]
		14	1	M	563	–	29	–	4.38 (2.82–6.80)[i]
		15	1	M	363	–	44	–	4.37 (2.44–7.82)[i]

[a] Estimates derived from data provided in source where necessary.
[b] In Sweden except for study of ESFA cohort, conducted in Finland.
[c] Abbreviations used: BROMS = Children Smoking and their Environment in Stockholm Region, VIP = Västerbotten Intervention Programme, SSLC = Swedish Survey of Living Conditions, ESFA = European Smoking Prevention Framework Approach.
[d] Number of never (or non) smokers at the start of the study.
[e] Number of never (or non) smokers at the start who were smoking at the end. Smoking is of cigarettes except for the SSLC cohort where it is any product. n not available for ESFA cohort.
[f] Snus use is regular or daily for the studies of adults and ever tried for the studies of adolescents.
[g] Galanti et al. (2008) report an odds ratio adjusted for sex and age at entry of 1.95 (95% CI 0.96–3.80).
[h] Estimates derived from additional data provided by Dr. Stenbeck.
[i] ORs, not RRs.

demonstrate an association of snus use and smoking actually exists. As shown in the Appendix, one can easily produce a hypothetical example data set which generates similarly reduced ORs, despite the data set being constructed assuming that smoking and snus use are completely independent. The ORs that the authors (Ramström and Foulds, 2006; Furberg et al., 2005) used are inherently biased by the time available for initiation not being controlled for in the analysis. For a given follow-up period, those starting on snus can only initiate smoking from that time point on, but those not starting on snus can initiate smoking from the start of the period.

It must be concluded that there is little reliable information on snus use and initiation. Cohort study analyses lack confounding control, while retrospective study analyses use biased methodology. Even if snus does affect initiation it seems unlikely to contribute much to total smoking incidence. Swedish twin data (Furberg et al., 2005) shows that, of 9151 ever smoking men, few (3.2%) used snus first. This low figure may be because the men, born pre-1959, were mainly adult before snus became popular among adolescents (Nordgren and Ramström, 1990). However, a later survey, of adult Swedes born after 1984 (Ramström and Foulds, 2006), also reported a low percentage (7.5%). Another cohort (Galanti et al., 2008) found that, among adolescents who used either product, only 11.2% started with snus. Other studies (Galanti et al., 2001a; Lundqvist et al., 2009; Ramström and Tibblin, 1988) also report results suggesting that, among mixed smokers and snus users, starting with smoking is much commoner than starting with snus. The low percentage of smokers in Sweden (Table 2) also suggests that snus does not increase smoking prevalence.

3.17. Does snus use affect smoking cessation?

This question can be investigated in cohort studies following up current smokers. Table 8 summarizes data from five studies in Sweden (Lindström and Isacsson, 2002; Lundqvist et al., 2009; Rodu et al., 2003; Stenbeck et al., 2009; Tillgren et al., 1996), all showing cessation is higher in snus users, significantly so (with minor exception) in the longer studies (Lundqvist et al., 2009; Rodu et al., 2003; Stenbeck et al., 2009; Tillgren et al., 1996). In one study involving a one year follow-up (Lindström and Isacsson, 2002), the association was clearer with the combined incidence of quitting or becoming an intermittent smoker. Table 8 also includes results of a one year study (Helgason et al., 2004) reporting a non-significant tendency for cessation to be likelier in snus users. Here, however, snus use was only assessed at the end. All the RRs in Table 8 are unadjusted for any potential confounding variable. Results for the telephone cohort (Helgason et al., 2004) showed that adjustment for age, sex and factors related to smoking abstention did not affect the association between quitting and snus.

Four publications (Furberg et al., 2005, 2008a; Gilljam and Galanti, 2003; Ramström and Foulds, 2006) presented analyses of retrospective studies. Although consistently showing an association between snus use and quitting, none are unbiased. Thus, a first set of analyses based on the Swedish Twin Registry (Furberg et al., 2005) compared smoking status (current or quit) at the time of interview in men using snus after they began smoking and in men who never used snus, reporting an OR of 3.7 (3.3–4.2) for quitting among snus users. This is not comparable to the Table 8 RRs, partly as the users include people starting snus after quitting smoking, and partly as snus users and never users have different time available to quit. However, since the time available should be less for snus users, who might not have started until near the time of interview, the bias seems unlikely to explain the association. Additional analysis of these data could clarify the relationship based on the information apparently available on age at starting and stopping smoking and snus use.

Another analysis based on the Swedish Twin Registry (Furberg et al., 2008a) reported that, among ever regular smokers, ever snus use was associated with not currently being a regular smoker, with a hazard ratio of 2.70 (2.30–3.20) after adjustment for other predictors of cessation. This has similar limitations to the earlier analysis (Furberg et al., 2005), which is also true for analyses of a telephone survey of smokers and ex-smokers (Gilljam and Galanti, 2003) which reported that the probability of being a former rather

Table 8
Smoking cessation during follow-up by initial snus use based on cohort studies of Swedish adults[a].

Study/start date[b]	Source	Follow-up (years)	Sex	No snus		Snus[e]		RR (95% CI)
				N^c	n^d	N^c	n^d	
VIP cohort 1990–94	Lundqvist et al. (2009)	10	M	1104	436	314	184	1.48 (1.32–1.67)
			F	1914	788	43	30	1.69 (1.38–2.08)
SSLC cohort 1980–81	Tillgren et al. (1996)	8	M	643	180	119	52	1.56 (1.23–1.98)
SSLC cohort 1988–89	Stenbeck et al. (2009)	8	M[f]	183	63	38	21	1.61 (1.13–2.28)
		8	M[f]	286	100	37	16	1.24 (0.83–1.85)
MONICA cohorts 1986, 90, 94	Rodu et al. (2003)	5, 9, 13	M	287	117	67	37	1.35 (1.05–1.75)
MSNS cohort 1992–94	Lindström and Isacsson (2002)	1	M + F	2893	207	82	8	1.36 (0.70–2.67)
			M + F	2893	388[g]	82	20[g]	1.82 (1.23–2.69)
Telephone helpline cohort 1999	Helgason et al. (2004)	1	M + F	400	106	59	21	1.34 (0.92–1.96)[h]

[a] Estimates derived from data provided in source where necessary.
[b] Abbreviations used: VIP = Västerbotten Intervention Programme, SSLC = Swedish Survey of Living Conditions, MONICA = Multinational Monitoring of trends and determinants in Cardiovascular disease, MSNS = Malmö Shoulder–Neck Study.
[c] Number of daily smokers at the start of the study. Smoking is of any product except for the VIP and MONICA cohorts where it is of cigarettes.
[d] Number of daily smokers at the start who were no longer smoking at the end of follow-up.
[e] Snus use at the start of the study – exceptionally in the telephone helpline cohort snus use is at the end of follow-up. Snus use is daily except for the VIP and MSNS cohorts where it is any use.
[f] Estimates derived from additional data provided by Dr. Stenbeck, ages 16–44 and 45–84.
[g] Number who had quit smoking or become intermittent smokers.
[h] The authors reported a crude odds ratio of 1.5 (0.9–2.7) which was unaffected by adjustment for age, sex and other potential confounding variables.

than a current smoker increased with ever snus use (OR 1.72, 1.30–2.28) or with current snus use (OR 1.81, 1.31–2.53). More relevant, as it avoids the possibility that the snus use is not concurrent with the smoking, is a report that having used snus at the latest quit attempt increased the probability of abstinence (OR 1.54, 1.09–2.20). However, even this analysis is biased by not adjusting for the time of the quit attempt. Similar issues relate to a cross-sectional survey (Ramström and Foulds, 2006) which found that the success of the latest quit attempt was greater for men using snus as their single cessation aid (66%) rather than nicotine gum (47%, OR 2.2, 1.3–3.7), or the nicotine patch (32%, OR 4.2, 2.1–8.6).

Also relevant may be data from successive MONICA surveys (Rodu et al., 2002) showing that the proportion of men with a history of snus is substantially greater for ex-smokers than current smokers (e.g. 1986 53% vs. 35%), though this does not directly relate to whether concurrent snus use affects quitting. Further data from these surveys (Rodu et al., 2003) suggests that, among ex-smokers, there is little difference in the relapse rate by previous snus use.

The analyses summarized above are consistent with snus use facilitating quitting, but have limitations. The cohort studies did not adjust for predictors of quitting, while the retrospective studies did not control for time available to quit or clearly distinguish effects on quitting of previous snus use, concurrent use, and use after quitting (perhaps to maintain abstinence). Even so, it seems unlikely from these data that snus use could discourage quitting.

4. Discussion

4.1. Possible health effects of snus

The evidence provides little support for the existence of any major adverse health effect of snus. Some associations are consistently demonstrated, but seem either of relatively minor consequence, or not necessarily causally related. Thus snuff-dipper's lesion (Kallischnigg et al., 2008) does not predict oral cancer (Roosaar et al., 2006), and a reported acute effect of snus on blood pressure (Hirsch et al., 1992; Rohani and Agewall, 2004) is unsupported by evidence of increased blood pressure in snus users from cross-sectional studies (Ahlbom et al., 1997; Ångman and Eliasson, 2008; Bolinder and de Faire, 1998; Bolinder et al., 1992; Eliasson et al., 1991, 1995; Hergens et al., 2005, 2008b; Janzon and Hedblad, 2009; Johansson et al., 2005; Wallenfeldt et al., 2001; Wennmalm et al., 1991). Whether the increased BMI in snus users (Hergens et al., 2005; Janzon and Hedblad, 2009; Nafziger et al., 2007; Norberg et al., 2006; Sundbeck et al., 2009) results from snus use is unclear, as is the less consistently reported increase in musculoskeletal disorders (Bolinder et al., 1992; Heir and Eide, 1997; Holmberg and Thelin, 2006; Jakobsson, 2008; Mattila et al., 2008), which may arise as participants in occupations or sports with increased risk of back problems may prefer snus to cigarettes for practical reasons.

For many endpoints, little evidence is available and, for some, isolated reports suggest a possible relationship. Reports that snus increases the risk of respiratory disease in older men (Roosaar et al., 2008), respiratory symptoms (Bolinder et al., 1992), Raynaud-type symptoms (Bolinder et al., 1992; Ekenvall and Lindblad, 1985), bruxism (Rintakoski et al., 2010) and reduced birthweight (England et al., 2003) have no other supportive evidence, while reports of an increased risk of preterm delivery if the mother used snus are based on two overlapping analyses of the same database (England et al., 2003; Wikström et al., 2010a).

For some endpoints, more evidence is available but reported associations are unconfirmed by other evidence. This is true for ulcerative colitis and Crohn's disease, where reported increases in risk (Persson et al., 1993) were not seen in the construction workers study (Carlens et al., 2010), and for preeclampsia, where an increased risk reported in 2003 (England et al., 2003) was not confirmed by a more extensive study of the same database (Wikström et al., 2010b). It is also the case for gingival diseases, where the associations seen (Modéer et al., 1980; Montén et al., 2006) are not replicated (Bergström et al., 2006; Rolandsson et al., 2005; Wickholm et al., 2004), and for diabetes, where one study (Persson et al., 2000), but not others (Eliasson et al., 2004; Hergens et al., 2005; Johansson et al., 2005; Norberg et al., 2006; Wändell et al., 2008) reported an association. Other examples are metabolic syndrome, where one study (Norberg et al., 2006), but not another (Wändell et al., 2008) reported an association; and triglyceride levels, where two studies reported an increase (Norberg et al., 2006; Wallenfeldt et al., 2001) but three found no relationship (Ahlbom et al., 1997; Bolinder et al., 1997a; Eliasson et al., 1991).

The discussion above does not concern the data for cancer and CID. For CID, eleven reports (Asplund et al., 2003; Haglund et al., 2007; Hansson et al., 2009; Hergens et al., 2005, 2007, 2008a;

Huhtasaari et al., 1992, 1999; Janzon and Hedblad, 2009; Roosaar et al., 2008; Wennberg et al., 2007) and meta-analyses consistently show no relationship, except for an early report from the construction workers study (Bolinder et al., 1994) of an increase in IHD/AMI and any CID, which contrasts with later reports from the same study (Hergens et al., 2007, 2008a). Although a weak effect of snus use on CID remains possible, the overall data are certainly consistent with no effect.

Boffetta and Straif (2009) have recently concluded that studies in Sweden show an increased risk of death from myocardial infarction and stroke, citing a combined RR estimate of 1.27 (1.07–1.52) for fatal myocardial infarction based on five studies (Haglund et al., 2007; Hergens et al., 2005, 2007; Huhtasaari et al., 1999; Wennberg et al., 2007) and of 1.25 (0.91–1.70) for fatal stroke based on two studies (Haglund et al., 2007; Hergens et al., 2008a). Their conclusion seems unjustified. For stroke, neither the combined nor the individual study RR estimates are statistically significant. For AMI the combined estimate is dominated by the estimate of 1.32 (1.08–1.61) from the construction workers study (Hergens et al., 2007), a study which is open to question, as discussed later, and the estimate must be interpreted in the light of the lack of evidence of an association for combined fatal and non-fatal cases.

For cancer, there are more reports of an association, but the meta-analyses are generally null. The claim by Boffetta et al. (2008) that smokeless tobacco increases risk of oropharyngeal, oesophageal and pancreatic cancer has been discussed fully elsewhere (Lee and Hamling, 2009a,b). While the discussion relates to smokeless tobacco use in North America and Sweden, some points relate to snus.

For pancreatic cancer, Boffetta et al. (2008) cited only the increases for never smokers from the construction workers study (Luo et al., 2007) and for the whole population from the Norway cohorts study (Boffetta et al., 2005), not mentioning the lack of increase for the whole population for the construction workers (Luo et al., 2007) and for never smokers for the Norway cohorts (Boffetta et al., 2005). For both whole population and never smokers, the meta-analyses only suggest a possible association.

The same is true for oesophageal cancer, three studies (Boffetta et al., 2005; Lagergren et al., 2000; Lewin et al., 1998) showing no relationship, and the construction workers study (Zendehdel et al., 2008) an increase only in never smokers. Remarkably, Boffetta et al. (2008) considered only the never smoker RR of 3.5 (1.6–7.6) for squamous cell carcinoma, not mentioning the RR of 0.2 (0.0–1.9) for adenocarcinoma, or the smoking-adjusted whole population RRs of 1.0 (0.8–1.4) for squamous cell carcinoma and 1.0 (0.6–1.5) for adenocarcinoma. Until the increase in squamous cell carcinoma in never smokers is confirmed, an association of snus use with oesophageal cancer is undemonstrated.

For oropharyngeal cancer, the analyses reported here are consistent with those of Boffetta et al. (2008) in finding no association. One study (Roosaar et al., 2008) reported an association, but six studies did not (Blomqvist et al., 1991; Boffetta et al., 2005; Lewin et al., 1998; Luo et al., 2007; Rosenquist et al., 2005; Schildt et al., 1998) and the combined data show no relationship. This is consistent with our earlier review (Lee and Hamling, 2009a) which noted an increased risk for past use in the USA, but found no evidence of an increase at all in studies published since 1990 in either the USA or Scandinavia.

For lung cancer, the two studies (Boffetta et al., 2005; Luo et al., 2007) show no association. Boffetta et al. (2008) considered insufficient evidence was available to study other cancers. However, there are five studies (Boffetta et al., 2005; Hansson et al., 1994; Lagergren et al., 2000; Ye et al., 1999; Zendehdel et al., 2008) on stomach cancer, the combined evidence showing no increase, despite the increased risk for never smoking construction workers (Zendehdel et al., 2008). For other cancers, the evidence is limited, the only significant association reported being the increase for smoking-related cancers in never smokers in the Uppsala county study (Roosaar et al., 2008). This requires confirmation, this study being the only one reporting an increase for oropharyngeal cancer.

The lack of clear relationship of snus use with cancer risk is consistent with the very low estimated risk predicted from extrapolation of the dose response relationships found in rodents to actual exposures to NNK and NNN from snus, which would be expected to result in pro-mutagenic DNA adduct levels that are more than an order of magnitude below those normally found in humans (Nilsson, 2006).

4.2. The construction workers study

The tendency for the construction workers study to report associations not found elsewhere is interesting. This is true for oesophageal cancer (Zendehdel et al., 2008), stomach cancer (Zendehdel et al., 2008), IHD/AMI (Bolinder et al., 1994), any CID (Bolinder et al., 1994), blood pressure (Bolinder et al., 1992; Hergens et al., 2008b), and some endpoints not investigated in other studies; respiratory symptoms, sleep disturbances, nervous problems and sick leave (Bolinder et al., 1992). Though the study is large, prospective, and involves long-term follow-up, there are two features of it that require comment. First, many later publications (e.g. Hergens et al., 2007, 2008a,b; Luo et al., 2007) from the construction workers study restricted attention to data collected since 1978 based on personal interviews, no data being collected on snus or smoking in 1976–77, and data collected earlier by questionnaire being limited for snus and ambiguously coded for smoking. Many papers reporting associations (including Bolinder et al., 1992, 1994) used the data collected earlier despite its limitations, and for IHD/AMI an association with snus was reported using the earlier data (Bolinder et al., 1994), but not using the later data (Hergens et al., 2007). Second, none of the publications adjusted for job type. One would imagine that for some jobs using snus is more convenient than is smoking, and associations may reflect the risk of the job rather than of snus use. Confounding by the reason for using snus might also affect reported relationships in other studies for other endpoints; e.g. back pain (Bolinder et al., 1992; Mattila et al., 2008).

4.3. Limitations of the evidence on health effects

There are limitations to the health data for snus. There are few studies on some endpoints, some studies include few cases using snus, data on extent and duration of use are limited, and confounding control is sometimes inadequate. No study adjusts for smoking misclassification, possibly relevant for strongly smoking-related diseases. Given that ever snus use and ever smoking are associated, analyses of self-reported never smokers are biased if some subjects deny their smoking.

There are also limitations to meta-analysis, used to summarize the evidence for circulatory disease and for cancer. These include doubts about combining RR estimates for exposures and outcomes defined somewhat differently in different studies, failure to account for study quality, and possible omission of relevant unpublished evidence.

4.4. Comparison with effects of smoking

Despite these limitations, it seems clear that any risks from snus are overall much lower than from smoking. Early reports (England et al., 2003; Persson et al., 1993) suggested possible increased risks of ulcerative colitis and preeclampsia in users, in contrast to the decreased risks in smokers (Conde-Agudelo et al., 1999; Mahid et al., 2006), but these have not been confirmed by later publica-

tions (Carlens et al., 2010; Wikström et al., 2010b), and generally it seems true for the wide range of conditions discussed that effects of snus are either non-existent or quite modest. In particular, there is convincing evidence that the risks of cancer and circulatory disease are much lower for snus users.

For cancer, Lee and Hamling (2009a) estimated that tobacco-attributable deaths would reduce by about 99% if all smokers switched to smokeless tobacco (as used in North America or Europe) and had the excess risks of smokeless tobacco users. As the association with cancer seems no greater for snus than smokeless tobacco (Lee and Hamling, 2009a), it can be concluded that snus-related cancer deaths (if they exist) are much lower than smoking-related deaths.

For CID, one can compare meta-analysis RR estimates of 1.01 (0.91–1.12) for IHD/AMI and 1.05 (0.95–1.15) for stroke with estimates for smoking of 2.95 (2.77–3.14) for AMI from a 52 country study (Teo et al., 2006) and a similar estimate for stroke from a review (Hankey, 1999). Again any excess risk from snus seems two orders of magnitude less.

Respiratory disease, particularly COPD, is another major cause of smoking-related death. Though evidence is lacking for snus, it seems unlikely that any major effect exists, partly as one might have been reported had it existed, and partly as snus does not produce smoke.

4.5. Does snus encourage initiation of smoking or discourage quitting?

Even if snus has little direct effect on health, there is concern that allowing sale in countries other than Sweden might encourage initiation of smoking or discourage quitting. While one cannot extrapolate with certainty from Sweden, such concerns seem unjustified. While ever snus users are clearly likelier ever to have smoked, and never smokers who use snus at one point in time are more likely to smoke later on, this does not demonstrate that snus use encourages initiation. These results are also explicable by confounding by "risk-taking", with non-risk takers tending not to try either product, and risk takers quite likely to try both. The evidence on initiation from cohort studies suffers from lack of confounding control, while the evidence from retrospective studies (Furberg et al., 2005; Ramström and Foulds, 2006) may be markedly biased. However the evidence shows that the proportion of ever smokers using snus before starting smoking is low [3.2% (Furberg et al., 2005), 7.5% (Ramström and Foulds, 2006)] and that among users of both products, the great majority start by smoking. It therefore seems probable that snus is at worst a minor determinant of smoking, consistent with smoking prevalence being low in Sweden.

Evidence from cohort studies following up current smokers (Lindström and Isacsson, 2002; Lundqvist et al., 2009; Rodu et al., 2003) and from retrospective studies (Furberg et al., 2005, 2008a; Gilljam and Galanti, 2003; Ramström and Foulds, 2006) consistently suggests that snus encourages rather than discourages quitting. However, this evidence is actually not so strong. The cohort study data are unadjusted for any potential confounding variable, and would fit in with risk takers trying both products, then generally choosing one. Furthermore, the analyses of retrospective data are generally not strictly valid, as they do not account for time at risk, or distinguish between using snus at the time of smoking or subsequently. Notwithstanding, it is notable that no published evidence actually suggests that snus discourages quitting.

5. Conclusions

Using snus is clearly much safer than smoking. While smoking substantially increases the risk of cancer and CID, any increase from snus use is undemonstrated, and if it exists is probably about 1% of that from smoking Even were isolated reports of some adverse health consequences of snus confirmed, switching to snus should improve the health prospects of those smokers who are unable or unwilling to relinquish nicotine. There is no good evidence that introducing snus in a population would encourage smoking initiation or discourage cessation.

Conflict of interest

The author is a long-term consultant to the tobacco industry. However, this is an independent scientific assessment, the views expressed being those of the author alone.

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Appendix

This example illustrates the potential for large bias in estimates of the effect of snus use on smoking published by Ramström and Foulds (Ramström et al., 2006) and by Furberg et al. (Furberg et al., 2005)

It is based on four assumptions:

1) At baseline there are 3000 men who have never used tobacco.
2) During the follow-up period 20% start smoking and 10% start snus.
3) Starting of smoking and starting of snus are independent.
4) The onset time distributions for both products are the same.

It is then possible to calculate the expected numbers in the five possible smoking groups at the end of follow-up

N_1	Never used either product	$3000 \times 0.8 \times 0.9$	=	2160
N_2	used snus only	$3000 \times 0.8 \times 0.1$	=	240
N_3	Smoked only	$3000 \times 0.2 \times 0.9$	=	540
N_4	Started on snus, then smoked	$3000 \times 0.2 \times 0.1 \times 0.1 / (0.1+0.2)$	=	20
N_5	Started smoking, then snus	$3000 \times 0.2 \times 0.1 \times 0.2 / (0.1+0.2)$	=	40
Total				3000
The probabilities for smoking initiation can then be derived				
P_1	among starters on snus	$N_4 / (N_2+N_4)$	=	0.077
P_2	among others	$(N_3+N_5) / (N_1+N_3+N_5)$	=	0.212
P_3	among never snus users	$N_3 / (N_1+N_3)$	=	0.200

Ramström and Foulds (Ramström et al., 2006) compared P_1 and P_2 and derived, as a test of independence, the odds ratio $(OR_1) = P_1(1–P_2) / (P_2(1–P_1))$ and assumed that values less than 1.0 indicated that snus use protected against initiation.

Furberg et al. (Furberg et al., 2005) compared P_1 and P_3 and similarly derived a test of independence based on the odds ratio $OR_2 = P_1(1–P_3) / (P_3(1–P_1))$ and also assumed that values less than 1.0 indicated protection against initiation.

For the hypothetical data, which was derived assuming independence, $OR_1 = 0.31$ and $OR_2 = 0.33$. The observation that these ORs are less than 1 therefore does not indicate a lack of independence, or that snus use protects against initiation.

References

Agewall, S., Persson, B., Lindstedt, G., Fagerberg, B., 2002. Smoking and use of smokeless tobacco in treated hypertensive men at high coronary risk: utility of urinary cotinine determination. Br. J. Biomed. Sci. 59, 145–149.

Ahlbom, A., Olsson, U.A., Pershagen, G., 1997. Health risks associated with Swedish snus, Symposium on snus arranged by the National Board of Health and Welfare, Stockholm, 19–20 September 1996. (Statistics of Sweden rapport 1997:11).

Ahmed, E., Stegmayr, B., Trifunovic, J., Weinehall, L., Hallmans, G., Lefvert, A.K., 2000. Anticardiolipin antibodies are not an independent risk factor for stroke: an incident case-referent study nested within the MONICA and Västerbotten cohort project. Stroke 31, 1289–1293.

Andersson, G., Axéll, T., 1989. Clinical appearance of lesions associated with the use of loose and portion-bag packed Swedish moist snuff: a comparative study. J. Oral Pathol. Med. 18, 2–7.

Andersson, G., Axéll, T., Curvall, M., 1995. Reduction in nicotine intake and oral mucosal changes among users of Swedish oral moist snuff after switching to a low-nicotine product. J. Oral Pathol. Med. 24, 244–250.

Andersson, G., Bjornberg, G., Curvall, M., 1994. Oral mucosal changes and nicotine disposition in users of Swedish smokeless tobacco products: a comparative study. J. Oral Pathol. Med. 23, 161–167.

Andersson, G., Warfvinge, G., 2003. The influence of pH and nicotine concentration in oral moist snuff on mucosal changes and salivary pH in Swedish snuff users. Swed. Dent. J. 27, 67–75.

Ångman, M., Eliasson, M., 2008. Snus och blodtrych. Tvärsnittsstudie av viloblodtryck hos män i MONICA-studien i norra sverige. (Snuff and blood pressure. Cross-sectional study of blood pressure in rest among men in the MONICA study in Northern Sweden). Lakartidningen 105, 3530–3535.

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

Attvall, S., Fowelin, J., Lager, I., Von Schenck, H., Smith, U., 1993. Smoking induces insulin resistance – a potential link with the insulin resistance syndrome. J. Intern. Med. 233, 327–332.

Axéll, T., Mörnstad, H., Sundström, B., 1976. The relation of the clinical picture to the histopathology of snuff dipper's lesions in a Swedish population. J. Oral Pathol. 5, 229–236.

Axéll, T.E., 1993. Oral mucosal changes related to smokeless tobacco usage: research findings in Scandinavia. Eur. J. Cancer B Oral Oncol. 29B, 299–302.

Berggren, U., Eriksson, M., Fahlke, C., Blennow, K., Balldin, J., 2007. Different effects of smoking or use of smokeless tobacco on platelet MAO-B activity in type 1 alcohol-dependent subjects. Alcohol Alcohol. 42, 267–271.

Bergström, J., Keilani, H., Lundholm, C., Rådestad, U., 2006. Smokeless tobacco (snuff) use and periodontal bone loss. J. Clin. Periodontol. 33, 549–554.

Blomqvist, G., Hirsch, J.-M., Alberius, P., 1991. Association between development of lower lip cancer and tobacco habits. J. Oral Maxillofac. Surg. 49, 1044–1047.

Boffetta, P., Aagnes, B., Weiderpass, E., Andersen, A., 2005. Smokeless tobacco use and risk of cancer of the pancreas and other organs. Int. J. Cancer 114, 992–995.

Boffetta, P., Hecht, S., Gray, N., Gupta, P., Straif, K., 2008. Smokeless tobacco and cancer. Lancet Oncol. 9, 667–675.

Boffetta, P., Straif, K., 2009. Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis (online first). BMJ 339, b3060.

Bolinder, G., Alfredsson, L., Englund, A., de Faire, U., 1994. Smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers. Am. J. Public Health 84, 399–404.

Bolinder, G., de Faire, U., 1998. Ambulatory 24-h blood pressure monitoring in healthy, middle-aged smokeless tobacco users, smokers, and nontobacco users. Am. J. Hypertens. 11, 1153–1163.

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

Bolinder, G., Norén, A., Wahren, J., de Faire, U., 1997b. Long-term use of smokeless tobacco and physical performance in middle-aged men. Eur. J. Clin. Invest. 27, 427–433.

Bolinder, G.M., Ahlborg, B.O., Lindell, J.H., 1992. Use of smokeless tobacco: blood pressure elevation and other health hazards found in a large-scale population survey. J. Intern. Med. 232, 327–334.

Brattwall, M., Warrén Stomberg, M., Rawal, N., Segerdahl, M., Houltz, E., Jakobsson, J., 2010. Postoperative impact of regular tobacco use, smoking or snuffing, a prospective multi-center study. Acta Anaesthesiol. Scand. 54, 321–327.

Broadstock, M., 2007. Systematic Review of the Health Effects of Modified Smokeless Tobacco Products (NZTA Report), vol. 10(1). New Zealand Health Technology Assessment, Christchurch. <http://nzhta.chmeds.ac.nz/publications/smokeless_tobacco.pdf> (accessed 10.10).

Carlens, C., Hergens, M.-P., Grunewald, J., Ekbom, A., Eklund, A., Höglund, C.O., Askling, J., 2010. Smoking, use of moist snuff and risk of chronic inflammatory diseases. Am. J. Respir. Crit. Care Med. 181, 1217–1222.

Christensen, T., 2004. Euro-barometer 58.2: health and developing countries, October–December 2002 [computer file]. Inter-University Consortium for Political and Social Research, Ann Arbor, Michigan. <http://www.data-archive.ac.uk/findingData/snDescription.asp?sn=4810> (accessed 10.10).

Colilla, S.A., 2010. An epidemiologic review of smokeless tobacco health effects and harm reduction potential. Regul. Toxicol. Pharmacol. 56, 197–211.

Conde-Agudelo, A., Althabe, F., Belizán, J.M., Kafury-Goeta, A.C., 1999. Cigarette smoking during pregnancy and risk of preeclampsia: a systematic review. Am. J. Obstet. Gynecol. 181, 1026–1035.

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

Danielson, M., 2003. Svenska skolbarns hälsovanor 2001/02. (Health behaviour in school-aged children. A WHO Collaborative Study). Statens Folkhälsoinstitut, (2003:50.) <http://www.fhi.se/shop/material_pdf/skolbarnshalsovanor0312.pdf> (accessed 10.10).

Ekenvall, L., Lindblad, L.E., 1985. Vibrationsutlösta raynaudfenomen och nikotinkonsumtion – en preliminär rapport. (Vibration induced white fingers and nicotine – a preliminary report). Opusc. Med. 30, 28–31.

Eliasson, B., Taskinen, M.-R., Smith, U., 1996. Long-term use of nicotine gum is associated with hyperinsulinemia and insulin resistance. Circulation 94, 878–881.

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

Eliasson, M., Asplund, K., Nasic, S., Rodu, B., 2004. Influence of smoking and snus on the prevalence and incidence of type 2 diabetes amongst men: the northern Sweden MONICA study. J. Intern. Med. 256, 101–110.

Eliasson, M., Lundblad, D., Hägg, E., 1991. Cardiovascular risk factors in young snuff-users and cigarette smokers. J. Intern. Med. 230, 17–22.

Ellingsen, D.G., Thomassen, Y., Rustad, P., Molander, P., Aaseth, J., 2009. The time-trend and the relation between smoking and circulating selenium concentrations in Norway. J. Trace Elem. Med. Biol. 23, 107–115.

England, L.J., Levine, R.J., Mills, J.L., Klebanoff, M.A., Yu, K.F., Cnattingius, S., 2003. Adverse pregnancy outcomes in snuff users. Am. J. Obstet. Gynecol. 189, 939–943. Presented at the Annual Meeting of the Society for Maternal-Fetal Medicine, San Francisco, 7 February.

Fang, F., Bellocco, R., Hernan, M.A., Ye, W., 2006. Smoking, snuff dipping and the risk of amyotrophic lateral sclerosis – a prospective cohort study. Neuroepidemiology 27, 217–221.

Fernberg, P., Odenbro, A., Bellocco, R., Boffetta, P., Pawitan, Y., Zendehdel, K., Adami, J., 2007. Tobacco use, body mass index, and the risk of leukemia and multiple myeloma: a nationwide cohort study in Sweden. Cancer Res. 67, 5983–5986.

Fernberg, P., Odenbro, A., Bellocco, R., Boffetta, P., Yudi Pawitan, Y., Adami, J., 2006. Tobacco use, body mass index and the risk of malignant lymphomas: a nationwide cohort study in Sweden. Int. J. Cancer 118, 2298–2302.

Fleiss, J.L., Gross, A.J., 1991. Meta-analysis in epidemiology, with special reference to studies of the association between exposure to environmental tobacco smoke and lung cancer: a critique. J. Clin. Epidemiol. 44, 127–139.

Forey, B., Hamling, J., Hamling, J., Lee, P. (Eds.), 2006–2009. International smoking statistics. A Collection of Historical Data from 30 Economically Developed Countries, web ed. P.N. Lee Statistics and Computing Ltd., Sutton, UK. <www.pnlee.co.uk/iss.htm>.

Forey, B.A., Hamling, J., Lee, P.N., 2010. International Mortality and Smoking Statistics IMASS Version 4.05. P.N. Lee Statistics and Computing Ltd., Sutton, Surrey. <http://www.pnlee.co.uk/IMASS.htm>.

Foulds, J., Ramstrom, L., Burke, M., Fagerström, K., 2003. Effect of smokeless tobacco (snus) on smoking and public health in Sweden. Tob. Control 12, 349–359.

Frithiof, L., Anneroth, G., Lasson, U., Sederholm, C., 1983. The snuff-induced lesion. A clinical and morphological study of a Swedish material. Acta Odontol. Scand. 41, 53–64.

Furberg, H., Bulik, C.M., Lerman, C., Lichtenstein, P., Pedersen, N.L., Sullivan, P.F., 2005. Is Swedish snus associated with smoking initiation or smoking cessation? Tob. Control 14, 422–424.

Furberg, H., Lichtenstein, P., Pedersen, N.L., Bulik, C.M., Lerman, C., Sullivan, P.F., 2008a. Snus use and other correlates of smoking cessation in the Swedish twin registry. Psychol. Med. 38, 1299–1308.

Furberg, H., Lichtenstein, P., Pedersen, N.L., Thornton, L., Bulik, C.M., Lerman, C., Sullivan, P.F., 2008b. The STAGE cohort: a prospective study of tobacco use among Swedish twins. Nicotine Tob. Res. 10, 1727–1735.

Galanti, M.R., Rosendahl, I., Post, A., Gilljam, H., 2001a. Early gender differences in adolescent tobacco use – the experience of a Swedish cohort. Scand. J. Public Health 29, 314–317.

Galanti, M.R., Rosendahl, I., Wickholm, S., 2008. The development of tobacco use in adolescence among "snus starters" and "cigarette starters": an analysis of the Swedish "BROMS" cohort. Nicotine Tob. Res. 10, 315–323.

Galanti, M.R., Wickholm, S., Gilljam, H., 2001b. Between harm and dangers. Oral snuff use, cigarette smoking and problem behaviours in a survey of Swedish male adolescents. Eur. J. Public Health 11, 340–345.

Gardner, M.J., Altman, D.G. (Eds.), 1989. Statistics with confidence. Confidence Intervals and Statistical Guidelines. British Medical Journal, London.

Gilljam, H., Galanti, M.R., 2003. Role of *snus* (oral moist snuff) in smoking cessation and smoking reduction in Sweden. Addiction 98, 1183–1189.

Grotvedt, L., Stigum, H., Hovengen, R., Graff-Iversen, S., 2008. Social differences in smoking and snuff use among Norwegian adolescents: a population based survey. BMC Public Health 8, 322–333.

Haglund, B., Eliasson, M., Stenbeck, M., Rosén, M., 2007. Is moist snuff use associated with excess risk of IHD or stroke? A longitudinal follow-up of snuff users in Sweden. Scand. J. Public Health 35, 618–622.

Halling, A., Halling, A., Unell, L., 2007. General health and tobacco habits among middle-aged Swedes. Eur. J. Public Health 17, 151–154.

Hankey, G.J., 1999. Smoking and risk of stroke. J. Cardiovasc. Risk 6, 207–211.

Hansson, J., Pedersen, N.L., Galanti, M.R., Andersson, T., Ahlbom, A., Hallqvist, J., Magnusson, C., 2009. Use of snus and risk for cardiovascular disease: results from the Swedish twin registry. J. Intern. Med. 265, 717–724.

Hansson, L.-E., Baron, J., Nyrén, O., Bergström, R., Wolk, A., Adami, H.-O., 1994. Tobacco, alcohol and the risk of gastric cancer. A population-based case-control study in Sweden. Int. J. Cancer 57, 26–31.

Haukkala, A., Vartiainen, E., de Vries, H., 2006. Progression of oral snuff use among Finnish 13–16-year-old students and its relation to smoking behaviour. Addiction 101, 581–589.

Hedman, L., Bjerg-Bäcklund, A., Perzanowski, M., Sundberg, S., Rönmark, E., 2007. Factors related to tobacco use among teenagers. Respir. Med. 101, 496–502.

Hedström, A.K., Bäärnhielm, M., Olsson, T., Alfredsson, L., 2009. Tobacco smoking, but not Swedish snuff use, increases the risk of multiple sclerosis. Neurology 73, 696–701.

Heir, T., Eide, G., 1997. Injury proneness in infantry conscripts undergoing a physical training programme: smokeless tobacco use, higher age, and low levels of physical fitness are risk factors. Scand. J. Med. Sci. Sports 7, 304–311.

Helgason, A.R., Tomson, T., Lund, K.E., Galanti, R., Ahnve, S., Gilljam, H., 2004. Factors related to abstinence in a telephone helpline for smoking cessation. Eur. J. Public Health 14, 306–310.

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

Hergens, M.-P., Alfredsson, L., Bolinder, G., Lambe, M., Pershagen, G., Ye, W., 2007. Long-term use of Swedish moist snuff and the risk of myocardial infarction amongst men. J. Intern. Med. 262, 351–359.

Hergens, M.-P., Lambe, M., Pershagen, G., Terent, A., Ye, W., 2008a. Smokeless tobacco and the risk of stroke. Epidemiology 19, 794–799.

Hergens, M.-P., Lambe, M., Pershagen, G., Ye, W., 2008b. Risk of hypertension amongst Swedish male snuff users: a prospective study. J. Intern. Med. 264, 187–194.

Hirsch, J.-M., Hedner, J., Wernstedt, L., Lundberg, J., Hedner, T., 1992. Hemodynamic effects of the use of snuff. Clin. Pharmacol. Ther. 52, 394–401.

Hirsch, J.-M., Heyden, G., Thilander, H., 1982. A clinical, histomorphological and histochemical study on snuff-induced lesions of varying severity. J. Oral Pathol. 11, 387–398.

Hirsch, J.M., Livian, G., Edward, S., Noren, J.G., 1991. Tobacco habits among teenagers in the city of Göteborg, Sweden, and possible association with dental caries. Swed. Dent. J. 15, 117–123.

Holm, H., Jarvis, M.J., Russell, M.A.H., Feyerabend, C., 1992. Nicotine intake and dependence in Swedish snuff takers. Psychopharmacology 108, 507–511.

Holmberg, S.A., Thelin, A.G., 2006. Primary care consultation, hospital admission, sick leave and disability pension owing to neck and low back pain: a 12-year prospective cohort study in a rural population. BMC Musculoskelet. Disord. 7, 66–73.

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

Huhtasaari, F., Lundberg, V., Eliasson, M., Janlert, U., Asplund, K., 1999. Smokeless tobacco as a possible risk factor for myocardial infarction: a population-based study in middle-aged men. J. Am. Coll. Cardiol. 34, 1784–1790.

Hvitfeldt, T., Nyström, S., 2009. Skolelevers drogvanor 2008. Centralförbundet för alkohol-och narkotikaupplysning, Stockholm. (CAN Report no. 114.) <http://www.can.se/documents/CAN/Rapporter/rapportserie/can-rapportserie-114-skolelevers-drogvanor-2008.pdf> (accessed 10.10).

Idris, A.M., Nair, J., Oshima, H., Friesen, M., Brouet, I., Faustman, E.M., Bartsch, H., 1991. Unusually high levels of carcinogenic nitrosamines in Sudan oral snuff (toombak). Carcinogenesis 12, 1115–1118.

International Agency for Research on Cancer, 2007a. Smokeless tobacco and some tobacco-specific *N*-nitrosamines, vol. 89. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, IARC, Lyon, France. <http://monographs.iarc.fr/ENG/Monographs/vol89/mono89.pdf>, (accessed 10.10).

International Agency for Research on Cancer, 1985. Tobacco habits other than smoking; betel-quid and areca-nut chewing; and some related nitrosamines, vol. 37. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. IARC, Lyon, France.

International Agency for Research on Cancer, 2007b. IARC Handbooks of Cancer Prevention, Tobacco Control, vol 11: Reversal of Risk after Quitting Smoking. IARC, Lyon, France.

Jakobsson, U., 2008. Tobacco use in relation to chronic pain: results from a Swedish population survey. Pain Med. 9, 1091–1097.

Janzon, E., Hedblad, B., 2009. Swedish snuff and incidence of cardiovascular disease. A population-based cohort study. BMC Cardiovasc. Disord. 9, 21–27.

Johansson, S.-E., Sundquist, K., Qvist, J., Sundquist, J., 2005. Smokeless tobacco and coronary heart disease a 12-year follow-up study. Eur. J. Cardiovasc. Prev. Rehabil. 12, 387–392.

Jungell, P., Malmström, M., 1985. Snuff-induced lesions in Finnish recruits. Scand. J. Dent. Res. 93, 442–447.

Kallischnigg, G., Weitkunat, R., Lee, P.N., 2008. Systematic review of the relation between smokeless tobacco and non-neoplastic oral diseases in Europe and the United States. BMC Oral Health 8, 13.

Katsika, D., Tuvblad, C., Einarsson, C., Lichtenstein, P., Marschall, H.U., 2007. Body mass index, alcohol, tobacco and symptomatic gallstone disease: a Swedish twin study. J. Intern. Med. 262, 581–587.

Koskinen, L.O., Blomstedt, P.C., 2006. Smoking and non-smoking tobacco as risk factors in subarachnoid haemorrhage. Acta Neurol. Scand. 114, 33–37.

Lagergren, J., Bergström, R., Lindgren, A., Nyrén, O., 2000. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. Int. J. Cancer 85, 340–346.

Larsson, Å., Axéll, T., Andersson, G., 1991. Reversibility of snuff dippers' lesion in Swedish moist snuff users: a clinical and histologic follow-up study. J. Oral Pathol. Med. 20, 258–264.

Lee, P.N., 2007. Circulatory disease and smokeless tobacco in Western populations: a review of the evidence. Int. J. Epidemiol. 36, 789–804.

Lee, P.N., Hamling, J.S., 2009a. Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. BMC Med. 7, 36.

Lee, P.N., Hamling, J.S., 2009b. The relation between smokeless tobacco and cancer in Northern Europe and North America. A commentary on differences between the conclusions reached by two recent reviews. BMC Cancer 9, 256.

Levander, S., Eberhard, J., Lindström, E., 2007. Nicotine use and its correlates in patients with psychosis. Acta Psychiatr. Scand. Suppl. 116 (Suppl 435), 27–32.

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

Lindquist, R., Nilsson, B., Eklund, G., Gahrton, G., 1987. Increased risk of developing acute leukemia after employment as a painter. Cancer 60, 1378–1384.

Lindström, M., Isacsson, S.-O., 2002. Smoking cessation among daily smokers, aged 45–69 years: a longitudinal study in Malmö, Sweden. Addiction 97, 205–215.

Lund, K.E., Tefre, E.M., Amundsen, A., Nordlund, S., 2008. Royking, bruk av snus og annen risikoatferd blant studenter (cigarette smoking, use of snuff and other risk behaviour among students). Tidsskr. Nor Laegeforen. 128, 1808–1811.

Lundqvist, G., Sandström, H., Öhman, A., Weinehall, L., 2009. Patterns of tobacco use: a 10-year follow-up study of smoking and snus habits in a middle-aged Swedish population. Scand. J. Public Health 37, 161–167.

Luo, J., Ye, W., Zendehdel, K., Adami, J., Adami, H.-O., Boffetta, P., Nyrén, O., 2007. Oral use of Swedish moist snuff (snus) and risk of cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. Lancet 369, 2015–2020.

Mahid, S.S., Minor, K.S., Soto, R.E., Hornung, C.A., Galandiuk, S., 2006. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin. Proc. 81, 1462–1471.

Mattila, V.M., Sahi, T., Jormanainen, V., Pihlajamäki, H., 2008. Low back pain and its risk indicators: a survey of 7040 Finnish male conscripts. Eur. Spine J. 17, 64–69.

Modéer, T., Lavstedt, S., Åhlund, C., 1980. Relation between tobacco consumption and oral health in Swedish schoolchildren. Acta Odontol. Scand. 38, 223–227.

Montén, U., Wennström, J.L., Ramberg, P., 2006. Periodontal conditions in male adolescents using smokeless tobacco (moist snuff). J. Clin. Periodontol. 33, 863–868.

Nafziger, A.N., Lindvall, K., Norberg, M., Stenlund, H., Wall, S., Jenkins, P.L., Pearson, T.A., Weinehall, L., 2007. Who is maintaining weight in a middle-aged population in Sweden? A longitudinal analysis over 10 years. BMC Public Health 12, 108–117.

Nilsson, M., Weinehall, L., Bergström, E., Stenlund, H., Janlert, U., 2009. Adolescent's perceptions and expectations of parental action on children's smoking and snus use; national cross sectional data from three decades. BMC Public Health 9, 74.

Nilsson, R., 1998. A qualitative and quantitative risk assessment of snuff dipping. Regul. Toxicol. Pharmacol. 28, 1–16.

Nilsson, R., 2006. De minimus non curat lex – virtual thresholds for cancer initiation by tobacco specific nitrosamines – prospects for harm reduction by smokeless tobacco. Int. J. Occup. Environ. Health 19, 6–35.

Norberg, M., Stenlund, H., Lindahl, B., Boman, K., Weinehall, L., 2006. Contribution of Swedish moist snuff to the metabolic syndrome: a wolf in sheep's clothing? Scand. J. Public Health 34, 576–583.

Nordgren, P., Ramström, L., 1990. Moist snuff in Sweden – tradition and evolution. Br. J. Addict. 85, 1107–1112.

Novo, M., Hammarström, A., Janlert, U., 2000. Smoking habits – a question of trend or unemployment? A comparison of young men and women between boom and recession. Public Health 114, 460–463.

Odenbro, Å., Bellocco, R., Boffetta, P., Lindelöf, B., Adami, J., 2005. Tobacco smoking, snuff dipping and the risk of cutaneous squamous cell carcinoma: a nationwide cohort study in Sweden. Br. J. Cancer 92, 1326–1328.

Osterdahl, B.-G., Slorach, S.A., 1984. N-Nitrosamines in oral snuff and chewing tobacco on the Swedish market in 1983. Food Addit. Contam. 1, 299–305.

Osterdahl, B.G., Jansson, C., Paccou, A., 2004. Decreased levels of tobacco-specific N-nitrosamines in moist oral snuff on the Swedish market. J. Agric. Food Chem. 52, 5085–5088.

Persson, J., Sjöberg, I., Johansson, S.-E., 2004. Bruk och missbruk, vanor och ovanor. Hälsorelaterade levnadsvanor 1980–2002 (Health related habits of life 1980–2002). Levnadsförhållanden (Living Conditions), Statistiska Centralbyrån, (105.) <http://www.scb.se/statistik/le/le0101/1980i02/le0101_1980i02_br_le105sa0401.pdf> (accessed 10.10) with additional data supplied by E. Högstorp, Statistiska Centralbyrån, 2005.

Persson, P.-G., Hellers, G., Ahlbom, A., 1993. Use of oral moist snuff in inflammatory bowel disease. Int. J. Epidemiol. 22, 1101–1103.

Persson, P.G., Carlsson, S., Svanström, L., Östenson, C.G., Efendic, S., Grill, V., 2000. Cigarette smoking, oral moist snuff use and glucose intolerance. J. Intern. Med. 248, 103–110.

Pindborg, J.J., Renstrup, G., 1963. Studies in oral leukoplakias. II. Effect of snuff on oral epithelium. Acta Derm. Venereol. 43, 271–276.

Ramström, L.M., 1986. Tobaksvanor i Sverige 1985. Resultat från NTS-Undersökningen 1985. (Tobacco Habits in Sweden 1985. Results from an NTS Study 1985). NTS, Stockholm. (Tema Tobak Nr. 3.).

Ramström, L.M., Foulds, J., 2006. Role of snus in initiation and cessation of tobacco smoking in Sweden. Tob. Control 15, 210–214.

Ramström, L.M., Tibblin, H., 1987. Tobaksvanor i Sverige 1986. Resultat från NTS-undersökningen 1986. (Smoking Habits in Sweden 1986. Results from a National Council on Smoking and Health [NTS] Study 1986). (Tema Tobak No 5.).

Ramström, L.M., Tibblin, H., 1988. Tobaksvanor i Sverige 1987. Resultat från NTS-undersökning 1987. (Tobacco habits in Sweden 1987. Results from study of National Association against Tobacco Damage 1987). NTS, Stockholm. (Tema Tobak Nr. 7.).

Richthoff, J., Elzanaty, S., Rylander, L., Hagmar, L., Giwercman, A., 2008. Association between tobacco exposure and reproductive parameters in adolescent males. Int. J. Androl. 31, 31–39.

Rintakoski, K., Ahlberg, J., Hublin, C., Lobbezoo, F., Rose, R.J., Murtomaa, H., Kaprio, J., 2010. Tobacco use and reported bruxism in young adults: a nationwide Finnish twin cohort study. Nicotine Tob. Res. 12, 679–683.

Rodu, B., Stegmayr, B., Nasic, S., Asplund, K., 2002. Impact of smokeless tobacco use on smoking in northern Sweden. J. Intern. Med. 252, 398–404.

Rodu, B., Stegmayr, B., Nasic, S., Cole, P., Asplund, K., 2003. Evolving patterns of tobacco use in northern Sweden. J. Intern. Med. 253, 660–665.

Roed-Petersen, B., Pindborg, J.J., 1973. A study of Danish snuff-induced oral leukoplakias. J. Oral Pathol. 2, 301–313.

Rogers, J.M., 2008. Tobacco and pregnancy: overview of exposures and effects. Birth Def. Res. C. Embryo Today 84, 1–15.

Rohani, M., Agewall, S., 2004. Oral snuff impairs endothelial function in healthy snuff users. J. Intern. Med. 255, 379–383.

Rolandsson, M., Hellqvist, L., Lindqvist, L., Hugoson, A., 2005. Effects of snuff on the oral health status of adolescent males: a comparative study. Oral Health Prev. Dent. 3, 77–85.

Roosaar, A., Johansson, A.L., Sandborgh-Englund, G., Axéll, T., Nyrén, O., 2008. Cancer and mortality among users and nonusers of snus. Int. J. Cancer 123, 168–173.

Roosaar, A., Johansson, A.L.V., Sandborgh-Englund, G., Nyrén, O., Axéll, T., 2006. A long-term follow-up study on the natural course of snus-induced lesions among Swedish snus users. Int. J. Cancer 119, 392–397.

Rosendahl, K.I., Galanti, M.R., Gilljam, H., Ahlbom, A., 2005. Knowledge about tobacco and subsequent use of cigarettes and smokeless tobacco among Swedish adolescents. J. Adolesc. Health 37, 224–228.

Rosenquist, K., 2005. Risk factors in oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Sweden. Swed. Dent. J. Suppl., 1–66.

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

Salonen, L., Axéll, T., Helldén, L., 1990. Occurrence of oral mucosal lesions, the influence of tobacco habits and an estimate of treatment time in an adult Swedish population. J. Oral Pathol. Med. 19, 170–176.

Schildt, E.-B., Eriksson, M., Hardell, L., Magnuson, A., 1998. Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. Int. J. Cancer 77, 341–346.

Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), 2008. Health effects of smokeless tobacco products. European Commission, Health and Consumer Protection Directorate-General, Brussels. <http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_013.pdf> (accessed 10.10).

Severson, H.H., Forrester, K.K., Biglan, A., 2007. Use of smokeless tobacco is a risk factor for cigarette smoking. Nicotine Tob. Res. 9, 1331–1337.

Sponsiello-Wang, Z., Weitkunat, R., Lee, P.N., 2008. Systematic review of the relation between smokeless tobacco and cancer of the pancreas in Europe and North America. BMC Cancer 8, 356–368.

Stegmayr, B., Eliasson, M., Rodu, B., 2005. The decline of smoking in northern Sweden. Scand. J. Public Health 33, 321–324.

Stegmayr, B., Johansson, I., Huhtasaari, F., Moser, U., Asplund, K., 1993. Use of smokeless tobacco and cigarettes – effects on plasma levels of antioxidant vitamins. Int. J. Vitam. Nutr. Res. 63, 195–200.

Stenbeck, M., Hagquist, C., Rosén, M., 2009. The association of snus and smoking behaviour: a cohort analysis of Swedish males in the 1990s. Addiction 104, 1579–1585.

Stepanov, I., Hecht, S.S., Ramakrishnan, S., Gupta, P.C., 2005. Tobacco-specific nitrosamines in smokeless tobacco products marketed in India. Int. J. Cancer 116, 16–19.

Sundbeck, M., Grahn, M., Lönngren, V., Månsson, N.O., Råstam, L., Lindblad, U., 2009. Snuff use associated with abdominal obesity in former smokers. Scand. J. Public Health 37, 487–493.

Teo, K.K., Ounpuu, S., Hawken, S., Pandey, M.R., Valentin, V., Hunt, D., Diaz, R., Rashed, W., Freeman, R., Jiang, L., Zhang, X., Yusuf, S., 2006. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. Lancet 368, 647–658.

Tillgren, P., Haglund, B.J., Lundberg, M., Romelsjö, A., 1996. The sociodemographic pattern of tobacco cessation in the 1980s: results from a panel study of living condition surveys in Sweden. J. Epidemiol. Community Health 50, 625–630.

Timberlake, D.S., Huh, J., Lakon, C.M., 2009. Use of propensity score matching in evaluating smokeless tobacco as a gateway to smoking. Nicotine Tob. Res. 11, 455–462.

W-Dahl, A., Toksvig-Larsen, S., 2007. No delayed bone healing in Swedish male oral snuffers operated on by the hemicallotasis technique. A cohort study of 175 patients. Acta Orthopaedica 28, 791–794.

Wadman, C., 2009. Levnadsvanor – Tobaksvanor. Statens Folkhälsoinstitut, <http://www.fhi.se/sv/Statistik-uppfoljning/Nationella-folkhalsoenkaten/Levnadsvanor/Tobaksvanor/> (accessed 10.10).

Wallenfeldt, K., Hulthe, J., Bokemark, L., Wikstrand, J., Fagerberg, B., 2001. Carotid and femoral atherosclerosis, cardiovascular risk factors and C-reactive protein in relation to smokeless tobacco use or smoking in 58-year-old men. J. Intern. Med. 250, 492–501.

Wändell, P.E., Bolinder, G., de Faire, U., Hellénius, M.-L., 2008. Association between metabolic effects and tobacco use in 60-year-old Swedish men. Eur. J. Epidemiol. 23, 431–434.

Waterhouse, J., Muir, C., Correa, P., Powell, J. (Eds.), 1976. Cancer incidence in five continents, vol. III. International Agency for Research on Cancer, Lyon, France.

Weitkunat, R., Sanders, E., Lee, P.N., 2007. Meta-analysis of the relation between European and American smokeless tobacco and oral cancer. BMC Public Health 7, 334.

Wennberg, P., Eliasson, M., Hallmans, G., Johansson, L., Boman, K., Jansson, J.-H., 2007. The risk of myocardial infarction and sudden cardiac death amongst snuff users with or without a previous history of smoking. J. Intern. Med. 262, 360–367.

Wennmalm, A., Benthin, G., Granström, E.F., Persson, L., Petersson, A.-S., Winell, S., 1991. Relation between tobacco use and urinary excretion of thromboxane A_2 and prostacyclin metabolites in young men. Circulation 83, 1698–1704.

Wickholm, S., Söder, P.-Ö., Galanti, M.R., Söder, B., Klinge, B., 2004. Periodontal disease in a group of Swedish adult snuff and cigarette users. Acta Odontol. Scand. 62, 333–338.

Wiium, N., Aarø, L.E., Hetland, J., 2009. Subjective attractiveness and perceived trendiness in smoking and snus use: a study among young Norwegians. Health Educ. Res. 24, 162–172.

Wikström, A.-K., Cnattingius, S., Galanti, M.R., Kieler, H., Stephansson, O., 2010a. Effect of Swedish snuff (*snus*) on preterm birth. BJOG 117, 1005–1010.

Wikström, A.K., Stephansson, O., Cnattingius, S., 2010b. Tobacco use during pregnancy and preeclampsia risk: effects of cigarette smoking and snuff. Hypertension 55, 1254–1259.

Wolk, K., Mallbris, L., Larsson, P., Rosenblad, A., Vingård, E., Ståhle, M., 2009. Excessive body weight and smoking associates with a high risk of onset of plaque psoriasis. Acta Derm. Venereol. 89, 492–497.

Ye, W., Ekström, A.M., Hansson, L.-E., Bergström, R., Nyrén, O., 1999. Tobacco, alcohol and the risk of gastric cancer by sub-site and histologic type. Int. J. Cancer 83, 223–229.

Zendehdel, K., Nyrén, O., Luo, J., Dickman, P.W., Boffetta, P., Englund, A., Ye, W., 2008. Risk of gastroesophageal cancer among smokers and users of Scandinavian moist snuff. Int. J. Cancer 122, 1095–1099.