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Peter N. Lee

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Health risks related to dual use of cigarettes and snus – a systematic review

Peter N Lee[a]

[a]*Address for correspondence*

P.N. Lee Statistics and Computing Ltd., 17 Cedar Road, Sutton, Surrey, SM2 5DA, UK

E-mail : PeterLee@pnlee.co.uk

Tel : +44 (0) 2086428265

Fax : +44 (0) 2086422135

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ABSTRACT

Reviews show that using snus (Swedish-type moist snuff) is much safer than smoking, with no increased risk from snus of cancer or circulatory disease yet demonstrated, but have not investigated possible health effects from dual use of cigarettes and snus. This review considers studies where health risks can be compared in dual users, those who only use snus or only smoke, and those who use neither product. The interaction RR, the ratio of RRs associated with snus use in smokers and in non-smokers, was used to test for special effects of dual use. Of 51 interaction RRs presented, only one (for gestational hypertension in a study based on the Swedish Medical Register) was significantly ($p<0.05$) above 1.0, and RRs below 1.0 were commoner, perhaps as cigarette consumption is lower in dual users than those who only smoke. Dual users more often initiate tobacco use with cigarettes than snus. Dual use is much commoner in adolescents than adults, possibly because many tobacco users try both products, eventually settling on one. Epidemiological evidence from various sources, though suffering from weaknesses, consistently suggests concomitant snus use increases smoking quit rates, and aligns with evidence from RCTs using snus to aid smoking cessation.

Abbreviations[1]

Keywords Cancer; Circulatory disease; Tobacco, Smokeless.

[1] AMI Acute myocardial infarction
CHD Coronary heart disease
CI Confidence interval
CVD Cardiovascular disease
IHD Ischaemic heart disease
OR Odds ratio
RR Relative risk

1. Introduction

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. The tobacco is often heat-treated (pasteurized). In the past, a pinch (or dip) was placed between the gum and upper lip, often for 11 to 14 hours daily (International Agency for Research on Cancer, 2007), but more recently the commonest application method is by portion-packed tobacco in a small sachet (similar to a tea-bag). Although the sale of snus is banned in other EU countries, Sweden has a special derogation due to its long history of use.

In the last decade, there has been increasing interest in snus as a possible safer alternative to smoking. Various reviews (e.g. Boffetta et al., 2008; Broadstock, 2007; Kallischnigg et al., 2008; Lee, 2007; Lee and Hamling, 2009; Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), 2008; Weitkunat et al., 2007) have considered possible health effects, with oral and pancreatic cancer, oral disease, and cardiovascular disease (CVD) receiving particular attention.

A recent summary, with meta-analyses, of the epidemiological evidence relating snus to health (Lee, 2011) found no statistically significant association with cancer of any site or with heart disease or stroke, and concluded that any possible risk from snus, if it exists, is much less than that from smoking. It also noted that "snuff dipper's lesion" (Axéll et al., 1976) does not predict oral cancer. Though that summary considered a wide range of possible health effects, and also found no reliable evidence that snus increases initiation of smoking or discourages quitting, it did not evaluate health effects associated specifically with dual use of cigarettes and snus.

In this systematic review, evidence directly relating dual use to various health endpoints is of primary interest. However, other aspects of dual use are also investigated, including comparison of cigarette and snus consumption in single and dual users, and a summary of data on the frequency of dual use and on various aspects of the interrelationship of snus use and smoking, such as which tobacco product dual users tend to start with. Associated with this, transitions to dual use and from dual use are considered, to gain insight into whether snus use affects initiation or cessation of smoking.

2. Materials and methods

2.1 Health effects

The searches concerned cancer, circulatory disease, respiratory and digestive disease, all-cause mortality, pregnancy and reproductive effects, psychiatric and neurodegenerative disorders, musculoskeletal disorders and other conditions, and general health, all these health effects being considered in the review of snus and health (Lee, 2011). The publications on these health effects cited in that review were considered, as well as additional publications obtained by updating the literature search to February 2013, using the same search criteria used in 2011. All these publications were then examined to assess whether they presented results allowing comparison of risk in those who smoked and used snus ("dual users"), those who smoked but did not use snus ("smoking only"), those who used snus but did not smoke ("snus only"), and those who neither smoked nor used snus ("neither"). Smoking and snus use could be based on current or on lifetime habits.

Comparisons were made separately for ever and never smokers, of health risks for ever and never snus use, and separately for current and non-current smokers of health risks for current and non-current snus use. For each comparison, standard

methods (Gardner and Altman, 1989) were used to estimate the relative risk (RR) or odds ratio (OR) and 95% confidence interval (CI) for snus only vs. neither, for dual use vs. smoking only, and for their interaction, i.e. the ratio of these two RR/OR estimates. The interaction tests whether the proportional increase in risk associated with snus is greater in smokers than in non-smokers (or equivalently whether the proportional increase in risk associated with smokers is greater in snus users than that associated with smoking in non-users of snus), i.e. whether there is any special hazard associated with dual use.

Where, as is usually the situation, a study provides a set of covariate-adjusted RR/ORs (with 95% CIs) for a complex two-way table of smoking by snus use (e.g. never/current/former smoking × never/current/former snus), the required RR/OR estimates were derived from the set using standard methods (Hamling et al., 2008). Only where covariate-adjusted RRs were not provided, were unadjusted estimates calculated directly from the given numbers of cases and controls. In some cases the required RRs/ORs were derived from estimates for ever snus use given separately for never smokers and for the whole population.

Where appropriate, meta-analyses of estimates were derived using standard methods (Fleiss and Gross, 1991).

2.2. Other aspects of dual use

The aim was to gain insight into seven questions: 1) How does the cigarette consumption of dual users compare to that of smokers of cigarettes only? 2) How does the snus consumption of dual users compare to that of users of snus only? 3) What is the frequency of dual use? 4) Are current snus users more likely to smoke than are current non-users of snus? 5) Are those who have ever used snus more likely ever to have smoked than are never users of snus? 6) Are snus users more likely to

initiate smoking than non-users? and 7) Are smokers who also use snus more likely to quit smoking than smokers who do not use snus? Again, publications cited in the earlier review (Lee, 2011) were considered, as well as additional publications from updated literature searches. References cited in the recently updated Scandinavian chapters of International Smoking Statistics (Forey et al., 2006-2013) were also examined.

For cross-sectional studies relating snus to smoking, ORs (with 95% CIs) relevant to questions 4 and 5 were derived from the numbers of subjects who were dual users, smoking only, snus only, or neither. RRs (with 95% CIs) relevant to question 6 were derived from cohort studies, using the numbers of non-smokers at baseline and the numbers subsequently initiating, separated by snus use at baseline. For cohort studies relating snus use at baseline to subsequent quitting, RRs (with 95% CIs) relevant to question 7 were also derived from cohort studies, here using the numbers of smokers at baseline and the numbers subsequently quitting. As many of the results relating to questions 3 to 7 were presented earlier (Lee, 2011), only selected results are presented for more recent, larger and more nationally representative surveys.

3. Results

3.1. Health effects

The literature search identified 21 relevant publications for which Table 1 presents study details. Four publications relate to the Swedish Construction Workers study, three (Carlens et al., 2010; Nordenvall et al., 2011; Zendehdel et al., 2008) concerning occurrence of various conditions seen during the more than 20 years follow-up, the other (Nordenvall et al., 2013) concerning survival among those with incident cancer seen after baseline. Another four publications (Gunnerbeck et al.,

2011; Wikström et al., 2010a; Wikström et al., 2010b; Wikström et al., 2010c) are based on the Swedish Medical Birth Register. The remaining thirteen publications describe separate studies, four prospective cohort studies, eight case-control studies (one nested within a prospective study), and one cross-sectional study. All the studies were conducted in Sweden, and apart from publications based on the Swedish Medical Birth Register, the snus users considered were either all or virtually all men.

Table 2 summarizes results for cardiovascular disease, with the main results presented in the body of the table and results for subgroups (e.g. for fatal and non-fatal cases separately) given in the footnotes. Most of the results relate to current tobacco use. None of the RR/ORs presented show a significant ($p<0.05$) increased risk associated with snus use, either in non-smokers or smokers, or a significant interaction associated with dual use. Based on seven results for current use for ischaemic heart disease (IHD), coronary heart disease (CHD) or acute myocardial infarction (AMI), meta-analysis gives non-significant estimates of 0.95 (0.83-1.09) for snus only vs. neither, 0.82 (0.67-1.01) for dual use vs. smoking only, and 0.85 (0.68-1.05) for the interaction, with no evidence of between-study heterogeneity. Results for ever use for IHD, CHD or AMI, and results for stroke and for all CVD are less numerous, but similarly do not suggest any effect of dual use.

Table 3 summarizes results for cancer. Here, most of the results relate to ever tobacco use. Of the fifteen interaction estimates shown, four are non-significantly above 1.0, two equal to 1.0, and nine less than 1.0, significantly ($p<0.05$) so in five cases. The significant negative interactions for squamous cell oesophageal cancer and for non-cardia stomach cancer seen in the Construction Workers Study (Zendehdel et al., 2008) arise from significant increases associated with snus being seen in never smokers but not in ever smokers. As noted elsewhere (Lee, 2011), the overall

evidence on effects of snus suggests no relationship with stomach cancer and at most suggestive evidence of a possible effect on oesophageal cancer. The negative interactions for smoking-related cancer and for mortality from any cancer (Roosaar et al., 2008) and on time from diagnosis to death from cancer of the same primary site (Nordenvall et al., 2013) again arise from increases associated with snus seen in never smokers that are not seen in smokers. Table 3 also includes results for respiratory mortality, for total non-cancer mortality, and for overall cancer, which also show no evidence of a positive interaction.

Table 4 summarizes results for nine conditions related to pregnancy and birth from a series of papers (Gunnerbeck et al., 2011; Wikström et al., 2010a; Wikström et al., 2010b; Wikström et al., 2010c) based on the Swedish Medical Register. For three conditions (pre-eclampsia, diabetes, antenatal bleeding) there is no evidence of an effect of snus use, in either exsmokers or smokers, or of an interaction. For five conditions (very preterm birth, preterm birth, stillbirths, small for gestational age, neonatal apnea), there is a significant ($p<0.05$) association with snus use in non-smokers, but not in smokers, and the interaction is non-significantly negative. The only condition showing a significant positive interaction is gestational hypertension, where an association with snus use is evident in smokers, but not in non-smokers.

Table 5 summarizes results for chronic inflammatory diseases. There is no consistent evidence of an effect of snus on any of the five diseases considered in either never or ever smokers, and no significant positive interaction. A significant ($p<0.05$) negative interaction for multiple sclerosis seen in one study (Carlens et al., 2010), due to an increased risk in never smokers but not in ever smokers, was not seen in the other study with relevant data (Hedström et al., 2009).

One further study (Aro et al., 2010) presented detailed results for gastrointestinal morbidity, allowing calculation of interactions, both for ever/never use and for current/noncurrent use, for a range of endpoints, including reflux symptoms, dyspepsia, irritable bowel syndrome, epigastric pain, abdominal pain, oesophagitis, and *H Pylori* infection. Of eighteen interactions calculated (details not shown), eight were greater than 1.0 and 10 less, with only one significant at $p<0.05$. This was for irritable bowel syndrome, where an association with current snus use was evident in current smokers (OR 2.90, 95% CI 1.10-7.62) but not in non-smokers (0.75, 0.43-1.30) with the interaction OR estimated as 3.89 (1.28-11.86). This interaction was not seen (0.76, 0.35-1.66) in analyses based on ever/never use.

3.2. Consumption of cigarettes and snus in single and dual users

Table 6 presents 12 comparisons from 10 studies of cigarette consumption in dual users and in those who smoke but do not use snus. All show reduced cigarette consumption in dual users, the mean ratio being 0.74 (SE 0.15). Table 6 also presents six comparisons of snus use in dual users and in those who use snus but do not smoke. With the exception of one small study of military conscripts, all show reduced snus use in dual users, the mean ratio being 0.80 (SE 0.15).

Two of those studies also compared cotinine levels, as a marker of total nicotine uptake, in dual users and single users. In one study (Eliasson et al., 1995), mean plasma cotinine levels in dual users, 308 ng/ml, were higher than in those who only smoked, 242 ng/ml, but lower than in those who only used snus, 351 ng/ml ($p<0.01$ for difference between groups). In the other (Wennmalm et al., 1991) a different pattern was seen, with median urinary cotinine higher in dual users, 1773

ng/ml, than in either those who only smoked, 1560 ng/ml, or those who only used snus, 1210 ng/ml (no significant difference between groups).

3.3. Frequency of dual use and the interrelationship of snus use and smoking

Table 7 presents data from selected recent surveys on current smoking and current snus use. Based on these data, and from more extensive data in Table 5 of the earlier review (Lee, 2011), it can be seen that in Swedish adults, the prevalence of dual use is quite low, with rates reducing with age, and lower in women than men. It is also evident that there is no strong association between snus use and smoking. In Norwegian adults, the prevalence of dual use is lower still, and smokers are less likely to use snus than are non-smokers. In Swedish adolescents, however, the prevalence of dual use may be higher, though dependent on the definitions used, and there is a consistent tendency for smokers to be much more likely than non-smokers to use snus. Odds ratios ranging from about 4 to 15 can be estimated from many other Swedish studies of adolescents (Lee, 2011).

For ever smoking and ever snus use, the situation is rather different. Table 8 presents data from the VIP survey (Norberg et al., 2011), and, based on this and additional data given in Table 6 of the earlier review (Lee, 2011), it can be seen that the frequency of dual ever use is much higher than the frequency of dual current use. Also, those who have ever smoked are much more likely than those who have never smoked to have ever used snus, a tendency which is even more strongly seen in adolescents.

The observations of a much higher prevalence of dual use and a much stronger association between the habits, when estimated based on ever use rather than current

use, is consistent with some people avoiding tobacco, and many of the rest trying both products, eventually settling for one.

3.4. Does snus use affect initiation of smoking?

Though evidence is somewhat limited, dual users are clearly more likely to have started on cigarettes than have started on snus. For example, in the Swedish twin study of men born before 1959 (Furberg et al., 2005), 2422 (89.3%) started on cigarettes as against 291 (10.7%) starting on snus, while in the Your Country and Your Life study in Stockholm (Ramström and Foulds, 2006) 338 (77.2%) started on cigarettes as against 100 (22.8%) starting on snus. The percentage starting on snus is likely to increase as the acceptability of snus among adolescents has increased. This may explain why, in a recent analysis of six surveys in Norway (Lund and McNeill, 2013) the proportion of men with a history of dual use who started on snus increased steadily with decreasing age, from 3.9% for age 45+ years, through 25.9% for age 25-44 years, to 42.3% for age 15-24 years. (Note that all the above estimates exclude the small proportion of dual users where the time of start of both products was the same.)

A number of cohort studies have presented data in which never smokers or non-smokers have been followed up, and the probability of smoking at the end of follow-up can be related to snus use at baseline. The largest study to present such data is the VIP study, which has recently reported results of 10-year follow-up from baseline during 1990-97 (Norberg et al., 2011). In both sexes, the probability of initiation during follow-up was significantly ($p < 0.05$) higher for those using snus at baseline users than for those not using snus (males 6.1% vs. 2.6%, RR 2.35 95%, CI 1.89-2.92; females 8.1% vs. 3.2%, RR 2.53, CI 1.76-3.63). An increased probability is also consistently seen in other studies (Lee, 2011). Interpretation of this association

is hindered by the minimal adjustment for factors predictive of initiation, one study (Haukkala et al., 2006) reporting that adjustment for school, sport participation, and school achievement substantially reduced the association.

Two studies of Swedish adults (Furberg et al., 2005; Ramström and Foulds, 2006) used retrospective data to study effects on initiation, both reporting that the percentage initiating smoking among those who started on snus was substantially lower than among those who had not started on snus. However, as demonstrated earlier (Lee, 2011), these analyses may be considerably 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, but those not starting on snus can initiate smoking from the start of the period.

There is thus little reliable information on snus use and initiation. The RRs in the analyses of the cohort data are biased upward by lack of confounder control, while the retrospective analyses are biased downwards.

3.5. Does snus use affect cessation of smoking?

A number of cohort studies have presented data in which smokers have been followed up, and the probability of quitting at the end of follow-up can be related to snus use at baseline. As for initiation, the VIP study presents the most comprehensive data. Recent results (Norberg et al., 2011) show that, in both sexes, the probability of quitting is higher for dual users at baseline than for those who only smoked (males 57.3% vs. 41.5%, RR 1.38, 95% CI 1.27-1.50; females 68.2% vs. 41.5%, RR 1.64, 95% CI 1.44-1.88). This increased probability is consistent with data presented in Table 8 of the earlier review (Lee, 2011), though the data generally suffer from lack of adjustment for any potential confounding variables. However, results from a

telephone helpline cohort (Helgason et al., 2004) showed that adjustment for age, sex and factors related to smoking abstention did not modify the association between snus use and quitting.

Consistent with the results of the cohort studies are findings from an analysis of seven Norwegian cross-sectional studies (Lund et al., 2011) which reported a consistent tendency for the quit ratio (the proportion of ever smokers who have quit) to be higher in those who were snus users at the time of interview, as compared to those who had never used snus. However, apart from being unadjusted for sex, age, or any factor possibly related to quitting, the analysis does not fully take into account the time sequence of tobacco product use. Thus, some of the current snus users who quit smoking may actually have not used snus until after they had quit.

A number of publications (Furberg et al., 2005; Furberg et al., 2008; Gilljam and Galanti, 2003; Ramström and Foulds, 2006) have presented analyses of retrospective studies which consistently show snus use is associated with increased quitting. However, as discussed earlier (Lee, 2011), these analyses are biased. This is partly because snus users may include some people who started snus use after quitting, and partly because the time available for quitting has not properly been controlled for. These biases, however, seem unlikely to explain the association, and generally all the evidence seems consistent with snus use facilitating quitting, though subject to limitations.

Randomized controlled trials avoid issues of bias. Two placebo-controlled trials of snus as a quitting aid have been conducted, one in the USA (Fagerström et al., 2011) and one in Serbia (Joksi et al., 2011). A meta-analysis based on the combined results (Rutqvist et al., 2013) recently reported a relative success rate of 2.83 (95% CI 1.63-7.75) of borderline significance for the primary outcome, which was biologically

confirmed cessation over a 6-month period. These results confirm the conclusions drawn from the epidemiological studies.

4. Discussion

The possibility of any special risk associated with dual use of snus and smoking has been investigated by testing whether the RR/OR associated with snus use in smokers exceeds that seen in non-smokers, i.e. whether there is any significant interaction (on a multiplicative scale). As can be seen from Tables 2 to 5, the available data on specific diseases are generally quite limited, except perhaps for IHD/CHD/AMI. Overall, however, there seems little evidence of any special risk from dual use, consistent with the findings of a review (Frost-Pineda et al., 2010) on dual use of smokeless tobacco and smoking, which also considered evidence from US studies . Of the 51 RR/OR estimates with 95% CIs shown in the main body of these tables, a significant ($p<0.05$) positive interaction was seen only for gestational hypertension (see Table 5), and that may be a chance finding given the number of estimates considered. In fact, there is some tendency for the interaction estimates to show a less than expected risk in dual users, with 32 of the 51 estimates below 1.0, 7 being significantly negative, as against only 15 above 1.0, with only that for gestational hypertension being significantly positive. This may be because where variation in risk by tobacco habit is seen, it is much more likely to be due to effects of smoking than to effects of snus, and cigarette consumption in dual users is clearly lower than in those who only smoke cigarettes, by an estimated 26% (SE 15%). It should be noted that the RRs in the tables comparing dual users vs. smoking only are generally unadjusted for amount smoked.

Dual use can be defined based on current use or on ever use, and the tables make it clear which definition relates to which RR estimate. RRs are more commonly

available for current use for CVD, and for ever use for cancer, but there is no real indication of any special hazard associated with dual use using either definition. It should be noted, however, that the available data provide no information on the duration of dual use. Long-term dual use may produce different risks than short-term dual use.

Also relevant is the fact that levels of tobacco-nitrosamines and other toxicants in snus in Sweden have declined markedly over time in relation to the implementation of the GothiaTek® standard for production and storage (Rutqvist et al., 2011). The fact that many of our results relate to who would have used snus in earlier years adds reassurance that special hazards of dual use from current products are unlikely.

In Sweden, the frequency of dual current use in adults is relatively low, particularly in older populations, but the frequency of dual ever use in adults, and the frequency of dual current use or dual ever use in adolescents is much higher. This is consistent with many tobacco users trying both products in adolescence, and tending later in life to settle for one or the other, given that they have not quit both. For diseases such as cancer or vascular disease, occurring mainly in older men and women, any special hazard from dual use (if indeed it existed) would have little overall effect on risk.

In older populations, dual users predominantly started tobacco use with cigarettes, and where dual users end up using snus only, it seems clear that they will be better off, health-wise, than if they had continued smoking. In younger populations, a larger proportion of dual users are starting on snus, and there is concern that this might act as a "gateway" to cigarette smoking. It is unfortunate that there is little reliable information on this. Retrospective studies suggest that initiation of smoking is reduced by previous snus use (Furberg et al., 2005; Furberg et al., 2008;

Gilljam and Galanti, 2003; Ramström and Foulds, 2006) but the analyses may be markedly biased by failure to control for the time available for initiation (Lee, 2011). Also, cohort studies (e.g. Norberg et al., 2011) which demonstrate a moderate tendency for previous snus use to be associated with increased initiation of smoking are also biased, by failure to control adequately for factors associated with initiation. This can be illustrated by a simple example in which a proportion of the population would never take up tobacco, the probabilities of uptake of smoking and of snus in the remainder being assumed to be independent. In this situation, it is easy to show that, in the whole population, if there is no control at all for factors associated with initiation, there will be an apparent tendency for previous snus use to be associated with initiation of smoking, despite this assumed independence.

The evidence relating dual use to the subsequent probability of quitting smoking is stronger, but still suffers from limitations due to failure to control for relevant confounding variables, though any biases seem less severe than for the evidence on quitting (Lee, 2011). Generally, the evidence consistently suggests that concomitant snus use is associated with an increased probability of quitting, a conclusion that is supported by recent results from randomized controlled trials (Rutqvist et al., 2013) using snus as an aid to smoking cessation.

5. Conclusions

Evidence for a wide variety of health endpoints does not suggest any special hazard associated with dual use of snus and smoking. Of 51 interactions tested, only that for gestational hypertension was significantly ($p<0.05$) positive, with the increase in risk associated with snus use generally somewhat lower in smokers than in non-smokers. In adults, the frequency of current dual use is quite low, with dual users more likely to quit smoking than are smokers who do not use snus.

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Conflict of Interest statement

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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Table 1

Study details for publications providing relevant evidence on health effects

Reference	Source Table	Study Design (size)[a]	Timing[b]	Sex[c]	Age (years)	Data on ST use[d]	Endpoint[e]
Huhtasaari et al., 1992	I	CCP (585)	1989-1991	M	35-64	C	AMI
Persson et al., 1993	1,2	CCP (63,82)[f]	1984-1997	M	15-79	E	CD, UC
Schildt et al., 1998	III	CCP (410)	1980-1989	M,F	Mean 69.6 (M) Mean 72.3 (F)	C,E	Oral cancer
Huhtasaari et al., 1999	1	CCP (687)	1991-1993	M	25-64	C	AMI
Ye et al., 1999	VII	CCP (375)	1989-1995	M,F	40-79	E	Gastric cancer
Hergens et al., 2005	3	CCP (1432)	1992-1994	M	45-70	C,E	AMI
Johansson et al., 2005	3	PC (3120)	1988-1989, 12 years	M	30-74	C	CHD
Haglund et al., 2007	III,IV	PC (5002)	1988-1989, 14-16 years	M	16-74	C	IHD, stroke
Wennberg et al., 2007	2,3	NCC (525)	1985-1999	M	30-74	C	AMI
Roosaar et al., 2008	II	PC (9976)	1973-1974, 28-29 years	M	15+	E	All cancer, oral cancer, all deaths, respiratory deaths
Zendehdel et al., 2008	III,IV	PC (336381)	1971-1993, Mean 22.2 years	M	Mean 34.7	E	Gastroesophageal cancer
Hansson et al., 2009	2	PC (16642)	1998-2002, 4.9 years	M	40+	C,E	CVD, IHD, stroke
Hedström et al., 2009	4	CCP (902)	2005-2008	M,F	16-70	E	MS
Aro et al., 2010	2-6	CS (1001)[g]	1998-2001	M,F	18-80	C,E	Gastrointestinal morbidity
Carlens et al., 2010	4	PC (277777)	1978-1993, Mean 20 years	M	Mean 36	E	RA, UC, CD, sarcoidosis, MS
Wikström et al., 2010c	1	CS (605203)[h]	1999-2006	F	Childbearing age	C	GH, pre-eclampsia
Wikström et al., 2010b	1	CS (610879)[h]	1999-2006	F	Childbearing age	C	Stillbirths, complications of pregnancy
Wikström et al., 2010a	2	CS (610199)[h]	1999-2006	F	Childbearing age	C	Preterm birth
Gunnerbeck et al., 2011	1	CS (609551)[h]	1999-2006	F	Childbearing age	C	Preterm birth, SGA, neonatal apnea
Nordenvall et al., 2011	2	PC (336381)	1971-1992, Mean 24 years	M	Mean 35	E	Colon cancer, rectal cancer, anal cancer

Nordenvall et al., 2013	2	PC (40230)[i]	1971-1992, To 2007[i]	M	Mean 67 at cancer diagnosis	E	Cancer, other causes

[a] CCP = case-control study with population controls, CS = cross-sectional study, NCC = nested case-control study, PC = prospective cohort study. Numbers in brackets are of cases for case-control study, of at risk for prospective cohort studies, and of subjects for the cross-sectional study

[b] The timing of the initial interviews is given, and then the length of follow-up for prospective cohort studies

[c] F = female, M = male

[d] C = data available for current use, E = data available for ever use

[e] AMI = acute myocardial infarction, CD = Crohn's disease, CHD = coronary heart disease, CVD = cardiovascular disease, GH = gestational hypertension, IHD = ischaemic heart disease, MS = multiple sclerosis, RA = rheumatoid arthritis, SGA = small for gestational age, UC = ulcerative colitis

[f] 63 cases of Crohn's disease, 82 of ulcerative colitis

[g] The 1001 subjects underwent an oesophagogastroduodenoscopy

[h] Births

[i] The study concerned survival of 40230 men with incident cancer among 336381 workers interviewed initially in 1971-1992

Table 2

Dual use and cardiovascular disease[a]

Disease	Source	Current or ever use	Cases in dual users	RR/OR (95% CI) Snus only vs. neither	Dual users vs. smoking only	Interaction[b]
IHD, CHD or AMI						
IHD incidence	Hansson et al., 2009	Ever	101	0.92 (0.61-1.39)	0.95 (0.74-1.22)	1.03 (0.64-1.67)
AMI cases[c]	Hergens et al., 2005	Ever	203	0.87 (0.48-1.55)	0.99 (0.80-1.22)	1.14 (0.62-2.13)[d]
IHD incidence	Haglund et al., 2007	Current	15	0.77 (0.51-1.15)	0.94 (0.56-1.59)	1.22 (0.63-2.37)[e]
IHD incidence	Hansson et al., 2009	Current	9	0.90 (0.67-1.21)	0.75 (0.36-1.55)	0.83 (0.38-1.82)
AMI cases[c]	Hergens et al., 2005	Current	66	1.21 (0.89-1.63)	0.80 (0.55-1.16)	0.66 (0.41-1.07)[f]
AMI cases[c]	Huhtasaari et al., 1992	Current	32	0.79 (0.54-1.13)	0.68 (0.40-1.17)	0.87 (0.45-1.67)[g]
AMI cases[c]	Huhtasaari et al., 1999	Current	20	0.96 (0.65-1.41)	0.73 (0.34-1.57)	0.76 (0.32-1.80)
CHD incidence	Johansson et al., 2005	Current	10[h]	0.99 (0.63-1.56)	1.19 (0.60-2.37)	1.20 (0.52-2.73)
AMI cases[c]	Wennberg et al., 2007	Current	30	1.00 (0.71-1.43)	0.82 (0.48-1.40)	0.82 (0.43-1.55)[i]
Total[j]	7 studies	Current	182	0.95 (0.83-1.09)	0.82 (0.67-1.01)	0.85 (0.68-1.05)
Stroke						
Stroke incidence	Hansson et al., 2009	Ever	43	1.24 (0.78-1.97)	0.83 (0.59-1.16)	0.67 (0.38-1.19)
Stroke cases[c]	Haglund et al., 2007	Current	9	1.07 (0.65-1.77)	1.41 (0.71-2.83)	1.32 (0.56-3.11)[k]
Stroke incidence	Hansson et al., 2009	Current	5	0.89 (0.61-1.31)	0.90 (0.36-2.27)	1.01 (0.37-2.73)
All CVD						
CVD incidence	Hansson et al., 2009	Ever	138	1.07 (0.79-1.45)	0.91 (0.75-1.11)	0.85 (0.59-1.22)
CVD incidence	Hansson et al., 2009	Current	14	0.93 (0.74-1.17)	0.81 (0.46-1.43)	0.87 (0.47-1.60)

[a] All RR/OR estimates are for males. All estimates are adjusted for age and other risk factors except for two studies (Huhtasaari et al., 1992; Huhtasaari et al., 1999), where the estimates are unadjusted
[b] Ratio of RR/OR for dual users vs. smoking only to RR/OR for snus only vs. neither
[c] Fatal and non-fatal cases
[d] Interaction 1.24 (0.62-2.46) for non-fatal AMI and 0.50 (0.16-1.58) for fatal AMI
[e] Interaction 0.74 (0.19-2.97) for IHD mortality
[f] Interaction 0.60 (0.36-0.99) for non-fatal AMI and 0.89 (0.36-2.18) for fatal AMI
[g] Interaction 0.82 (0.34-1.98) for age 35-54 and 0.70 (0.23-2.10) for age 55-64
[h] Estimated
[i] Interaction 0.25 (0.06-1.03) for fatal AMI in 28 days and 0.16 (0.03-0.89) for sudden cardiac death with survival less than 24 hours
[j] Results of fixed-effects meta-analysis are shown, there being no significant heterogeneity between studies
[k] Interaction 4.17 (0.78-22.36) for stroke mortality

Table 3

Dual use and cancer, respiratory and all cause mortality[a]

Disease	Source	Cases in dual users	RR/OR (95% CI) Snus only vs. neither	Dual users vs. smoking only	Interaction[b]
Oral cancer – squamous cell	Schildt et al., 1998	10	0.86 (0.51-1.44)	0.40 (0.17-0.93)	0.47 (0.17-1.26)
Oral cancer – squamous cell	Schildt et al., 1998	39	1.20 (0.67-2.15)	0.73 (0.45-1.19)	0.61 (0.29-1.30)
Oropharyngeal cancer	Roosaar et al., 2008	6	2.30 (0.70-8.30)	3.66 (1.45-9.24)	1.59 (0.34-7.46)
Oesophageal cancer – adenocarcinoma	Zendehdel et al., 2008	26	0.20 (0.02-1.90)	1.00 (0.60-1.50)	5.00 (0.50-49.74)
Oesophageal cancer – squamous cell	Zendehdel et al., 2008	40	3.50 (1.60-7.60)	0.80 (0.60-1.20)	0.23 (0.10-0.54)
Gastric cancer	Ye et al., 1999	72	0.50 (0.20-1.22)	0.80 (0.57-1.13)	1.60 (0.61-4.18)
Stomach cancer – cardia	Zendehdel et al., 2008	50	0.90 (0.40-2.20)	0.90 (0.70-1.30)	1.00 (0.42-1.37)
Stomach cancer – non cardia	Zendehdel et al., 2008	185	1.40 (1.10-1.90)	1.00 (0.90-1.20)	0.71 (0.52-0.97)
Colon cancer[c]	Nordenvall et al., 2011	440	1.08 (0.91-1.29)	1.08 (0.97-1.21)	1.00 (0.82-1.24)
Rectal cancer	Nordenvall et al., 2011	319	1.05 (0.85-1.31)	1.04 (0.92-1.19)	0.99 (0.77-1.28)
Anal cancer	Nordenvall et al., 2011	14	0.61 (0.07-5.07)	1.44 (0.74-2.81)	2.37 (0.25-22.28)
Smoking-related cancer – incidence[d]	Roosaar et al., 2008	32	1.60 (1.10-2.50)	0.79 (0.54-1.16)	0.50 (0.28-0.87)
Any cancer – incidence	Roosaar et al., 2008	99	1.10 (0.90-1.40)	0.94 (0.78-1.12)	0.85 (0.64-1.13)
Any cancer – mortality	Roosaar et al., 2008	NA[e]	1.28 (0.96-1.69)	0.80 (0.62-1.04)	0.63 (0.43-0.92)
Any cancer – survival[f]	Nordenvall et al., 2013	2122	1.15 (1.05-1.26)	0.94 (0.89-0.99)	0.82 (0.74-0.91)
Respiratory mortality - age <80	Roosaar et al., 2008	NA[e]	0.80 (0.20-3.00)	0.80 (0.36-1.79)	1.00 (0.21-4.84)
Respiratory mortality - age 80+	Roosaar et al., 2008	NA[e]	2.00 (1.20-3.40)	1.53 (0.86-2.92)	0.77 (0.33-1.75)
Non-cancer mortality[g]	Nordenvall et al., 2013	1579	1.12 (1.01-1.25)	1.02 (0.97-1.08)	0.91 (0.81-1.03)
Any cause – survival[h]	Nordenvall et al., 2013	3859	1.13 (1.05-1.20)	0.97 (0.93-1.00)	0.86 (0.79-0.92)

Total mortality	Roosaar et al., 2008	NA [e]	1.23 (1.09-1.40)	0.97 (0.85-1.11)	0.79 (0.66-0.95)

[a] All RR/OR estimates are for males, and are for ever use, except for one study (Schildt et al., 1998), where the estimates are for sexes combined and current use. All estimates are adjusted for age and other risk factors

[b] Ratio of RR/OR for dual users vs. smoking only to RR/OR for snus only vs. neither

[c] Interactions 1.18 (0.86-1.63) for cancer of right colon and 0.91 (0.65-1.27) for cancer of left colon

[d] As defined by Levitz et al., 2004; it includes oral, pharyngeal, oesophageal, gastric, pancreatic, laryngeal and pulmonary cancer as well as cancer of the kidney, bladder and other urinary organs

[e] NA = not available

[f] Death from cancer at the same site as the primary cancer – analysis is based on follow-up of incident cancer cases

[g] Death from causes other than cancer or from cancer of a site other than the primary cancer – analysis is based on follow-up of incident cancer cases

[h] Analysis is based on follow-up of incident cancer cases

Table 4

Dual use and conditions related to pregnancy and birth[a]

Disease	Source	Cases in dual users	RR/OR 95% CI Snus only vs. neither	Dual users vs. smoking only	Interaction[b]
Very preterm birth	Wikström et al., 2010a	4	1.34(1.03-1.74)	0.84(0.31-2.23)	0.63(0.23-1.72)
Preterm birth	Wikström et al., 2010a	24	1.24(1.12-1.37)	0.94(0.64-1.40)	0.76(0.51-1.14)
Pre-eclampsia	Wikström et al., 2010c	13	1.11(0.97-1.28)	1.20(0.65-2.20)	1.08(0.58-2.01)
Gestational hypertension	Wikström et al., 2010c	7	0.89(0.68-1.15)	2.72(1.30-5.69)	3.06(1.40-6.69)
Stillbirths	Wikström et al., 2010b	4	1.91(1.40-2.62)	1.67(0.62-4.49)	0.87(0.31-2.47)
Diabetes	Wikström et al., 2010b	7	0.93(0.76-1.14)	0.88(0.42-0.84)	0.95(0.44-2.04)
Antenatal bleeding	Wikström et al., 2010b	5	1.21(0.98-1.48)	0.66(0.27-1.58)	0.55(0.22-1.34)
Small for gestational age	Wikström et al., 2010b	23	1.18(1.01-1.38)	1.12(0.75-1.67)	0.95(0.62-1.46)
Neonatal apnea	Gunnerbeck et al., 2011	0	1.96(1.30-2.96)	0.00	0.00

[a] RR/ORs for pre-eclampsia, gestational hypertension, stillbirths and neonatal apnea are adjusted for age and other characteristics. Others are unadjusted and are calculated based on rates (%) to 1 decimal place, so are subject to some inaccuracy. All estimates are for current use

[b] Ratio of RR/OR for dual users vs. smoking only to RR/OR for snus only vs. neither

Table 5

Dual use and chronic inflammatory disease[a]

Disease	Source	Cases in dual users	RR/OR 95% CI Snus only vs. neither	Dual users vs. smoking only	Interaction[b]
Rheumatoid arthritis	Carlens et al., 2010	141	1.20(0.80-1.80)	0.87(0.71-1.06)	0.72(0.46-1.14)
Sarcoidosis	Carlens et al., 2010	41	1.10(0.80-1.50)	1.00(0.70-1.42)	0.91(0.57-1.46)
Ulcerative colitis	Carlens et al., 2010	191	1.00(0.80-1.20)	1.17(0.98-1.39)	1.17(0.89-1.52)
Ulcerative colitis	Persson et al., 1993	15	1.10(0.40-3.10)	3.25(1.23-8.56)	2.95(0.72-12.09)
Crohn's disease	Carlens et al., 2010	108	1.00(0.80-1.40)	0.93(0.75-1.16)	0.93(0.65-1.33)
Crohn's disease	Persson et al., 1993	11	0.90(0.30-3.10)	2.65(0.94-7.47)	2.94(0.62-14.02)
Multiple sclerosis	Carlens et al., 2010	37	1.80(1.10-2.90)	0.76(0.51-1.12)	0.42(0.23-0.79)
Multiple sclerosis	Hedström et al., 2009	87	0.40(0.03-5.34)	0.40(0.19-0.82)	1.00(0.07-13.34)

[a] All RR/OR estimates are for males, and for ever use, except for one study (Hedström et al., 2009) where they are for sexes combined, and snus use is current/non-current. All estimates are adjusted at least for age

[b] Ratio of RR/OR for dual users vs. smoking only to RR/OR for snus only vs. neither

Table 6

Consumption of cigarettes and snus in single and dual users[a]

Source	Sex	Age (yrs)	Year	No. of dual users	Current or ever use	Cigarettes per day		Snus use		Units
						Smoking only	Dual use	Snus only	Dual use	
Aro et al., 2010	M+F	20+	1998-2001	22	C	11.5	6.2	3.2	2.2	cans/wk
Carlens et al., 2010[b]	M	Mean 36	1978-1993	43425	E	12	9	22	16	g/day
Eliasson et al., 1995	M	25-64	1990	38	C	16.5(0.6)	10.1(1.1)	3.2(0.2)	2.5(0.2)	cans/wk
Gilljam and Galanti, 2003	M	25-55	2000	84	C	15.1(0.5)	11.0(1.1)			
	F	25-55	2000	14	C	12.3(0.3)	11.7(3.1)			
Hansson et al., 2009	M	20+	1998-2002	1647	C[c]	16.7	16.5			
Hergens et al., 2005	M	45-70	1992-1994	60	C[d]	18.6	16.4			
Janzon and Hedblad, 2009	M	45-73	1991-1996	250	C	16.1(0.2)	12.3(0.6)			
	F	45-73	1991-1996	21	C	12.9(0.1)	7.8(0.7)			
Lund and McNeill, 2013	M	16-74	2005-2010	226	C	11.5(0.3)	8.1(0.5)			
Rodu et al., 2002	M	25-64	1986-1999	NA	C	15.8	10.8	0.42	0.25	cans/wk
Sundbeck et al., 2009	M	30-75	2001-2003	116	C[e]			3.7	3.4	cans/wk
Wennmalm et al., 1991	M	18-19	Unknown	30	C	12.2(0.8)	7.8(1.3)	25(1)	27(3)	g/day

[a] Standard errors are given in brackets, where available

[b] The source also presents data showing that dual users have consistently lower cigarette consumption and snus use than do single users in each of five age groups (<24, 25-34, 35-44, 45-54 and 55+ years)

[c] Current snus use; ever smoking

[d] Among former smokers, consumption was 20.6 cigs/day in non-snus users and 18.4 cigs/day in snus users

[e] Current snus use; former smoking

Table 7

Current smoking and current snus use – selected recent data for Sweden (or other Nordic countries)[a]

Source	Year	Age (yrs)	Sex	N[b]	Frequency (%) Dual	Snus[c]	Smoking[c]	Neither	OR (95% CI)
Studies in adults									
VIP survey[d]	2002-7	40	M	6055	5.6	28.1	7.1	59.1	1.66 (1.42-1.93)
		50	M	6348	5.9	23.8	11.3	58.9	1.29 (1.13-1.48)
		60	M	6413	3.5	17.5	13.1	66.0	1.01 (0.86-1.18)
		40	F	6286	2.1	11.8	12.2	74.0	1.08 (0.88-1.32)
		50	F	6698	2.0	6.2	19.4	72.3	1.20 (0.98-1.47)
		60	F	6610	0.6	2.5	18.2	78.7	1.04 (0.73-1.48)
Skåne Public Health survey[e]	2004	18-80	M	11855	3.8	15.7	15.3	65.2	1.03 (0.92-1.16)
		18-80	F	14050	0.5	1.8	21.8	75.9	1.01 (0.78-1.32)
SIRUS Norway[f]	2006	21-30	M	1198	1.5	15.3	16.4	66.8	0.40 (0.24-0.67)
Stockholm Public Health survey[g]	2006	18+	M	15428	2.4	17.0	11.3	69.3	0.86 (0.76-0.97)
		18+	F	18761	0.5	3.1	15.2	81.2	0.88 (0.71-1.10)
SSB Norway[h]	2008/9	16-74	M	4444	0.9	9.9	20.0	69.1	0.31 (0.23-0.44)
		16-74	F	4592	0.1	1.3	20.2	78.4	0.30 (0.12-0.77)
SSLC survey[i]	2008-11	16-34	M	1729	4.3	35.6	15.9	0.8	0.95 (0.72-1.24)
		35-54	M	1631	5.6	42.8	21.9	1.2	0.78 (0.61-1.00)
		55-64	M	1760	2.4	28.8	29.7	1.1	0.42 (0.30-0.58)
		75+	M	1128	0.5	8.0	7.0	0.4	1.12 (0.47-2.67)
		16-34	F	1711	0.8	7.2	25.0	0.9	0.63 (0.35-1.13)
		35-54	F	1848	0.8	8.0	32.9	0.8	0.47 (0.27-0.81)
		55+	F	3212	0.3	1.8	25.4	0.2	0.92 (0.44-1.93)
Health on equal terms survey[j]	2009-12	16-29	M	2554	1.8	17.4	6.8	74.1	1.10 (0.78-1.56)
		30-44	M	3524	1.8	20.4	7.0	70.7	0.91 (0.68-1.21)
		45-64	M	6491	3.0	17.8	12.3	66.9	0.92 (0.77-1.09)
		65-84	M	5246	1.2	10.0	9.0	79.8	1.09 (0.83-1.43)
		16-29	F	3465	0.4	4.5	11.3	83.8	0.71 (0.41-1.22)
		30-44	F	4748	0.5	4.2	9.8	85.6	1.05 (0.68-1.63)
		45-64	F	7621	0.5	3.0	16.9	79.6	0.74 (0.52-1.05)
		65-84	F	5559	0.3	1.4	10.7	87.6	1.67 (0.96-2.90)
Studies in adolescents									
Postal surveys[k]	2003	13,15,17	M	1398	3.0	6.0	3.0	88.0	14.6 (9.05-23.7)
Norway telephone survey[l]	2004,7	16-20	M	2441	5.9	15.7	12.6	65.8	1.96 (1.56-2.46)
		16-20	F	2374	1.4	3.5	18.4	76.7	1.73 (1.15-2.62)
Norway school survey[m]	2005	15-16	M	809	2.5	5.4	6.1	86.0	6.53 (3.58-11.9)
Finnish adolescents[n]	2005-11	14	M	3360	0.1	0.3	6.0	93.6	7.02 (2.30-21.5)
		16	M	2739	0.8	1.3	20.5	77.4	2.22 (1.29-3.83)
		18	M	2190	1.0	1.8	28.7	68.6	1.34 (0.78-2.28)
Norway telephone survey[o]	2006	15-18	M	2896	12.7	25.6	7.6	54.2	3.56 (2.94-4.29)
CAN school surveys[p]	2009-12	15-16	M	9578	1.0	4.6	4.8	89.6	4.02 (3.16-5.11)
		17-18	M	7513	1.5	12.0	7.0	79.5	1.38 (1.11-1.71)
		15-16	F	9615	0.1	0.3	7.3	92.3	7.45 (3.86-14.4)
		17-18	F	7446	0.3	1.7	12.7	85.3	1.20 (0.76-1.89)

[a] Except where stated, surveys are national, and are in Sweden
[b] Number of subjects. Where annual or bi-annual data are available, results shown are pooled from the four most recent surveys
[c] Only the stated habit
[d] VIP = Västerbotten Intervention Program. Current snus = regular, current smoking = daily or intermittent. Source : Norberg et al., 2011
[e] Postal survey conducted in Skåne County. Current snus = daily, current smoking = daily or intermittent. Source : Lindström, 2007
[f] SIRUS = Statens institutt for rusmiddelforskning (Norwegian Institute for Alcohol and Drug Research). Drug use among young adults survey (Rusmiddelbruk blant unge voksne). Source : Lund et al., 2007
[g] Definitions of smoking and snus are for daily use. Source : Engström et al., 2010
[h] SSB = Statistisk sentralbyrå (Statistics Norway). Definitions of smoking and snus are for daily use. Source : Helleve et al., 2010
[i] SSLC = Swedish Survey of Living Conditions (Undersknigar on levnadsförhållanden, ULF). Definitions of smoking and snus are for daily use. Source : Statistiska Centralbyrån (SCB Statistics Sweden), 2013
[j] Definitions of smoking and snus are for daily use. Source : Statens Folkhalsoinstitut (Swedish National Institute of Public Health), 2012
[k] Definitions of smoking and snus include regular and occasional use. Source : Nilsson et al., 2009
[l] Definitions of smoking and snus include daily or weekly use. Source : Øverland et al., 2010
[m] Definitions of smoking and snus are for daily use**.** Source : Aaro et al., 2008
[n] Survey conducted in alternate years. Definitions of smoking and snus are for daily use. Source : Raisamo et al., 2011
[o] Survey conducted in 11 of 19 Norwegian counties with high prevalence of snus use. Definitions of smoking and snus include daily or weekly use. Source: Larsen et al., 2013
[p] CAN = Central Alliance for Alcohol and Drug Information. Definitions of smoking and snus are for daily use**.** Source : Liefman, 2013

Table 8

Ever smoking and ever snus use – data from the VIP survey for 2002-2007 (Norberg et al., 2011)

Sex	Age (yrs)	N[c]	Frequency of ever use[b]				OR (95% CI)
			Dual	Snus[d]	Smoking[d]	Neither	
Males	40	6055	24.6	22.4	8.7	44.2	5.58 (4.95-6.28)
	50	6348	34.2	14.2	17.5	34.0	4.68 (4.21-5.70)
	60	6413	32.2	6.5	29.8	31.6	5.25 (4.65-5.94)
Females	40	6286	15.9	6.2	25.2	52.8	5.37 (4.71-6.13)
	50	6698	11.5	1.1	46.0	41.3	9.39 (7.35-12.0)
	60	6610	4.1	0.2	50.4	45.3	18.4 (10.6-32.1)

[a] VIP = Västerbotten Intervention Program
[b] Daily or intermittent
[c] N = number of subjects
[d] Only ever used

Highlights

- Snus use is far safer than smoking, but reviews have not studied effects of dual use
- Available evidence on risk relates to cancer, vascular disease and birth effects
- There is no indication of any special risk associated with dual use
- Dual use is commoner in adolescents than adults, who generally settle on one product
- Concomitant snus use appears to increase smoking quit rates