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Circulatory disease and smokeless tobacco in Western populations: a review of the evidence

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Background Use of oral snuff or 'snus' has risen in Sweden. Sales of snuff in the US have also risen, overtaking sales of chewing tobacco. There is some evidence that nicotine contributes to circulatory disease (CID) from smoking. We therefore reviewed the evidence relating smokeless tobacco (ST) to CID and related risk factors.

Methods Publications that described relevant cohort, case-control and cross-sectional studies were identified from in-house files, a Medline search in December 2005 and reference lists. Relative risks (RRs) and odds ratios (ORs) for ischaemic heart disease, stroke and all CID for ST use, stratified by smoking habit, were estimated and combined by meta-analysis to provide an overall RR estimate. For diabetes, increased blood pressure, and other risk factors, evidence was qualitatively reviewed, with results from clinical studies also considered.

Results ST use in non-smokers was associated with an increased risk of heart disease (RR 1.12, 95% CI 0.99–1.27, $n = 8$), stroke (1.42, 1.29–1.57, $n = 5$) and CID (1.25, 1.14–1.37, $n = 3$). The increases mainly derived from two large US studies. The Swedish studies provided little evidence of an increase for heart disease (1.06, 0.83–1.37, $n = 5$) or stroke (1.17, 0.80–1.70, $n = 2$), although the estimates by country are not notably heterogeneous, even for stroke ($P = 0.29$). No dose–response was evident. No increase was seen in former users of ST, or in ST users who also smoked. No clear relationship to diabetes was seen. In the US, an acute blood pressure rise following ST use was consistently reported, and isolated reports linked specific risk factors to ST. In Sweden, though one study reported that snuff acutely increased blood pressure, and two linked snuff to Raynaud-type symptoms, the overall evidence for an effect was inconclusive. Swedish studies generally showed no chronic effect of snuff on blood pressure or various risk factors.

Conclusions Any CID risk from ST appears to be substantially less than from smoking, and no clear risk from Swedish snuff is seen. However, the overall evidence is limited.

Keywords Heart diseases, cerebrovascular disorders, tobacco, smokeless, diabetes mellitus, blood pressure

Introduction

Smokeless tobacco (ST) is mainly used orally, and nasal use has become rare.[1–3] The two major products used in North America and Europe are chewing tobacco and snuff. There are several types of chewing tobacco and snuff, differing in their formulation and how the tobacco is treated.

In the United States, ST has formed an important part of total tobacco consumption for many years, e.g. 11.2% of all tobacco products by weight in 1950, 9.6% in 1980 and 12.9% in 2000.[4] For many years sales of chewing tobacco were two or three times those of snuff, but since the early 1980s sales of snuff have risen sharply and have recently overtaken sales of chewing tobacco.[4] Partly this may be because some types of fine-cut ST classified as chewing tobacco prior to 1981 are now categorized as moist/fine-cut snuff.[1]

In most other economically developed countries, ST forms only an unimportant part of the tobacco market.[4] Though ST

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forms a few per cent of the market in Canada, Iceland and Norway, the most notable exception is Sweden where snuff ('snus') has always formed a large proportion of total sales of tobacco by weight (70% in 1920, 31% in 1950, 29% in 1980, 53% in 2000), though sales of chewing tobacco there are negligible. As in the US, the use of snuff in Sweden has increased sharply in recent decades.

ST is also widely used in parts of Central and South-East Asia. Use occurs in various ways, with the tobacco used alone or in combination with other products, such as betel nut quid, slaked lime, areca nut and even snail shells.[1–3]

Studies conducted in Sweden[5–12] and the US[13–17] and also in the UK[18] provide evidence that the use of snuff and chewing tobacco involves an exposure to nicotine that is fairly equivalent to that from cigarette smoking. Indeed some of the studies in Sweden[5–10] reported higher plasma cotinine levels in users of snuff. Since nicotine has been implicated in several processes related to cardiovascular disease,[19] the possibility that ST, like cigarette smoking, might result in an increased risk, therefore deserves consideration. In this context, however, it should be noted that pipe smoking, which also results in nicotine exposure similar to that from cigarette smoking, is associated with an increase in heart disease risk that is substantially lower than that for cigarette smoking.[20,21]

This review is concerned with evidence relating ST use to circulatory disease (CID). Attention is restricted to chewing tobacco and snuff, with no consideration of the limited data on nicotine chewing gum. Attention is also restricted to studies in Western populations (in practice this means US and Sweden), omitting studies in Central and South-East Asia where, as noted above, products used are variable and often involve the inclusion of non-tobacco material.

The review concentrates on evidence from epidemiological studies linking use of ST to mortality from or onset or prevalence of ischaemic heart disease (IHD), acute myocardial infarction (AMI), stroke, or all CID. A briefer summary is also given of evidence linking use of ST to risk factors for heart disease such as diabetes, hypertension, cholesterol, fibrinogen, platelet function and ultrasonographic measurements of atherosclerosis.

An earlier review by Critchley and Unal[22] which concluded that 'there may be an association between ST use and cardiovascular disease' was limited, partly because it did not include meta-analyses, partly because studies of stroke were not included and partly because it only included three[23–25] of the eight epidemiological studies now available on IHD or AMI. Four were published in 2005[26–28] and one earlier.[29]

Methods

In December 2005, publications describing results of epidemiological case-control, cohort and cross-sectional studies relating ST use to risk of CID were sought from our in-house files, supplemented by a MEDLINE search (using the terms smokeless tobacco and cardiovascular disease) and from reference lists of articles retrieved. Publications relating to risk factors relevant to CID were similarly sought, with clinical studies also considered.

From the studies of CID risk, details were extracted of the study design, location and timing and of the potential confounding variables considered. Where available, estimates of the relative risk (RR) or odds ratio (OR) associated with ST use were extracted together with their associated 95% confidence interval (CI). The RRs and ORs extracted related to AMI (international classification of diseases (ICD) 9th revision 410), IHD (ICD 410–414, equivalent to coronary heart disease), stroke ICD 430–438 = cerebrovascular disease], all CID (390–459 = cardiovascular disease), or other CID. Attention was limited to estimates where the groups being compared differed only in exposure to ST use and not in exposure to smoking. Thus, if for example the source article presented RRs for each combination of ST use (ever, never) and smoking (current, former, never) relative to a totally unexposed denominator (never ST, never smoking), the RRs were recalculated, using standard methods,[30–32] to compare ever and never ST users separately for current, former and never smokers. Fixed-effects meta-analysis[33] would then be used to combine these estimates to produce a smoking-adjusted overall RR estimate. Fixed-effects meta-analysis was also used to combine RRs reported separately by age. Where RRs for a given comparison were available with varying degrees of confounder adjustment that adjusted for the most variables was selected for analysis.

In order to obtain an overall estimate of the risk associated with ST use, RR and OR estimates were combined by meta-analysis.[33] Since an OR is an approximation to an RR, the combined estimate is referred to as being a RR estimate. Results are presented in the tables for both fixed-effects and random-effects models, with the random-effects estimates being cited in the text where appropriate.

The studies of risk factors related to CID were reviewed in a less detailed manner, mainly to summarize the number of studies which did and did not report associations of ST use with the various endpoints considered.

Results

CID

The studies

Table 1 summarizes details of five cohort studies, two in Sweden[23,27] and three in the US,[26,29] for which results have been reported relating ST use to risk of CID mortality or incidence. For the study of Swedish construction workers,[23] some earlier results had been reported[34] based on a cross-sectional analysis of the baseline sample. All of the studies presented results for males, with only one[29] also presenting results for females. All of the studies involved follow-up for at least 10 years. The number of ST users considered in the analytical cohort followed up varied from 437 to 7745. Only one of the cohort studies, CPS-II,[35] separated current and former use of ST, with CPS-I[35] and the two Swedish studies[23,27] only considering current ST use and the NHANES follow-up study[29] only considering ever ST use. Smokers were excluded in the analyses of CPS-I and CPS-II,[35] with the analyses of the Swedish construction workers study[23] excluding those who had used pipes or cigars and those with mixed use of ST and cigarettes. All of the cohort studies took a range of potential confounding variables into account, though in one study[23] detailed analyses were only presented adjusted for age and

Table 1 Cohort studies of ST and CID

	Study name				
	Swedish construction workers study	SALLS[a] follow-up study	First NHANES[b] follow-up study	American Cancer Society CPS-I[c]	American Cancer Society CPS-II[d]
Source	Bolinder *et al*.[23]	Johansson *et al*.[27]	Accortt *et al*.[29]	Henley *et al*.[26]	Henley *et al*.[26]
Country	Sweden	Sweden	US	US	US
Location	Nationwide	Nationwide	Nationwide	25 states	Nationwide
Baseline survey	1971–74	1988–89	1971–75	1959	1982
Sex[e]	Males	Males	Males and females	Males	Males
Age at baseline[e]	16–65	30–74	45–75	30+	30+
Exclusions[e]	Used ST and cigarettes Smoked pipes or cigars Died before 1974 Did not attend for health examination	Self-reported health not good Recent IHD hospitalization	Race other than White or Black	Smokers of any product Relevant disease at baseline[f] Reported past ST use[g]	Smokers of any product Relevant disease at baseline[f]
Follow-up[h]	1974–85	To 2000	To 1992	To 1972	To 2000
	(12 years)	(12 years)	(20 years)	(12 years)	(18 years)
Sample size[e]	84 781	3120	12 172	77 407	114 809
	(6297 ST users)	(437 ST users)	(1457 ST users)	(7745 ST users)	(3327 ST users)
Data on ST use	Current ST	Current snuff (daily)	Ever ST[i]	Current chewing tobacco or snuff (occasional or regular)	Current/former chewing tobacco and current/former snuff (regular[j])
Endpoints	Mortality from IHD, stroke, all CID[k]	First fatal or non-fatal IHD	Mortality from IHD, stroke, all CID	Mortality from IHD, stroke, other CID, all CID	Mortality from IHD, stroke, other CID, all CID
Potential confounding variables adjusted for	Age, region[l]	Age, blood pressure, body mass index, diabetes, exercise[m]	Age, alcohol, blood pressure, body mass index, cholesterol, exercise, fruit/vegetables, poverty, race[n]	Age, alcohol, aspirin, body mass index, dietary fat, education, exercise, fruit/vegetables, race	Age, alcohol, aspirin, body mass index, dietary fat, education, employment status and type, exercise, fruit/vegetables, race

[a] SALLS: Swedish Annual Level-of-Living Survey.

[b] NHANES: National Health and Nutrition Examination Survey.

[c] CPS-I: Cancer Prevention Study I.

[d] CPS-II: Cancer Prevention Study II.

[e] In analyses of ST (except where noted in Table 3).

[f] Analyses of CID excluded men who reported prevalent heart disease, diabetes or stroke at baseline, while analyses of IHD excluded men who reported prevalent heart disease or diabetes at baseline and analyses of stroke excluded men who reported prevalent stroke at baseline.

[g] Questions were not asked about past ST use, but some men volunteered answers.

[h] Years are approximate, as described by the authors.

[i] Questions on ST use were only asked of a sample in 1971–75, but were asked of everyone in a follow-up survey in 1982–84. Individuals reporting current ST use in 1971–75 or ever use in 1982–84 were considered ever users of ST.

[j] For both chewing tobacco and snuff, regular = at least once a week for at least a year.

[k] Bolinder *et al*.[34] also presents results from this survey based on cross-sectional analysis of the 1971–74 sample relating ST use to risk of disability retirement due to CID.

[l] Further adjustment for blood pressure, body mass index, diabetes and history of heart symptoms or blood pressure medication had little effect.

[m] Further adjustment for socio-economic status had no effect.

[n] Cholesterol and body mass index not adjusted for in analyses of stroke.

region, it being noted that additional adjustments had little effect on the risk estimates.

Table 2 similarly summarizes details of the five case-control studies that have been carried out, all in Sweden.[24,25,28,36,37] Four of the five studies were conducted in the two northernmost counties, Norrbotten and Västerbotten. Two of these[24,25] were non-overlapping case-control studies of AMI, while the other two[36,37] were overlapping nested case-control studies of stroke, both based on new cases occurring in a combined sample from the same two (MONICA and VIP) studies, one based on cases occurring between 1985 and 1996, the other also including cases up to 2000. The other case-control study,[28] of AMI, was conducted in two other Swedish counties, Stockholm and Västernorrland. With the exception of the earlier study of stroke, all of the case-control studies restricted attention to males. All of the cases were first occurrences of the index disease (AMI or stroke), with controls representative of the population studied. While four of the studies matched controls to cases on a 1:1 or 2:1 basis on age, region and other factors, the earliest study of AMI[24] did not, selecting controls in the same age range and population. The three studies of AMI[24,25,28] included fatal and non-fatal cases, relying on surrogate interviews for the fatal cases, but not for their matched controls. The number of cases in the studies varied between 589 and 1432 for AMI and between 123 and 276 for stroke. All the case-control studies reported results relating to current and former snuff use, with the exception of the earlier study of stroke,[36] which considered only current use. Consideration of potential confounding variables was variable, with one study[36] only presenting crude results for sexes combined, and two studies[25,37] reporting results adjusted for a variety of factors.

Risk associated with smokeless tobacco use

Virtually all the evidence relating ST use to risk of CID is for males. There are only two exceptions to this:

(i) In females in the First NHANES follow-up study[29] there was little evidence that ST increased risk of death from all CID (hazard ratio 1.2, 95% CI 0.7–1.9 in never smokers) after adjustment for age, race and poverty, or that ST increased risk of IHD (1.4, 0.8–2.2 in never smokers; 1.1, 0.4–3.2 in ever smokers) or stroke (1.0, 0.3–2.9 in never smokers; 1.7, 0.4–7.0 in ever smokers) after adjustment for a longer list of potential confounding variables (Table 1);

(ii) In males and females combined in the first MONICA/VIP study[36] the crude OR for stroke was not increased (0.56, 95% CI 0.25–1.27).

This evidence is clearly too sparse to allow a reliable conclusion, so, in the following, attention is restricted to males.

Table 3 presents RR or OR estimates relating to various indices of ST use, smoking groups and vascular endpoints. The first estimate listed is an OR deriving from a cross-sectional study[34] which formed the baseline of a cohort study,[23] while estimates 2–25 are RRs from cohort studies and estimates 26–43 are ORs from case-control studies. Of the 43 estimates, the lowest is 0.56 and the highest 1.89, with 23 estimates >1.00 and $19 < 1.00$. Considered in isolation, the strongest statistical evidence of a positive relationship comes from estimates 1, 2 and 4 in the Swedish construction workers study, 14, 15 and 17 in CPS-I and 18, 19 and 21 in CPS-II.

Meta-analyses

Table 4 presents the results of various meta-analyses based on the estimates in Table 3. The first three of these are presented as forest plots in Figure 1.

For IHD or AMI, the eight RR/OR estimates for current ST use among never smokers (or the nearest equivalent available) showed some heterogeneity ($\chi^2 = 13.11$ on 7 df, $P = 0.07$), varying from 0.60 to 1.41. The random-effects estimate was not clearly increased overall (1.12, 95% CI 0.99–1.27), or when results were considered separately for the US (1.14, 0.96–1.34) or Sweden (1.06, 0.83–1.37). Excluding estimate 9, which was for ever rather than current use, the random-effects estimate for Sweden and US combined changed slightly to 1.15 (1.03–1.29). Estimates were increased for cohort studies but not for case-control studies (heterogeneity $\chi^2 = 4.58$ on 1 df, $P = 0.03$). Although the combined estimates in Table 4 provide some indication of a weak association of IHD or AMI with current ST use in never smokers, they provided no indication of any increase in risk associated with current ST use in current smokers or in all individuals, or of any increase in risk associated with former ST use.

For stroke, the five estimates for current ST use among never smokers showed no heterogeneity ($\chi^2 = 3.53$ on 4 df, $P = 0.47$) with the meta-analysis showing an increased risk (1.42, 1.29–1.57). The increase seemed less evident for Sweden (1.17, 0.80–1.70) than for the US (1.41, 1.17–1.71), but there was no clear heterogeneity ($\chi^2 = 1.12$ on 1 df, $P = 0.29$).

For all CID, the three estimates for current ST use among never smokers showed no marked heterogeneity ($\chi^2 = 4.58$ on 2 df, $P = 0.10$), and the random-effects estimate was increased (1.25, 1.13–1.37).

The analyses of risk associated with current ST use in never smokers were heavily dependent on the contributions of the two large US CPS studies. Thus, for IHD or AMI, CPS-I provided 62.3% and CPS-II 17.0% of the total weight of the combined estimate. Corresponding percentages were 76.3% and 16.2% for stroke and 68.2% and 18.5% for all CID, respectively. Excluding CPS-I and CPS-II the random-effects estimates showed little evidence of an association for IHD or AMI (0.99, 0.76–1.30) or for stroke (1.11, 0.78–1.59).

Risk by age

Although there is clear evidence that the association of smoking with IHD is age-dependent, with an increasing RR with decreasing age, only two of the 10 studies presented RRs or ORs for ST by age. In the Swedish construction workers study,[23] the risk of IHD associated with current ST use in never smokers was higher ($P = 0.02$) in men aged 35–54 at entry into the study (RR 2.0, 95% CI 1.4–2.9) than in men aged 55–65 at entry (RR 1.2, 95% CI 1.0–1.5). In contrast, in the first MONICA study,[24] the risk of AMI was somewhat lower ($P = 0.31$) in men aged 35–54 (OR 0.96, 95% CI 0.56–1.67) than in men aged 55–64 (OR 1.24, 95% CI 0.78–2.30).

Dose response

Only two studies presented any dose–response results for ST use. In CPS-II,[26] frequency and duration of use among current

Table 2 Case-control studies of ST and CID in Sweden

	Study name				
	First MONICA[a] study of AMI	Second MONICA[a] study of AMI	Two counties study of AMI	First MONICA/VIP[b] study of stroke	Second MONICA/VIP[b] study of stroke
Source	Huhtasaari *et al*.[24]	Huhtasaari *et al*.[25]	Hergens *et al*.[28]	Ahmed *et al*.[36]	Asplun *et al*.[37]
Location	Norrbotten and Västerbotten	Norrbotten and Västerbotten	Stockholm and Västernorrland	Norrbotten and Västerbotten	Norrbotten and Västerbotten
Type of study	Case-control	Case-control	Case-control	Nested case-control	Nested case-control
Timing	1989–91 (cases) 1990 (controls)	1991–93	1992–94	1985–96[c]	1985–2000[d]
Sex[e]	Males	Males	Males	Males and females	Males
Age[e]	35–64	25–64	45–70	25–74	25–74
Cases	First AMI	First AMI	First AMI	First stroke	First stroke (not subarachnoid haemorrhage)
Controls	Population	Population	From sample interviewed	From sample interviewed	From sample interviewed
Matching	No	Individually on age and county	Individually on age and hospital catchment area	2:1 on sex, age, survey, date of survey, and region	2:1 on age, survey, date of survey and region
Exclusions	Controls with AMI	Controls with AMI Either member of pair has incomplete tobacco data	Controls with previous MI	Previous MI, stroke or cancer, or inadequate blood sample	Previous CID or cancer
Surrogate respondents	Fatal cases only	Fatal cases only	Fatal cases only	None	None
Sample size	585 cases 589 controls	687 case-control pairs	1432 cases 1810 controls	123 cases 241 controls	276 cases 551 controls
Data on ST use	Current/former snuff (daily)	Current/former snuff (daily)	Current/former snuff	Current snuff (daily)	Current/former snuff (daily)
Potential confounding variables adjusted for	Age, education	Matching factors plus blood pressure, cholesterol, diabetes, education, family history of early MI, marital status	Age, area, smoking[f]	None	Matching factors plus blood pressure, cholesterol, diabetes, education, marital status

[a] MONICA: *moni*toring of trends and determinants in *car*diovascular disease.

[b] MONICA/VIP; combined MONICA study and Västerbotten Intervention Program (VIP).

[c] Interviews took place in 1986, 1990 and 1994 in the MONICA study and from 1985 to 1996 in the VIP study. Occurrences of stroke took place after interview and before 1996.

[d] Interviews took place in 1986, 1990, 1994 and 1999 in the MONICA study and from 1985 to 2000 in the VIP study. Occurrences of stroke took place after interview and before 2000.

[e] In analyses of ST.

[f] Further adjustment for blood pressure, body mass index, cholesterol, diabetes, exercise and job strain had no effect.

Table 3 RR/OR of CID associated with ST use in men

	ST use				RR/OR			
Study[a]	Type	Comparison	Smoking	CID endpoint	No	Cases[b]	Estimate (95% CI)	Notes
Swedish construction workers[34]	ST	Current vs never	Never	CID	1(OR)	77	1.51 (1.17–1.96)	c,d,e
Swedish construction workers[23]	ST	Current vs never	Never	IHD	2(RR)	172	1.35 (1.13–1.62)	e,f,g
			Never	Stroke	3(RR)	30	1.29 (0.83–1.99)	e,f,g
			Never	All CID	4(RR)	220	1.40 (1.20–1.60)	f
SALLS follow-up[27]	Snuff	Current vs	Never	IHD	5(RR)	6	1.41 (0.61–3.28)	e,f
		non-current	Former	IHD	6(RR)	16	0.80 (0.47–1.38)	e,f
			Current	IHD	7(RR)	10	1.19 (0.60–2.37)	e,f
			Any	IHD	8(RR)	32	1.01 (0.69–1.48)	e,f,h
First NHANES follow-up[29]	ST	Ever vs never	Never cigs	IHD	9(RR)	NA	0.60 (0.30–1.20)	f
			Never cigs	Stroke	10(RR)	NA	0.70 (0.20–2.00)	f
			Never cigs	All CID	11(RR)	NA	1.00 (0.70–1.50)	i
			Ever cigs	IHD	12(RR)	NA	0.67 (0.42–1.05)	e,f
			Any cigs	IHD	13(RR)	NA	0.65 (0.44–0.95)	e,f,h
CPS-I[26]	ST	Current vs never	Never	IHD	14(RR)	799	1.12 (1.03–1.21)	f
			Never	Stroke	15(RR)	460	1.46 (1.31–1.64)	f
			Never	Other CID	16(RR)	255	1.05 (0.91–1.22)	f
			Never	All CID	17(RR)	1399	1.18 (1.11–1.26)	f
CPS-II[26]	ST	Current vs never	Never	IHD	18(RR)	172	1.26 (1.08–1.47)	f
			Never	Stroke	19(RR)	71	1.40 (1.10–1.79)	f
			Never	Other CID	20(RR)	58	1.07 (0.82–1.39)	f
			Never	All CID	21(RR)	278	1.23 (1.09–1.39)	f
		Former vs never	Never	IHD	22(RR)	44	0.70 (0.52–0.95)	f
			Never	Stroke	23(RR)	29	1.21 (0.83–1.76)	f
			Never	Other CID	24(RR)	31	1.20 (0.83–1.72)	f
			Never	All CID	25(RR)	96	0.92 (0.75–1.13)	f
First MONICA[24]	Snuff	Current vs non-current	Non-current cigs	AMI	26(OR)	59	0.89 (0.62–1.29)	d

			Any cigs	AMI	27(OR)	91	1.01 (0.66–1.55)	e,h,j
Second MONICA[25]	Snuff	Current vs non-current	Non-current	AMI	28(OR)	59	0.93 (0.65–1.33)	e,k
			Current	AMI	29(OR)	20	0.73 (0.34–1.57)	e,k
			Any	AMI	30(OR)	79	0.89 (0.64–1.23)	e,h,k
		Current vs never	Non-current	AMI	31(OR)	59	0.93 (0.65–1.34)	e,k
		Former vs never	Non-current	AMI	32(OR)	48	1.02 (0.68–1.52)	e,k
		Current vs Non-current	Non-current	AMI	33(OR)	59	0.58 (0.35–0.94)	j
Two counties[28]	Snuff	Current vs never	Never	AMI	34(OR)	10	0.73 (0.35–1.50)	j
			Former	AMI	35(OR)	71	1.23 (0.87–1.73)	e,j
			Current	AMI	36(OR)	66	0.82 (0.56–1.20)	e,j
			Any	AMI	37(OR)	147	0.99 (0.78–1.26)	e,h,j
		Former vs never	Never	AMI	38(OR)	7	1.20 (0.46–3.10)	j
			Former	AMI	39(OR)	36	0.85 (0.56–1.29)	e,j
			Current	AMI	40(OR)	30	1.89 (0.96–3.75)	e,j
			Any	AMI	41(OR)	73	1.07 (0.77–1.50)	e,h,j
First MONICA/VIP[36]	ST	Current vs non-current	Any	Stroke	42(OR)	8	0.56 (0.25–1.27)	k
Second MONICA/VIP[37]	Snuff	Current vs non-current	Non-current	Stroke	43(OR)	30	0.87 (0.41–1.83)	l

[a] Abbreviations used for study names explained in Tables 1 and 2.
[b] Cases in ST users as defined. Cases in non-users (available on request from the author) are always higher than in users, for the great majority of estimates by a factor of at least 4. NA = not available.
[c] Endpoint is pension due to a disability diagnosis of CID.
[d] OR adjusted for age.
[e] RR/OR estimated from data in source article (applies also to number of cases for SALLS follow-up study).
[f] RR adjusted for factors listed in Table 1.
[g] Age 35–65.
[h] RR/OR also adjusted for smoking.
[i] RR adjusted for age, race, poverty index.
[j] OR adjusted for factors listed in Table 2.
[k] Unadjusted OR.
[l] OR adjusted for matching factors.

Table 4 Various meta-analyses of the estimates in Table 3

ST use	Smoking	Endpoint	No. of estimates included (RR/OR Nos)[a]	Total cases[b]	Overall RR (95% CI) Fixed-effects	Random-effects
Sweden and US						
Current (or near equivalent[c])	Never (or near equivalent[d])	IHD or AMI	8 (2, 5, 9, 14, 18, 26, 31, 34)	1277 +	1.15 (1.08–1.22)	1.12 (0.99–1.27)
		Stroke	5 (3, 10, 15, 19, 43)	591 +	1.42 (1.29–1.57)	1.42 (1.29–1.57)
		All CID[e]	3 (4, 17, 21)	1897	1.22 (1.15–1.28)	1.25 (1.13–1.37)
	Current	IHD or AMI	3 (7, 29, 36)	96	0.87 (0.64–1.18)	0.87 (0.64–1.18)
	Any[f]	IHD or AMI	5 (8, 13, 27, 30, 37)	349 +	0.92 (0.79–1.06)	0.92 (0.79–1.06)
Current[g]	Never (or near equivalent[d])	IHD or AMI	7 (2, 5, 14, 18, 26, 31, 34)	1277	1.15 (1.08–1.23)	1.15 (1.03–1.29)
Former[h]	Never (or near equivalent[d])	IHD or AMI	3 (22, 32, 38)	99	0.82 (0.65–1.04)	0.85 (0.63–1.15)
Sweden						
Current (or near equivalent[c])	Never (or near equivalent[d])	IHD or AMI	5 (2, 5, 26, 31, 34)	306	1.17 (1.01–1.35)	1.06 (0.83–1.37)
		Stroke	2 (3, 43)	60	1.17 (0.80–1.70)	1.17 (0.80–1.70)
US						
Current (or near equivalent[c])	Never (or near equivalent[d])	IHD or AMI	3 (9, 14, 18)	971 +	1.14 (1.06–1.22)	1.14 (0.96–1.34)
		Stroke	3 (10, 15, 19)	531 +	1.44 (1.30–1.60)	1.41 (1.17–1.71)
Cohort studies						
Current (or near equivalent[c])	Never (or near equivalent[d])	IHD or AMI	5 (2,5,9,14,18)	1149 +	1.17 (1.09–1.25)	1.20 (1.05–1.36)
Case-control studies						
Current (or near equivalent[c])	Never (or near equivalent[d])	IHD or AMI	3 (26,31,34)	128	0.89 (0.70–1.13)	0.89 (0.70–1.13)
Excluding CPS-I and CPS-II						
Current (or near equivalent[c])	Never (or near equivalent[d])	IHD or AMI	6 (2,5,9,26,31,34)	306 +	1.14 (0.99–1.31)	0.99 (0.76–1.30)
		Stroke	3 (3,10,43)	60 +	1.11 (0.78–1.59)	1.11 (0.78–1.59)
		All CID	1 (4)	220	1.40 (1.20–1.60)	1.40 (1.20–1.60)

[a] RR/OR Nos as shown in Table 3.
[b] In ST users. + indicates that the totals exclude numbers in the first NHANES follow-up[29] which are not known.
[c] Includes (in order of preference) current vs. never, current vs. non-current and ever vs. never.
[d] Includes never, never cigs, non-current and non-current cigs.
[e] Not including RR/OR No 1 as this is from the same source population as RR/OR No 4.
[f] Includes any or any cigs.
[g] Includes (in order of preference) current vs never and current vs non-current.
[h] Former vs Never.

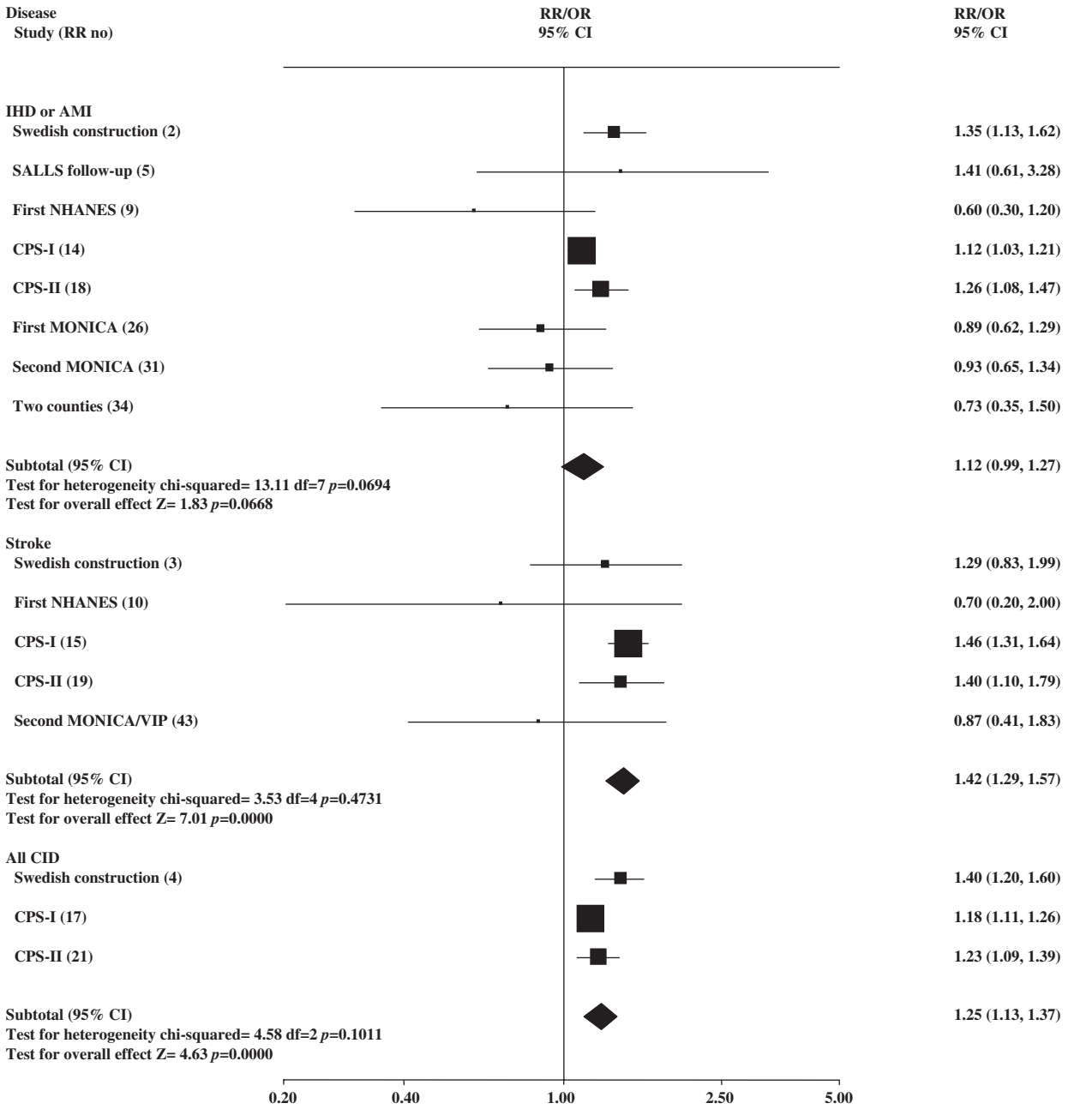

Figure 1 Forest plot of selected random-effect meta-analyses shown in Table 4: data from Sweden and the US; current ST use (or near equivalent) in never smokers (or near equivalent)

ST users was unrelated to risk of IHD, stroke or all CID, despite there being over 200 cases of CID in ST users. In the first MONICA study,[24] users of 2+ cans of snuff a day had no increased risk of AMI, though power to detect a dose–response was limited.

Separate associations with chewing tobacco and snuff

In CPS-II,[26] RRs for IHD, stroke and all CID did not differ notably between those who chewed tobacco and never used snuff and those who used snuff and never chewed. However, the number of deaths in the second category was relatively low.

Effect of smoking

All of the seven studies that reported little or no evidence of an increased risk of CID associated with ST use[24,25,27–29,36,38] reported a clear association of CID with smoking, with RRs typically exceeding 2. Similarly in the Swedish construction workers study,[23] the RRs for IHD, stroke and all CID were always higher for smokers than for ST users. The source article[26] for the ST results in CPS-I and CPS-II did not give results for smoking, but other publications[39–41] made it clear that in these studies the RRs for smoking exceeded those seen for ST use.

Joint effects of smokeless tobacco use and smoking

Five studies[24,25,27–29] provided estimates of the RR or OR of IHD or AMI associated with current (or ever) ST use separately for never (or non-current) smokers and for current smokers. As shown in Table 5, the smoker/non-smoker ratio of these estimates was close to 1 and provided no indication of a multiplicative interaction between the effects of smoking and the possible effects of ST. Thus, the data did not indicate any special hazard in relation to the dual use of smoking and ST.

Other outcomes

Diabetes

Ten publications[9,10,26–28,42–46] have reported results relating the use of ST to diabetes or related endpoints such as glucose intolerance, glucose levels, insulin levels or insulin resistance. Except for the publications reporting results from the large American CPS-I and CPS-II studies,[26] all the studies described were conducted in Sweden.

Of the six studies that provided results for diabetes incidence, prevalence or mortality (Table 6), the only notable association was reported by Persson *et al*.[44] That study reported an OR of 3.9 (95% CI 1.1–14.3) comparing current exclusive snuff users and those who had never used tobacco and an OR of 2.7 (95% CI 1.3–5.5) in current heavy snuff users, regardless of tobacco consumption. These ORs did not compare diabetic patients with individuals with normal glucose tolerance. All the studies involved a small number of cases of diabetes in ST users, at most 20 in the CPS-I study. For the combined data, no clear association was seen, random-effects meta-analysis for current ST use giving estimates of 1.16 (95% CI 0.72–1.87, $n=5$) for never smokers and 1.39 (95% CI 0.95–2.02, $n=3$) for studies reporting all individuals regardless of smoking habit. The inconclusive results contrast with those for smoking where a clear association with diabetes risk has been reported in a number of large cohort studies.[47–49]

Two[44,46] of the three studies of diabetes also presented further results for glucose intolerance, but neither reported any notable relationship with either snuff use or smoking.

No effect of snuff use or smoking was seen on fasting glucose levels in three studies[9,10,45] or on glucose levels during a euglycaemic clamp in another study.[42] One study[10] reported no effect of snuff or smoking on post-load glucose levels in men, but did observe some decrease with smoking in women. The clamp study[42] reported that basal glucose utilization was reduced by smoking but unaffected by snuff use.

The evidence relating to insulin levels following fasting is unclear. Evidence of increases relating to snuff and smoking was seen in two studies.[9,45] In contrast, no increase was seen in an experimental study[42] or in either sex in another study.[10] Indeed, women who smoked had a clearly lower fasting insulin than non-users in that study, which also reported somewhat lower post-load insulin levels in male snuff users and smokers of either sex. Insulin levels during a euglycaemic clamp were unaffected by snuff use or smoking.[42]

In an experimental study[42] smoking, but not snuff use, was found to impair insulin action, mainly due to a lower peripheral glucose uptake. A cross-sectional study[44] found that, in men with impaired glucose tolerance, the odds of a low insulin response were increased in smokers and in former but not current snuff users. No such association was seen in individuals with normal glucose tolerance.

Blood pressure

In the US, nine experimental studies,[13,14,50–56] mainly of crossover design, consistently reported an acute rise in blood pressure following use of ST. They also consistently reported an acute rise in heart rate. The studies[13,14] comparing acute effects of smoking with ST found them to be similar in respect of effects on heart rate and blood pressure. An acute rise in blood pressure following ST use has also been noted in some case reports emanating from the US.[57–60] Some authors[14,60–62] have suggested that sodium or liquorice in ST may contribute to the blood pressure increase, though a direct effect of nicotine is more commonly referred to. Two studies,[55,56] in which the controls were given, as a placebo, snuffs that did not contain tobacco and were nicotine-free, observed no acute rise in blood pressure.

In Sweden, only one experimental study,[63] of crossover design, has investigated acute effects of oral snuff. Clear rises in blood pressure and heart rate were seen during rest, but not during exercise. Smoking was not investigated in this study.

A number of cross-sectional studies have been carried out comparing blood pressure in ST users and non-users. Six such studies have been conducted in the US[29,50,64–67] and nine in Sweden.[8–10,12,27,28,34,45,68] Four of the six US studies[29,50,64,65] provided evidence of an increased blood pressure in ST users. However, in two of these studies,[29,65] no age adjustment was

Table 5 Testing for interaction between effects of smoking and ST on risk of IHD or AMI based on results for five studies

Current[a] ST use in never smokers[b]		Current[a] ST use in smokers		Smoker/never smoker ratio
RR/OR No[c]	RR/OR (95% CI)	RR/OR No[c]	RR/OR(95% CI)	RR/OR (95% CI)
5	1.41 (0.61–3.28)	7	1.19 (0.60–2.37)	0.84 (0.50–1.44)
9	0.60 (0.30–1.20)	12	0.67 (0.42–1.05)	1.12 (0.76–1.64)
26	0.89 (0.62–1.29)	27	1.01 (0.66–1.55)	1.14 (0.86–1.50)
28	0.93 (0.65–1.33)	29	0.73 (0.34–1.57)	0.79 (0.57–1.09)
34	0.73 (0.35–1.50)	36	0.82 (0.56–1.20)	1.12 (0.80–1.57)
		Meta-analysis estimate		1.01 (0.87–1.18)
		Heterogeneity chisquared		4.08 on 4 d.f.

[a] Current or ever.

[b] Never or non-current.

[c] As numbered in Table 4.

Table 6 ST and diabetes in men

Country/Study	Study type (year)	Endpoint	Other tobacco	Smokeless tobacco	Cases	Association	Adjustment variables
Unites States							
Henley *et al.*[26]	Cohort (1959–1972)	Diabetes mortality[a]	Never cigar,	Chew or snuff		RR	
- CPSI			pipe, cigarettes	- Never	97	1.00	Adjusted for age, race, education,
				- Current	20	0.88 (0.53–1.47)	body mass index, exercise, alcohol, dietary fat, fruit/vegetable intake, aspirin use
Henley *et al.*[26]	Cohort (1982–2000)	Diabetes mortality[a]	Never cigar,	Chew or snuff		RR	
- CPSII			pipe, cigarettes	- Never	250	1.00	Adjusted for age, race, education,
				- Former	8	2.16 (0.95–4.91)	body mass index, exercise,
				- Current	6	1.12 (0.55–2.29)	alcohol, employment, dietary fat, fruit/vegetable intake, aspirin use
Sweden							
Persson *et al.*[44]	Cross-sectional	Prevalence of	All men[b]	Snus		OR	
- Stockholm	(1992–1994)	type II diabetes		- Never	34	1.0	Age, bodymass index, family history
				- Former	5	0.8 (0.3–2.0)	of diabetes, alcohol, physical
				- Current	13	1.5 (0.8–3.0)	activity As above
				- Current (3 + box/wk)	12	2.7 (1.3–5.5)	
			Never cigarettes	Snus		OR	
				- Never	9	1.0	
				- Current	4	3.9 (1.1–14.3)	
Eliasson *et al.*[46]	Cross-sectional (1986,	Prevalence of	Never smoked	Snus		OR	
- MONICA	1990, 1994	diabetes		- Never	29	1.00	Age, waist circumference
Northern Sweden	or 1999)			- Former	5	1.45 (0.54–3.87)	
				- Current	6	1.06 (0.43–2.64)	
	Cohort (to 1999)	Incidence of	Never smoked	Snus		OR	
		diabetes[a]		- Never	6	1.00	Age follow-up, waist circumference,
				- Former	1	1.72 (0.20–14.8)	weight gain
				- Current	0	0.00	
Hergens *et al.*[28]	Cross-sectional[c]	Prevalence of	All men	Snus		OR	
- Stockholm,	(1992–1994)	diabetes		- Never	77[d]	1.0	Age, smoking, hospital
Västernorrland				- Former	4	1.1 (0.40–3.3)	catchment area
				- Current	11	1.5 (0.76–2.9)	
Johansson *et al.*[27]	Cross-sectional	Prevalence of	All men	Snus		OR	
- National	(1988–1989)	diabetes		- Not current	43	1.0	Smoking[e]
				- Current	10	1.19 (0.61–2.33)	

[a] The analyses relate to those with no prevalent diabetes at baseline.

[b] The authors stated that the results were unaffected by adjustment for smoking.

[c] From controls in a case-control study.

[d] Numbers estimated from percentages.

[e] Numbers, ORs and 95% CI estimated from data in source paper.

carried out despite the ST users being markedly older than the non-tobacco users, and in one[64] the increase related only to men aged 18 to 25, with no results reported for older men, or for women. Only one of the nine studies in Sweden[34] reported increased blood pressure in ST users. This was the study of construction workers, noted earlier to have reported an association with cardiovascular mortality and incidence of MI.

Other CID risk factors

Eight publications from the US[29,56,66,69–73] and 11 from Sweden[6,7,9,10,12,28,34,45,68,74,75] provided information relating ST use to a range of other CID-related endpoints.

The material from the US included two case reports of Buerger's disease associated with the use of chewing tobacco,[69,70] one study which reported that smoking but not ST was associated with reduced exercise performance,[71] one study which reported an increased plasma lactate concentration and decreased stroke volume associated with ST use[73] and one study[56] which reported that snuff use was associated with an increase in mean arterial pressure and epinephrine, but not peripheral vascular resistance, muscle sympathetic nerve activity or norepinephrine. Two studies reported results relating to lipid levels. One of these studies[72] reported that risk of hypercholesterolaemia was increased in both smokers and ST users. The RR in ST users implausibly increased from 1.08 to 2.51 after adjustment for potential confounding factors. A second study[66] found no notable association of ST use with total cholesterol or HDL cholesterol levels, but did find some evidence of a reduction in HDL levels with increasing serum cotinine. One US study[29] reported a number of differences (including lower blood cholesterol and higher dietary fat intake) between exclusive ST users and those who had never used tobacco. However, these analyses, though based on a large sample, were not adjusted even for age and sex.

The studies in Sweden concerned a range of endpoints, but the results generally showed a consistent picture. Apart from two reports[34,74] of a similar increase in prevalence of Raynaud-type symptoms in both ST users and smokers, a report of an increase in triglycerides[45] in ST users that was less marked than that seen in smokers, and a report[28] that current snuff users were more likely to be overweight, the studies all showed little evidence of an adverse effect of ST use for endpoints that are virtually all associated with smoking. This conclusion applies to endpoints such as atherosclerosis,[7,45] response to exercise,[6,12] cholesterol levels,[7,9,28,45,68] triglycerides,[7,9,68] fibrinogen,[7,9,10,68] markers of platelet activity[12] and levels of antioxidant vitamins.[75] Exceptionally, one study[10] reported no effects of either ST use or smoking on cholesterol levels and triglycerides.

Discussion

This review was carried out to investigate in detail the epidemiological and clinical evidence relating CID and risk factors for CID to use of ST in Western populations. Since the use of ST, whether in the US or Sweden, involves an exposure to nicotine that is quite comparable with that from cigarette smoking, since cigarette smoking is associated with an increased risk of CID, and since nicotine has been implicated in several processes related to the disease, there is concern that the use of ST also might increase risk. Although, in view of the much lower heart disease risk in pipe smokers, such concern might not be fully justified, it was decided to review the available evidence relevant to this concern.

CID

Based on 10 epidemiological studies of mortality or disease onset (Tables 1 and 2), three conducted in the US and seven in Sweden, meta-analyses have been conducted based on the results for men, the available data for women being extremely limited. Among never smokers, the combined evidence (Table 4) gave some indication of a weak association of IHD or AMI with current ST use in never smokers, but no indication of any increase in risk in current smokers or with former ST use. The associations with stroke and with all CID among never smokers were somewhat more clearly seen.

The analyses have a number of strengths. These include quite a substantial total number of cases in the meta-analyses, availability of estimates adjusted for a wide range of relevant potential confounding variables in the majority of the studies and long-term follow-up in all the cohort studies. Limitations include variations in the definitions of exposure and of disease endpoints between study, small numbers of individuals and lack of confounder control in a few studies, the fact that five of the seven Swedish studies were conducted in the same area of Sweden and particularly the lack of good recent data from the US.

The appropriateness of carrying out meta-analysis at all deserves some comment. While recognizing that there is an active discussion about the use of meta-analysis to pool data from observational studies,[76] and that the uncertainty about the meta-analytic estimates may not be fully expressed by the conventional statistical indices, failure to combine estimates might have produced conclusions that are more uncertain than the data warrant. The meta-analyses were conducted by combining RRs from cohort studies and ORs from case-control studies. ORs somewhat overestimate RRs where, as here, the disease is not rare,[77] but the overestimation is of little practical importance for ORs in the range considered[78] (e.g. for a disease with an incidence of 10% an OR of 1.20 is equivalent to an RR of 1.18) and has been ignored.

The first meta-analysis shown in Table 4 combines results for fatal and non-fatal AMI. In theory, effects of ST may differ for the two types, but in practice only two of the studies investigated this possibility. The two counties' study[28] reported that such analysis did not change its conclusion of a lack of increased risk of AMI from ST, while though the second MONICA study[25] reported a higher OR with snuff for fatal cases (1.50, 95% CI 0.45–5.03) than it did for fatal and non-fatal cases combined (0.58, 0.35–0.94), the two estimates were not clearly heterogeneous ($\chi^2 = 2.04$ on 1 df, $P = 0.15$). More data are needed here.

Although the clearest way to evaluate possible effects of ST is to compare risks in current (and former) users who have never smoked with those who have never used tobacco, the limited data on risks of ST use in smokers or in the whole population

(with adjustment for smoking) have also been considered. Given the large effect of smoking and the scope for imprecise classification, there are inevitably uncertainties about smoking-adjusted risks, but joint use of ST and smoking is very far from uncommon and it is important to gain some insight into whether it involves unexpected risks. In fact, the data provided no evidence of an association of ST use with increased risk of IHD or AMI in current smokers or in all individuals. Although the apparent lack of effect of ST use in smokers, taken together with the evidence of a possible effect in never smokers, might at first suggest the existence of some interaction of ST and smoking on risk, in fact, formal analysis (Table 5) did not confirm this.

Evidence of an association of current ST use with risk was only apparent in three studies, the two US CPS studies for IHD, stroke and all CID and the Swedish construction workers study for IHD and all CID (Table 3). When attempting to interpret the data it is important to note that, of those seven studies which found no evidence of an increased risk of IHD or AMI associated with ST use, none reported any results for all CID and only two did so for stroke.

The overall evidence is dependent particularly on the two CPS studies, which together provide 76% of the total studied cases of IHD or AMI and 90% of those of stroke. Although these studies are large, of cohort design and adjust for quite a wide range of confounding variables, a number of their features require comment. First, the questions on ST use were asked in 1959 (CPS-I) and 1982 (CPS-II), and it is unclear how relevant the products used at that time are to the ST currently on the market. Second, the question used in CPS-I—'Do you chew tobacco or use snuff?' with answers recorded as 'Never,' 'Occasionally' or 'Regularly'—made no specific provision for former use, though those respondents who happened to volunteer such information were excluded from analysis. Third, all the multivariate-adjusted estimates shown in Table 3 were lower than the age-adjusted estimates given by Henley *et al*.[26] reflecting the generally poorer lifestyle characteristics of ST users than non-tobacco users, and bringing into question the possibility of some residual confounding. Finally, Table 5 of Henley *et al*.[26] showed, based on over 200 cases of cardiovascular disease in ST users in CPS-II, that there was no indication of a dose–response relationship with IHD, stroke or all CID, such a relationship usually being considered a prerequisite for demonstrating causality. Evidence on dose–response from other studies was extremely limited, and more information is clearly needed here.

The meta-analyses provide no clear evidence from studies in Sweden of an association of current ST use with IHD or AMI or with stroke. While there is no significant heterogeneity by country, and the evidence, particularly for stroke, is quite limited, the data are consistent with Swedish snus having little or no true effect on risk of CID. Given the ST products used in Sweden and in the US have historically been very different, there is no compelling reason to expect any effects of ST to be the same in the two countries.

Although the analyses are mainly concerned with quantifying risks for ST use in comparison with no ST use, comparisons were also made with risks associated with smoking. In both Sweden and the USA, risks for IHD/AMI, stroke and all CID were always clearly higher in relation to smoking than in relation to ST.

One of the problems in obtaining reliable evidence on the risk of CID associated with ST as currently used is the lack of recent data, particularly in the US, where the nature of the product has changed over time,[79] and the only three epidemiological studies providing information are cohort studies where the baseline information was collected 25 years or more ago (Table 1). There is a need for a substantial case-control study of CID to be conducted in the US (and perhaps also in Sweden) which would obtain detailed data on use of ST, smoking history and potential confounding factors.

Other outcomes

The approach taken here was to review the evidence qualitatively. Because of limitations in how the data were reported, useful meta-analyses could not practically be carried out.

For the risk factors associated with CIDs, which have been discussed in this report, there is little clear evidence of any effect of snuff as used in Sweden. One study reported an association with diabetes,[44] but other studies in Sweden did not (Table 6), and no effect on insulin levels or on glucose levels or uptake has been consistently reported. In Sweden, blood pressure levels have generally been found to be similar in snuff users and non-users, though one experimental study[63] reported an acute rise in blood pressure at rest from oral snuff, a finding which needs replication. Use of snuff has been repeatedly reported in Swedish studies to have no evident effect on a variety of other endpoints, including atherosclerosis, response to exercise, cholesterol levels, triglycerides and fibrinogen. However, there have been two reports of an increase in prevalence of Raynaud-type symptoms in snuff users.[34,74] While it is possible that larger and better designed studies in Sweden may detect other circulatory effects of snuff, it seems clear for many risk factors that if there is an effect it is less than that of smoking.

As used in the US, ST does have effects on risk factors relevant to CID. The most commonly reported is an acute rise of blood pressure and heart rate, seen in many experimental studies. There may also be a chronic effect on blood pressure, though some of the cross-sectional studies reporting an increase suffer from evident weaknesses. Whether cross-sectional studies can be regarded as providing evidence on chronic effects, as suggested by Westman,[62] seems dubious, because while people are unlikely to be using ST while their blood pressure is being taken, it seems eminently possible that, unless instructions have been given to the contrary, some people may have been using it very recently, when its acute effects are still occurring. While four of the nine cross-sectional studies conducted in Sweden appear to have attempted to avoid acute effects, by insisting on abstention from tobacco overnight,[9] for at least 8 h,[8] for an hour[10] or in the waiting room[34], none of the six US studies reported that it did so. No notable effect on diabetes mortality was seen in the CPS-I and CPS-II studies.[26] There are also two case reports of Buerger's disease associated with the use of chewing tobacco[69,70] and isolated reports of a variety of endpoints relative to CID. As for mortality or disease onset, the findings for ST as used in the US are more

suggestive of a possible effect on the circulatory system than is the case for the findings for snuff as used in Sweden.

Conclusion

The overall evidence on use of snuff taken from a substantial number of studies in Sweden does not demonstrate any increase in the risk of CID, any chronic effect on blood pressure or any increased risk of a range of other risk factors relevant to CID. More evidence is needed to confirm whether Swedish oral snuff causes an acute rise in blood pressure. It may increase risk of Raynaud-type symptoms.

The evidence of a possible effect of ST as used in the US is more compelling. Two large cohort studies have reported finding evidence of an increased risk of IHD and stroke, with the increase substantially less than seen in smokers. However, these studies have limitations and were conducted many years ago, and more up-to-date evidence is needed. An acute effect of ST on blood pressure and heart rate is well documented, but a chronic effect has not been clearly shown. The evidence on circulatory risk factors is difficult to generalize, but shows more associations with ST than seen in the Swedish studies.

Risk of CID associated with ST use is clearly substantially less than that associated with smoking and it has in fact not been clearly demonstrated that Swedish oral snuff is associated with any adverse effect at all in either non-smokers or smokers. However, the number of studies available is still limited and more evidence is needed.

Although smokers who wish to reduce their risk of CID would clearly do best to reduce their risk of CID by giving up smoking, many find great difficulty in doing so and may find that switching to ST is easier. The evidence suggests strongly that switching would indeed substantially reduce their risk, though studies which compared risks of those who switched and those who continued to smoke would be needed to confirm this.

CID is clearly only one of the possible consequences of ST use, and reliable data are needed on a variety of other endpoints before any overall judgement can be made as to its health effects in non-smokers and the benefits of switching to smokers.

[Subsequent to our searches, the INTERHEART case-control study of tobacco use and risk of AMI conducted in 52 countries reported that chewing tobacco alone was associated with an OR of 2.23 (1.41–3.52), but numbers of snuff users were too small to draw conclusions. However, since the majority of ST users in this study were from South Asia, with no separate results reported for Western populations, these findings do not affect our conclusions.]

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Conflicts of interest: None declared.

KEY MESSAGES

- ST use has risen in Sweden and the US, and knowledge of its possible effects on circulatory disease is important.
- The available evidence, much published recently, is reviewed.
- No clear risk from Swedish snuff is evident for heart disease and stroke or for CID risk factors such as diabetes and blood pressure.
- In the US, ST is associated with some increase in risk of CID but this conclusion mainly derives from two large studies conducted many years ago.
- Although data remain limited, it is clear that any increases in risk are substantially less than that from smoking.

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