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# APPENDIX 2

## CARDIOVASCULAR DISEASE AND SMOKELESS TOBACCO

## A REVIEW OF THE EVIDENCE

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EXECUTIVE SUMMARY

This review was carried out to investigate in detail the epidemiological and clinical evidence relating cardiovascular disease and risk factors for it to smokeless tobacco use.

It is clear that the use of smokeless tobacco, whether as typically used in the USA or Sweden, involves an exposure to nicotine that is quite comparable to that from cigarette smoking. Since cigarette smoking is associated with an increased risk of cardiovascular disease and since nicotine has been implicated in several processes related to the disease, there is some concern that the use of smokeless tobacco also might increase risk. Although, in view of the lack of increased 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.

Four epidemiological studies have been conducted. These include two case-control studies of myocardial infarction (MI) in Northern Sweden, one prospective study of Swedish construction workers and one prospective study of a representative sample of the US population. All involve moderately large numbers of cases of cardiovascular disease and, though all have some potential limitations, they all provide some useful information. Endpoints considered vary from study to study, and include all MI, fatal MI and mortality from ischaemic heart disease (IHD), stroke, all cardiovascular disease and all circulatory disease, and the results predominantly relate to men.

As expected, the evidence of an increased risk in smokers (compared to non-users of tobacco) is generally clear. The evidence of an increased risk in smokeless tobacco users is much less compelling. The two studies in Northern Sweden and the US study show no significant increase in risk, and it is only the study of Swedish construction workers where a significant increase is seen, which even then is less than that seen in smokers. Combining estimates of the relative risk (RR) of smokeless tobacco users compared to non-tobacco users for MI from the two case-control studies and for IHD from the two prospective studies by random-effects meta-analysis gives an estimate of 1.09 (95% confidence interval = CI 0.80-1.49) for the sexes combined which is not significant. Similarly combining estimates for fatal MI from one of the

Swedish case-control studies with those for all cardiovascular disease death from the Swedish construction workers study and for all circulatory disease death from the US prospective study gives an estimate of 1.30 (CI 0.95-1.77) for the sexes combined. These two estimates are little changed if attention is restricted to males (1.04, CI 0.73-1.49 and 1.33, CI 0.91-1.95 respectively).

Combining estimates of the relative risk of smokers to smokeless tobacco users (here only available for males), in contrast, shows significant results, with RRs of 2.14 (CI 1.31-3.49) for MI/CHD and of 1.51 (CI 1.09-2.09) for fatal MI/cardiovascular disease/circulatory disease.

Overall the epidemiological data do not demonstrate the existence of an association between smokeless tobacco use and risk of cardiovascular disease. If some increase in risk does exist, and this cannot be ruled out with the relatively limited data, it will clearly be weaker than that with smoking.

Evidence has also been reviewed relating to the association of smokeless tobacco use with hypertension and other risk factors for cardiovascular disease. Here the conclusions to be drawn seem quite different for US smokeless tobacco and for Swedish snuff.

For US smokeless tobacco the evidence consists of a number of case reports suggesting an acute effect of smokeless tobacco on blood pressure, a number of experimental studies which generally found an acute rise in blood pressure and/or in heart rate, a number of cross-sectional studies, all but one of which report an increased blood pressure in smokeless tobacco users, two case reports of Buerger's disease associated with smokeless tobacco and single reports of reduced exercise performance, increased tachycardiac response to exercise and increased hypercholesterolaemia in smokeless tobacco users.

Though some of the cross-sectional studies fail to distinguish possible acute and chronic effects of smokeless tobacco, there certainly seems to be adequate evidence of an effect of US smokeless tobacco on the cardiovascular system. Some of the evidence allows comparison of effects in smokers and in smokeless tobacco

users, with some studies on blood pressure and on cholesterol levels suggesting the possibility that effects might be greater in smokeless tobacco users. However, the evidence here is inconclusive.

Limited data from studies in India also suggest an effect of smokeless tobacco on cardiovascular variables.

For Swedish snuff (snus) the evidence of any effect on cardiovascular risk factors is very limited. Most cross-sectional studies found no real suggestion of an increased blood pressure in snuff users, and although one found that smokeless tobacco users showed clear increases in both blood pressure and a disability diagnosis of hypertension, this was the same study of construction workers which unusually found an association with cardiovascular mortality. Similarly, although there are two reports of an increase in Raynaud-like symptoms in smokeless tobacco users, the evidence generally shows little or no association with cardiovascular risk factors, including levels of fibrinogen, cholesterol and other lipids or antioxidant vitamins, sonographic evidence of atherosclerosis, markers of platelet activity, and response to exercise.

While one would certainly like to have an explanation of the unusual results from the study of Swedish construction workers, the overall data in relation to Swedish snuff provides little evidence that it has any effect at all on risk of cardiovascular disease or on factors that are generally associated with an increased risk. Even if it does have some effects, they are likely to be substantially less than those from smoking.

While the one US study of cardiovascular mortality did not find an increased risk in smokeless tobacco users, there is clear evidence of an effect on blood pressure and possibly also other endpoints related to vascular disease.

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# 1. Introduction

## 1.1 Usage of smokeless tobacco

Smokeless tobacco is mainly used orally, and nasal use has become rare.[1] 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.

Chewing usually involves placing a plug of tobacco in the gingival buccal area, where it is held or chewed. Many users chew tobacco for many hours in a day.

Snuff is usually described as moist or dry.[1] Moist snuff is mainly used in the USA and Scandinavia. In Sweden it is generally placed under the upper lip, while in Denmark the lower lip is preferred, and in the USA it is generally kept in the gingival buccal area.[2] Dry snuff is placed in the oral cavity or administered through the nasal passage.

In the United States, smokeless tobacco has formed an important part of total tobacco consumption for many years. Available data[3] show that chewing tobacco and snuff represented 11.2% of all tobacco products by weight in 1950, 6.5% in 1965, 9.6% in 1980 and 12.1% in 1995. For many years sales of chewing tobacco were two or three times that of snuff, but since the early 1980s sales of snuff have risen sharply so that, by 1995, sales of chewing tobacco and snuff were about equal[3] (see table below). However it should be noted that "there has been a reclassification of products within the two major categories [of smokeless tobacco], and some types of fine-cut smokeless tobacco that were classified as 'chewing tobacco' prior to 1981 are now categorized as 'moist/fine-cut snuff'".[1]

| Annual sales in tonnes | 1920 | 1950 | 1960 | 1970 | 1975 | 1980 | 1985 | 1990 | 1995 |
|---|---|---|---|---|---|---|---|---|---|
| Chewing tobacco | NA | 38960 | 28940 | 30930 | 36560 | 48040 | 38560 | 32070 | 28210 |
| Snuff | 16370 | 18140 | 15740 | 12110 | 11430 | 10840 | 22040 | 23270 | 26940 |
| All tobacco | 298640 | 511990 | 588190 | 612290 | 634653 | 612037 | 569865 | 494054 | 454542 |

In the great majority of the other 30 economically developed countries considered by Forey *et al*[3] smokeless tobacco forms only an unimportant part of the tobacco market. The most notable exception is Sweden where, though sales of chewing tobacco are negligible, snuff has always formed a large proportion of total sales of tobacco (70% in 1920, 31% in 1950, 19% in 1965, 29% in 1980 and 45% in 1995). As in the USA, the use of snuff has increased sharply in recent decades. In Canada, Iceland and Norway smokeless tobacco forms a few percent of the market, but in the other economically developed countries sales (if any) are very low.

Smokeless tobacco is also widely used in parts of Central and South-East Asia.[1] Tobacco may be used alone or in combination with other products, such as betel nut quid, ash, slaked lime, areca nut and even snail shells. In India there are various forms, called khaini, mishri, zarda and kiwan, in which the tobacco is prepared in different ways. Nass is common in Central Asia, with prevalence rates of up to 20% in some countries. Nass is usually made with local tobacco, ash and cotton or sesame oil, but the composition varies regionally, as in India.[2]

More details of variations over time and country in the extent of tobacco chewing and snuff taking, and of the various types of chew used and snuff taken can be found in IARC Monograph 37 on tobacco habits other than smoking.[1]

## 1.2 Uptake of nicotine from smokeless tobacco

Although there have been many studies of nicotine absorption from cigarettes, fewer studies have investigated nicotine absorption from smokeless tobacco. The boost in blood nicotine from a pinch of Swedish moist snuff and from a pinch of dry nasal snuff have both been found to be similar to that from smoking a cigarette.[4,5] Peak blood nicotine levels have also been found to be similar in cigarette smokers and in smokeless tobacco users in Sweden,[4] the UK[5] and in the USA.[6-8] One experimental study in the USA reported that total absorption of nicotine was greater from smokeless tobacco than from cigarettes.[6] In Sweden, plasma cotinine levels have generally been found to be about 40% higher in smokeless tobacco users than in smokers.[4,9-13] However another study in Sweden found urinary cotinine levels to be about 20% lower in smokeless tobacco users.[14] In the USA, a study of baseball players[15] found relatively low cotinine levels in those who used snuff or chewing tobacco, but this may reflect intermittent use when playing baseball.[16]

Overall, the evidence is abundantly clear that the use of snuff and chewing tobacco involved an exposure to nicotine that is fairly equivalent to that from cigarette smoking. Since nicotine has been implicated in several processes related to cardiovascular disease,[17] the possibility that smokeless tobacco, like cigarette smoking, might result in an increased risk therefore deserves consideration. In this context, however, it should be noted that pipe smoking, which results in nicotine exposure similar to that from cigarette smoking, is not associated with an increase in heart disease risk, an observation that Froggatt and Wald[18] considered "on the fact of it dismisses chronic exposure to nicotine as a significant cardiovascular hazard."

1.3 Types of evidence relevant to cardiovascular disease and smokeless tobacco

The most important evidence relating cardiovascular disease to smokeless tobacco use comes from epidemiological studies where the endpoint is mortality from an appropriate cause of death grouping (such as ischaemic heart disease, stroke, or all circulatory disease) or onset of myocardial infarction (MI), with comparisons made of non-tobacco users, smokeless tobacco users and smokers. Cross-sectional studies where the endpoint is a symptom, such as angina or intermittent claudication, known to be a predictor of increased mortality from cardiovascular disease also provide some useful information. Such data are considered in section 3 of this report.

In view of the known relationship of hypertension to heart disease risk, evidence on blood pressure is also of some importance. Such evidence may come from case reports, from experimental studies, or from cross-sectional studies, and is considered in section 4 of this report, along with evidence on possible effects of smokeless tobacco use on heart rate.

Other relevant evidence, considered in section 5, relates to blood chemistry measurements known to be predictors of heart disease (such as cholesterol, fibrinogen and indices of platelet function), ultrasonagraphic measurements of atherosclerosis, cardiovascular response to exercise, body mass index and Buerger's disease.

## 1.4 Previous reviews of the evidence relating cardiovascular disease to smokeless tobacco use

Resolution 57, adopted at the 1984 Interim Meeting of the House of Delegates, requested that the American Medical Association (AMA) review the health effects of smokeless tobacco. Following a meeting in December 1985, a council report was prepared in 1986.[19] While the abstract concluded that "... studies suggest that snuff and chewing tobacco also may affect ... the cardiovascular system ..." the only relevant evidence cited, other than that it increased plasma nicotine, was one study[20] that reported an increase in heart rate and blood pressure associated with the use of snuff.

In January 1986, the National Cancer Institute, the National Institute of Dental Research and the National Institutes of Health Office of Medical Applications of Research convened a consensus development conference on Health Applications of Smokeless Tobacco Use. The report on this conference[21] noted that "blood levels of nicotine achieved by cigarette smoking, which are similar to those achieved by smokeless tobacco use, cause elevations of blood pressure, heart rate, certain blood lipid levels, and catecholamine values," but asserted that "no direct epidemiological data are available on cardiovascular morbidity and mortality in association with smokeless tobacco use."

In their report on "The Health Consequences of Using Smokeless Tobacco" in 1986,[22] the Advisory Committee to the Surgeon General discussed possible cardiovascular effects. The only actual evidence related to smokeless tobacco that was mentioned was a study in dogs which found that single doses of smokeless tobacco can produce effects on heart rate, blood pressure, myocardial contractility and blood flow similar to those of cigarette smoking,[20] a study in young men suggesting higher blood pressure in users of smokeless tobacco than in cigarette smokers or nonsmokers[23] and a case report of a patient with a phaeochromocytoma who developed paroxysmal hypertension and angina pectoris following the use of snuff.[24] The discussion also referred to the fact that the user of smokeless tobacco is systematically exposed to significant amounts of nicotine, and mentioned a number of pieces

of evidence that they considered suggested that nicotine may contribute to coronary and peripheral vascular disease. No mention was made, however, of the important observation that pipe smokers, who have high intakes of nicotine, do not have a materially increased risk of ischaemic heart disease. The Advisory Committee did, however, note that it "has not been proven" that "nicotine causes human disease *de novo*."

In a review article published in 1986 warning against the "reemergence of smokeless tobacco" Connolly *et al*[25] noted that blood pressure elevation in users of smokeless tobacco may arise because of the sodium or nicotine content of the product. An analysis of six brands of snuff was noted to yield an average of 845 mg sodium per 34 grams of tobacco.[26] Two small studies were cited as demonstrating an acute increase in blood pressure in smokeless tobacco users.[23,27] The authors noted that "whether smokeless tobacco could contribute to sustained hypertension is unknown."

In 1987, Ricer[28] commented on an "alarming" increase in smokeless tobacco use in the USA. He noted that "several" studies have shown that acute use raises heart rate and blood pressure, though the reference he cited was to only one study[29]. He considered that "the long-term effects on blood pressure and other cardiovascular functions have yet to be determined, but the potential for profound effects (e.g. acceleration of processes such as coronary artery disease, peripheral vascular disease, hypertension, renal failure, deep venous thrombosis) is strong."

In the introduction to their 1992 paper, Huhtasaari *et al*[30] note that "although smokeless tobacco has been implicated in the pathogenesis of circulatory disorders, including coronary artery disease, the evidence is mostly circumstantial," citing two references as support. One is the 1986 US Surgeon-General's report referred to above,[22] the other a 1988 report of a WHO study group on "smokeless tobacco control."[31] I have been unable to obtain this report from the British Library.

In his review published in 1994 proposing that smokeless tobacco be "recommended as a cigarette substitute by persons who cannot stop smoking," Rodu[32] stated that cardiovascular disease risks are "reduced in smokeless tobacco users compared with cigarette smokers." However, this was based only on results from a single epidemiological study by Huhtasaari *et al.*[30]

In 1995, Westman[33] reviewed the literature to answer the question "does smokeless tobacco cause hypertension?". From 12 pertinent articles, he found that "smokeless tobacco caused a clinically significant acute elevation of systolic blood pressure, diastolic blood pressure, or pulse in 5 of 6 experimental trials ... and was weakly associated with chronic hypertension in 4 of 6 cross-sectional studies." He concluded that "smokeless tobacco use should be considered a potential cause of sodium retention and poor blood pressure control because of its nicotine, sodium, and licorice content."

In a review on smokeless tobacco published in 1996, Pershagen[2] noted that the available evidence on the effects of smokeless tobacco on hypertension or hypercholesterolaemia was inconsistent, as were results from the only two epidemiological studies on risk of cardiovascular disease, conducted in Sweden by Huhtasaari *et al*[30] and by Bolinder *et al.*[34] Pershagen noted that effects on the cardiovascular system are potentially of great public health importance and that further studies were "urgently needed" to clarify the "limited and inconclusive" evidence so far available.

In a quite detailed review paper published in 1997, Winn[35] of the US National Institutes of Health noted that "because of the pharmacological properties of nicotine and other constituents of smokeless tobacco, there is also concern that smokeless tobacco products may lead to cardiovascular diseases as well [as to oral cancer]." However, Winn considered that "the relatively few human populations to date conflict with respect to whether smokeless tobacco use elevates cardiovascular risk factors or leads to cardiovascular disease or death from cardiovascular causes."

Ahlbom *et al*,[36] in a report on health risks associated with Swedish snuff (snus) presented to a symposium arranged by the Swedish National Board of Health and Welfare in 1996 and published in 1997, included a section on cardiovascular diseases. They considered that the data suggested long-term snuff dipping had no tangible effects on the dominant risk factors for cardiovascular disease, though the findings were somewhat ambiguous as regards raised blood pressure. They also considered that the results of the only two epidemiological studies on risk of cardiovascular disease in snuff dippers[30,34] were somewhat contradictory.

In another review published in 1997, considering whether smokeless tobacco was "a less harmful alternative?", Bolinder[37] included sections on acute cardiovascular effects, long-term use of smokeless tobacco and cardiovascular disease, and metabolic risk factors for cardiovascular disease. The summary of evidence considered that smokeless tobacco did not seem to have effects on atherosclerosis in the same way as smoking, though it may produce a more pronounced tendency to develop hypertension. Effects of smokeless tobacco on coronary blood flow, myocardial infarction and myocardial excitability were considered to be largely unknown. Effects on physical performance, regularly found in smokers, were not seen in users of smokeless tobacco. As regards the long-term clinical consequences, Bolinder stated that "even if smokeless tobacco use might have less negative health effects than smoking, potential long-term adverse effects cannot yet be dismissed."

In 1997, Benowitz[16] reviewed the evidence relating to the "systemic absorption and effects of nicotine from smokeless tobacco." He noted that "Systemic absorption and levels of nicotine are similar in users of smokeless tobacco and smokers of cigarettes" and considered that "Health hazards caused by cigarette smoking and suspected to be related to chronic nicotine exposure are expected to be a hazard of habitual smokeless tobacco use." Noting that "There are conflicting epidemiological data on snuff use and the occurrence of cardiovascular disease," he considered that "the nature and magnitude of the cardiovascular hazards remains to be elucidated." He also

pointed out that "Sodium absorption from smokeless tobacco is substantial and could contribute to blood pressure elevation and/or aggravation of cardiac failure and other sodium-retaining conditions."

In 1998 Nilsson[38] published "a qualitative and quantitative risk assessment of snuff dipping." He noted that, though it was reasonable to implicate nicotine in the increased risk of Buerger's disease and the decreased risk of ulcerative colitis in smokers (and therefore to expect an effect on these diseases to be seen in snuff dippers), for cardiovascular disease it was difficult to distinguish the effects of nicotine from the complex actions of tobacco smoke. He included a detailed assessment of the study by Bolinder *et al* in Sweden[10,34,39] which implicated snuff dipping as a risk factor for cardiovascular disease and criticised it for inadequate medical follow-up and for incomplete control of confounding. He regarded the evidence for a causal link between the use of Swedish snuff and increased risk for cardiovascular disease as "insufficient."

In a review of "the adverse health effects of tobacco and tobacco-related products," Mitchell *et al*[40] noted in 1999 that "smokeless tobacco generally contains a higher concentration of nicotine relative to cigarettes" and that because of this "all the systemic effects of nicotine mentioned above," which included elevated LDL and lowered HDL, elevated triglycerides, accelerated atherosclerosis, thrombosis (platelet aggregation) and increased cardiovascular mortality, "can occur with smokeless tobacco use." As regards cardiovascular mortality, the review was selective in referring only to the criticized study by Bolinder *et al*,[34] with no mention of the Huhtasaari *et al* study[30] finding no such effect.

In a brief review of the "oral effects of smokeless tobacco" published in 2000, Walsh and Epstein[41] noted merely that "systemic effects include ... transient increases in blood pressure and cardiovascular disease." The review was again selective in only citing the Bolinder *et al* study,[34] when considering cardiovascular disease. The review was written by dentists and concentrated mainly on oral leukoplakia, oral cancer and periodontal disease.

Nyren,[42] in a presentation at the European Respiratory Society's annual meeting in Berlin in 2001, summarized data relating smokeless tobacco use to cardiovascular disease outcomes, indices of atherosclerosis, physical performance, blood pressure, lipid profile and other cardiovascular risk factors. He concluded that "although it appears that smokeless tobacco use affects traditional cardiovascular risk factors only marginally, and less severely than smoking, and notwithstanding that snuff use seems to leave cardiovascular morphology and function intact, a moderately increased risk for cardiovascular death cannot be excluded. A possibility that should be entertained is that the incidence of myocardial infarction is not increased, but that the case fatality is higher among snuff users who sustain this disease."

Asplund, in an editorial published in 2001 entitled "Snuff – how dangerous is it? The controversy continues"[43] devoted a section to snuff and cardiovascular disease. He concluded that "there is now evidence that snuff (i) does not adversely influence known mediators of atherosclerosis the way smoking does, (ii) has little, if any, effect as promoter of atherosclerosis and (iii) does not increase the risk of myocardial infarction." However, Asplund noted that "(iv) the question whether or not snuff is arythmogenic and thus enhances the risk of sudden death is not yet settled." He also stated that "it is evident that the use of snuff involves much lower risks of cardiovascular disease ... than cigarette smoking does."

It can be seen that the more recent reviews are not completely consistent in their interpretation, with Swedish reviewers tending to have somewhat different views from those of US reviewers. Thus, while the conclusions of the Swedish reviewers Ahlbom *et al*,[36] Bolinder,[37] Nilsson,[38] Nyrén[42] and Asplund[43] all consider (albeit with varying degrees of certainty) that smokeless tobacco has less cardiovascular effect than smoking, the US reviewers Benowitz,[16] and Winn[35] consider the question unresolved, while Mitchell *et al*[40] seem to suggest that cardiovascular effects from smokeless tobacco use are likely to be at least as great as those from smoking.

## 1.5 Objectives of this review

The objective of this review is to investigate in detail the epidemiological and clinical evidence relating cardiovascular disease and risk factors for it to smokeless tobacco use.

## 2. Methods

Relevant papers were obtained from a MEDLINE search using the MESH terms "Tobacco, smokeless" and "cardiovascular disease." Further relevant papers were sought from the reference lists of papers already obtained.

Where appropriate, relative risks and 95% confidence intervals (CIs) have been calculated using standard methods.[44,45]

Fixed- and random-effects meta-analysis have been carried out to obtain a combined estimate of relative risk from a set of independent estimates, as described by Fleiss and Gross.[46] Fixed-effects meta-analysis assumes a common underlying relative risk estimate and only takes into account within-study variability in calculating the combined relative risk estimate and its CI. Random-effects meta-analysis also takes into account between-study variability. Where there is no evidence of heterogeneity between the sets of estimates, the two analyses give the same results.

## 3. Summary of evidence relating smokeless tobacco use to cardiovascular mortality or incidence of myocardial infarction

### 3.1 Introduction

Four studies, three in Sweden and one in the United States, have investigated the relationship between smokeless tobacco use and cardiovascular mortality or incidence of myocardial infarction. Two of these are case-control studies, and two are prospective studies. These are described and discussed in detail in the sections that follow, after which conclusions are drawn from the combined evidence.

## 3.2 STUDY 1 – Huhtasaari 1992 case-control study

In 1988, Huhtasaari *et al*[47] reported the results of a cardiovascular risk factor survey conducted in 1985 in Norrbotten and Västerbotten, the two northernmost counties of Northern Sweden. They found that 22% of men used snuff (though very few women did) and commented that "this is one of the few areas where it would be possible to explore the interactions between snuff and CVD."

Four years later Huhtasaari *et al*[30] reported the results of a case-control study conducted in these two provinces. Between April 1989 and April 1991, 629 occurrences of first myocardial infarction (MI) in men aged 35-64 were identified from a variety of medical records using the standardized procedures of the well known WHO MONICA project,[48] and attempts were made to obtain information on tobacco consumption, by direct interview for survivors, and by a questionnaire sent to family members or "significant others" for those who had died. Information on tobacco consumption was available for 585 men, who became the cases in the study. In 1990 a population survey (using the same questionnaire as used for the decedents) was conducted in the same area, and 589 men aged 35-64 with no history of MI and with data available on tobacco habits became the controls in the study.

The main analyses classified cases and controls into three groups of men who did not smoke cigars, cigarillos or a pipe:

A. Non-tobacco users (including ex smokers and ex snuff users).
B. Current regular snuff dippers (at least once daily) who did not smoke cigarettes,
C. Current regular smokers (of at least one cigarette/day) who did not use snuff.

It can be seen that those men who used both cigarettes and snuff were excluded. Analyses compared the age-adjusted risk of MI in each pair of groups. As shown below, no differences were seen between the snuff dippers (group B) and the non-users (group A) but the smokers (group C) had higher risks than either of the other groups, particularly in younger men.

| Comparison | Relative risk (95% CI) Age 35-54 | 55-64 | All subjects[a] |
|---|---|---|---|
| C v A (smokers v non users) | 3.11 (2.09-4.63) | 1.35 (0.87-2.10) | 1.87 (1.40-2.48) |
| B v A (snuff dippers v non users) | 0.96 (0.56-1.67) | 1.24 (0.67-2.30) | 0.89 (0.62-1.29) |
| C v B (smokers v snuff dippers) | 3.22 (1.82-5.70) | 1.09 (0.55-2.16) | 2.09 (1.39-3.15) |

[a] Note that the all subjects analyses are unadjusted for age

The authors also reported results of a multiple regression analysis, in which adjustment was also made for education. This confirmed the association of MI with cigarette smoking but not snuff dipping.

Compared to non-users, the risk of MI was noted to be increased in smokers of more than 10 cigarettes a day, but not in smokers of 1-10 a day, snuff users of less than two cans daily, or in snuff users of two or more cans daily.

Former smokers who did not take snuff had a much increased risk of MI (RR = 4.50, 95% CI = 2.72-7.47) compared to former snuff users who did not smoke.

In the control group, cholesterol levels, blood pressure and prevalence of diabetes were noted to be similar in cigarette smokers and snuff dippers (but no such comparisons were made with non-users).

The authors concluded that "in middle aged men snuff dipping is associated with a lower risk of myocardial infarction than cigarette smoking," though they noted that "a considerably larger study than ours would be needed to finally rule out any detrimental effects of snuff dipping on the risk of developing ischaemic heart disease and myocardial infarction."

Although the study involves a reasonably large number of cases of MI, and both cases and controls are likely to be quite representative of the study area, in view of the fairly high response rates (93% of cases and 81% of controls), there are some concerns about the comparability of data collection

for the cases and controls. The fact that all data in controls were obtained by a questionnaire completed by the subject, but data in cases were either obtained by interview of the subject or by a questionnaire completed by a surrogate, means that like is not being compared with like. The authors do not consider this issue at all, neither reporting the proportion of cases for which a surrogate response was obtained nor testing whether relative risk estimates varied according to whether the case data were obtained from the subject or a surrogate. The surrogate may not have been fully aware of the subject's history of tobacco use.

There is also some concern about the adequacy of the analysis in relation to past tobacco use or joint snuff and cigarette use. A table is presented giving a relatively detailed breakdown of cases and controls by present and past tobacco and snuff use, but the categories overlap and mutually exclusive categories cannot be obtained. It would have been useful to have given the joint distribution of the cases and controls by current/former/never snuff use and by current/former/never cigarette use and to have estimated the relative risks of:

(a) current/never and former/never snuff use in an analysis adjusting (using stratification methods) for current/former/never cigarette use and for age, and

(b) current/never and former/never cigarette use in an analysis adjusting for current/former/never snuff use and for age.

Although there are some limitations in the design and analysis of this study, its results do not suggest an adverse effect of Swedish snuff use on the risk of myocardial infarction.

3.3 STUDY 2 - Bolinder 1994 prospective study

In 1992, Bolinder *et al*[39] reported results from a cross-sectional study of 97586 male Swedish construction workers who underwent health examinations in 1971-74. Each subject was examined by a nurse, completed a questionnaire concerning *inter alia* tobacco use, symptoms and disorders, and had blood pressure, pulse, height and weight measured. Information about sick-leave frequency and disability pension diagnoses was also obtained. Comparisons, adjusted for age, were made between three groups, 23885 who had never used any type of tobacco, 5014 who used smokeless tobacco daily and had never smoked, and 8823 who smoked 15+ cigarettes per day and had never regularly used smokeless tobacco.

Of the symptoms reported in the questionnaire, three related to the vascular system: "Chest pain walking up hill," "Pain in the leg while walking" and "White finger symptoms." Compared to the non-users of tobacco, the odds ratios of each were significantly increased in smokeless tobacco users, being respectively 1.2 (CI 1.1-1.4), 1.3 (CI 1.1-1.5) and 1.4 (CI 1.3-1.6). However, these odds ratios were in each case lower than those associated with smoking 15+ cigs/day, respectively 1.8 (CI 1.7-2.1), 2.1 (CI 1.8-2.4) and 1.6 (CI 1.5-1.8).

Of the disability pension diagnoses, two were of relevance to this section. In smokeless tobacco users, odds ratios were non-significantly increased for cardiovascular diagnoses at age 46-55 (OR = 1.6, CI = 0.7-3.5), and significantly increased for cardiovascular diagnosis at age 56-65 (OR = 1.5, CI = 1.1-1.9). In smokers increases were also seen in these two categories (OR = 2.2, CI = 1.3-3.9 and OR = 1.3, CI = 0.9-1.9).

Evidence was also presented (see section 4 for further details) that smokeless tobacco use was associated with an increased risk of a disability pension diagnosis of hypertension and of having measured blood pressure, and the authors concluded that "these findings indicate that an increased cardiovascular risk is associated with the use of smokeless tobacco."

Two years later, in 1994, Bolinder *et al*[34] presented results of mortality follow up to 1985 of those members of their study population who were alive in 1974. Subjects were divided into six groups, non users of tobacco (n = 32546), smokeless tobacco users who never smoked (n = 6297) and cigarette smokers who had never used pipes, cigars or smokeless tobacco divided into current smokers of <15 and 15+ cigarettes/day (n = 14983 and 13516 respectively) and ex-smokers who had given up for 1-5 or 5+ years (n = 6761 and 9800 respectively). Age- and region-adjusted relative risks (CIs) are shown in the table below for various disease categories and age groups:

| Age at entry | Non users | Ex smokers for >5 years | Ex smokers for 1-5 years | Smokeless tobacco | Cigarette smokers <15 | Cigarette smokers 15+ |
|---|---|---|---|---|---|---|
| | Ischaemic heart disease[a] | | | | | |
| 35-54 | 1.0 | 1.2 (0.9-1.6) | 1.4 (1.0-2.1) | 2.0 (1.4-2.9) | 2.6 (2.1-3.4) | 3.3 (2.6-4.2) |
| 55-65 | 1.0 | 1.1 (0.9-1.2) | 1.3 (1.1-1.6) | 1.2 (1.0-1.5) | 1.7 (1.4-1.9) | 1.4 (1.2-1.8) |
| | Stroke[b] | | | | | |
| 35-54 | 1.0 | 0.7 (0.2-1.9) | 1.2 (0.4-3.7) | 1.9 (0.6-5.7) | 2.7 (1.4-5.4) | 3.0 (1.5-5.7) |
| 55-65 | 1.0 | 0.8 (0.5-1.2) | 1.5 (0.9-2.5) | 1.2 (0.7-1.8) | 0.7 (0.4-1.2) | 1.6 (1.0-2.5) |
| | All cardiovascular disease[c] | | | | | |
| 35-54 | 1.0 | 1.1 (0.9-1.5) | 1.4 (1.0-2.0) | 2.1 (1.5-2.9) | 2.7 (2.2-3.4) | 3.2 (2.6-3.9) |
| 55-65 | 1.0 | 1.0 (0.9-1.2) | 1.3 (1.1-1.6) | 1.1 (1.0-1.4) | 1.5 (1.3-1.7) | 1.5 (1.3-1.7) |
| Total | 1.0 | 1.1 (0.9-1.2) | 1.4 (1.1-1.6) | 1.4 (1.2-1.6) | 1.8 (1.6-2.0) | 1.9 (1.7-2.2) |

[a] Based on 552 deaths for age (at entry) 35-54 and 1180 for age 55-65
[b] Based on 65 deaths for age (at entry) 35-54 and 195 for age 55-65
[c] Based on 690 deaths for age (at entry) 35-54 and 1530 for age 55-65

The results for cigarette smoking for ischaemic heart disease and all cardiovascular disease show a pattern evident in many epidemiological studies, with an increased risk in cigarette smokers, more evident at younger ages, with no marked dose-response, a smaller risk in short-term ex-smokers and no real increase in longer term ex-smokers. In both age groups, the increase associated with smokeless tobacco use is less than that seen with current smoking and is more clearly seen in the younger age group. The authors note that "when potential confounding due to age, area of domicile, body mass index, blood pressure, diabetes, and history of heart symptoms or blood pressure medication at the time of entering the study was analysed according to the Mantel-Haenszel procedure, the relative risks of death from cardiovascular diseases remained essentially unchanged."

The results for stroke in the table above are based on far fewer deaths than for ischaemic heart disease and though evidence of an increased risk is seen in current cigarette smokers, particularly of age 35-54, there is no clear evidence of an association with smokeless tobacco use.

It is also of relevance that the authors found no increase in lung cancer risk in smokeless tobacco users but a very large increase in smokers, particularly current smokers of 15+ cigarettes/day, as this result was considered by them to argue against the possibility of serious misclassification of cigarette smokers as smokeless tobacco users.

Some results from the 1992 and 1994 papers by Bolinder *et al*[34,39] are also presented in a paper in a Swedish journal in 1997.[49]

Possible limitations of this study have been discussed by Nilsson.[38] One is the possibility of selection bias due to 25% of the registered workers not turning up for the initial medical examination (which was voluntary) and so not having entered the study. Certainly attendance may depend both on health status and on smoking habits. Another is possible inadequate control for confounding. It would certainly also have been preferable to present some results in the paper that were adjusted for more than age and area of residence, and also to consider additional variables. For example, the type of job carried out, which may relate both to tobacco use and to risk of heart disease, was not considered, though data seemed to be available.

The authors themselves also discuss other possibilities of bias, such as might be caused by failure to take into account change in tobacco use habits over the follow-up period (e.g. some smokeless tobacco users may have taken up smoking).

In a letter commenting on the paper by Bolinder *et al*,[34] Rodu and Cole[50] compared mortality in the construction workers with that of the general population. For cardiovascular diseases, all other causes and overall mortality, they estimated the standardized mortality ratio (SMR) for non-users

of tobacco were respectively 49, 49 and 49, while for users of smokeless tobacco they were 116, 97 and 104. They argued that this was a more appropriate comparison than Bolinder *et al*[34] had used, and that the results expressed in this way suggested merely that the non-users were a particularly health conscious group and that smokeless tobacco did not actually have an adverse effect.

In reply, Bolinder and Alfredsson saw no valid argument for this suggestion to use the general population as a comparison group, pointing out that many occupational groups have lower mortality than the general population due to the "healthy worker effect." Why was the expected reduction in risk not observed among the smokeless tobacco users? Does this not suggest an effect of smokeless tobacco use?

The original approach used by Bolinder *et al*[34] seems preferable to the alternative proposed by Rodu and Cole.[50] Furthermore, none of the possibilities of bias raised by Nilsson[38] or by the authors of the study provide any clear explanation of the increased risk of heart disease seen in the smokeless tobacco users. While the analyses relate to a specific occupational group and to a period (1971-85) some time ago, they do suggest an increased cardiovascular risk in smokeless tobacco users, though less than in smokers.

3.4 STUDY 3 – Huhtasaari 1999 case-control study

In 1999, in the Journal of the American College of Cardiology, Huhtasaari *et al*[51] reported the results of a further case-control study conducted in the same two northernmost provinces of Sweden as their 1992 study.[30] Between May 1991 and December 1993, 879 occurrences of first fatal or non-fatal MI were identified in men aged 25-64 using, as in their 1992 study,[30] the MONICA methodology.[48] Again, information on tobacco consumption (and other variables) was sought by direct interview in hospital for survivors and by a questionnaire sent to family members for those who had died. The procedure used for selecting controls differed from that in the 1992 study.[30] The controls were men without MI, selected from population registers, individually matched to the cases on age and county of residence, with information on smoking (and other variables) being obtained by a telephone interview for controls matched to living cases and by a questionnaire (the same as sent to family members) for controls matched to dead cases. In the end responses adequate for analysis were received for 687 case-control pairs, 117 of these relating to fatal MI (dying within 28 days).

In unadjusted analysis, risks of first MI were increased, relative to those who never used tobacco, in current smokers with no snuff use (RR = 3.65, CI = 2.67-4.99) and in current smokers and snuff users (RR = 2.66, CI = 1.24-5.71). They were not materially or significantly increased in other groups including current snuff users who did not currently smoke (RR = 0.96, CI = 0.65-1.41, based on 59 cases and 90 controls) and in former snuff users who did not currently smoke (RR = 1.23, CI = 0.54-2.82, based on 11 cases and 13 controls).

Additional, conditional logistic regression, analyses were conducted to take into account matching variables and other risk factors for MI. In the analyses of cigarette smoking, snuff dippers were excluded, and the association was confirmed, both for all MI (RR = 3.53, CI = 2.48-5.08) and for fatal MI (RR = 8.57, CI = 2.48-30.3). In the analyses of effects of snuff dipping, cigarette smokers were excluded, and the results showed that risk of all MI was significantly lower than that of never tobacco users (RR = 0.58,

CI = 0.35-0.94). For fatal MI the RR estimate was higher, 1.50, but had wide CI (0.45-5.03) due to small numbers of subjects. The multivariate analyses of snuff use adjusted for potential confounding effects of hypertension, diabetes, cholesterol, a family history of early cardiac death, education and marital status. Adjustment for variables which might be affected by snuff use, such as hypertension, could be regarded as over adjustment. However the authors noted that snuff use was not associated with MI if adjustment was made only for social variables, though the relative risk was not presented.

The study is clearly an important one, as it provides data on a relatively large and representative data set. Response rates (77% of cases were studied) were fairly high and seem unlikely to have affected the conclusion materially, while the method of obtaining information from controls seems an improvement on their earlier study.[30] However elements of non-comparability remain between the methods used for cases and controls. Thus, living cases were interviewed in hospital while controls of living cases were interviewed by telephone, and questionnaires for dead cases were answered by family members, while questionnaires for their matched control, though the same, were answered by the control subject himself. While this may engender some bias, it is difficult to imagine it could explain why a very clear effect of cigarette smoking, but not snuff use was shown. Another limitation was that the analyses concerned the question "do you use snuff at present?" with no analyses relating to amount or duration of use or to the type of snuff. Given the main finding was of a somewhat lower risk of MI in snuff users, it seems unlikely that a subgroup of snuff users with very heavy exposure could have had a substantially increased risk of MI.

The authors conclude "the risk of MI is not increased in snuff dippers. Nicotine is probably not an important contributor to ischaemic heart disease in smokers. A possible small or modest detrimental effect of snuff dipping on the risk for sudden death could not be excluded in this study due to a limited number of fatal cases." In an editorial on the three following pages of the journal Benowitz *et al*[52] noted that "nicotine is always less hazardous than using tobacco" and considered that "The Huhtasaari study and others ...

support … the safety of using nicotine for smoking cessation, even in patients with active cardiovascular disease."

The study appears to be quite a good one, suggesting strongly that the risk of cardiovascular disease in Swedish snuff users is much less than that in smokers and probably no greater than in non users of tobacco.

3.5 STUDY 4 – Accortt 2002 prospective study

In 2002 Accortt *et al*[53] described the results of 20-year mortality follow-up of subjects who took part in the First National Health and Nutrition Examination Survey (NHANES1) conducted in the US in 1971 to 1975. As data on smokeless tobacco use were only collected in a random sample of NHANES1, information on smokeless tobacco obtained during the NHANES1 Epidemiologic Followup Study (NHEFS) conducted in 1982-84 was also used to classify subjects. For the purposes of analysis, 6805 White or Black subjects aged 45-75 at baseline were divided into four groups, based on smokeless tobacco use (ever/never) and cigarette smoking (ever/never) into four groups; no tobacco (n = 2986), exclusive smokeless tobacco use (n = 414), exclusive smoking (n = 2751) and both smokeless tobacco use and smoking (n = 654). Analyses compared the smoking groups in respect of mortality up to 1992 (by which time almost a third of subjects had died) from major causes, with relative risk estimates adjusted for age, race, an index of poverty and in some analyses also for alcohol, exercise, fruit/vegetable intake, systolic blood pressure, serum cholesterol and body mass index.

Preliminary analyses compared the four groups according to baseline characteristics (see Table below). Subjects in the exclusive smokeless tobacco use group showed a number of major differences compared to the no tobacco use group or the exclusive smoking group. Thus, exclusive smokeless tobacco users were more likely to be Black, live in the South, be poorer, eat less fruit and vegetables, have lower blood cholesterol, vitamin A and vitamin C intake and higher blood pressure and body mass index than either of the other two groups, while they were more often male and had higher dietary fat intake than the no tobacco use group and had lower alcohol consumption and lower dietary fat intake than the exclusive smoking group.

| Characteristic | No tobacco | Exclusive smokeless tobacco use | Exclusive smoking | Both |
|---|---|---|---|---|
| Males (%) | 24.2 | 56.0 | 55.7 | 92.7 |
| Blacks (%) | 8.0 | 33.4 | 7.0 | 9.3 |
| Poverty index ratio (mean)[a] | 2.4 | 1.8 | 2.5 | 2.0 |
| Residence in South (%) | 21.7 | 50.9 | 23.0 | 38.6 |
| Drinks alcohol (%) | 58.5 | 57.8 | 80.9 | 74.1 |
| Fruit and veg (%)[b] | 94.2 | 71.8 | 91.6 | 84.5 |
| Blood cholesterol (mg/dl) (mean) | 237.8 | 228.7 | 235.1 | 226.9 |
| Systolic blood pressure (mm Hg)(mean) | 142.3 | 147.8 | 136.6 | 139.2 |
| Body mass index ($kg/m^2$)(mean) | 26.8 | 27.5 | 25.5 | 25.7 |
| Vitamin A intake (IU)(mean) | 5699.9 | 5203.5 | 5620.2 | 4376.3 |
| Vitamin C intake (mg)(mean) | 94.4 | 76.1 | 88.5 | 77.3 |
| Dietary fat intake (g)(mean) | 62.4 | 72.1 | 77.6 | 84.6 |

[a] Low values indicate greater poverty
[b] At least one serving a day

After adjustment for age, race and poverty index, exclusive smokeless tobacco users, compared to non-tobacco users, had no significant increased risk of death from diseases of the circulatory system in either males (RR = 1.0, 95% CI = 0.7-1.5) or females (RR = 1.2, 95% CI 0.7-1.9).

After adjustment for the longer list of potential confounding variables, smokeless tobacco users, again compared to non-tobacco users, had no significant increased risk of death from ischaemic heart disease (IHD) or stroke, regardless of sex or whether the subject smoked.

| Sex | Smoking habits | Adjusted RR (95% CI) for smokeless tobacco use | |
|---|---|---|---|
| | | IHD[a] | Stroke[b] |
| Males : | never smokers | 0.6 (0.3-1.2) | 0.7 (0.2-2.0) |
| : | ever smokers | 1.0 (0.6-1.7) | 0.7 (0.3-1.5) |
| Females : | never smokers | 1.4 (0.8-2.2) | 1.0 (0.3-2.9) |
| : | ever smokers | 1.1 (0.4-3.2) | 1.7 (0.4-7.0) |

[a] Adjusted for age, race, poverty index, alcohol, exercise, fruit/vegetable intake, systolic blood pressure, serum cholesterol and body mass index.
[b] Adjusted for same factors as above except serum cholesterol and body mass index.

Further analyses in males confirmed the lack of increased risk of IHD (relative to non-tobacco users) in those who were both smokeless tobacco users and smokers, regardless of whether they were current smokers (RR =

0.8, 95% CI 0.5-1.3) or former smokers (RR = 1.1, 95% CI 0.6-2.1), but did demonstrate a significantly increased risk in exclusive smokers (RR = 1.5, 95% CI 1.1-2.1), particularly in current smokers (RR = 2.0, 95% CI 1.4-2.8).

The results from this study do not suggest that exclusive smokeless tobacco use is associated with an increased risk of circulatory disease, including IHD and stroke. Nor do they show any increased risk of IHD or stroke in those who both use smokeless tobacco and smoke cigarettes.

The study has the advantage of being of prospective design and having taken a large number of relevant confounding variables into account, but does have some limitations. These include:

(i) A relatively small number of deaths among smokeless tobacco users, so that many of the CIs given are quite wide. [Note that this conclusion is drawn from the width of the CIs as numbers of deaths were not actually given];

(ii) Lack of data on amount of smokeless tobacco used or whether smokeless tobacco use is current or in the past;

(iii) No distinction between chewing tobacco and snuff;

(iv) Reliance, for a follow-up period starting in 1971-75, on smokeless tobacco data that is often only reported in 1982-84 sometimes by proxy respondents answering for those who had died; and

(v) No confirmation of tobacco use by biological markers such as cotinine.

Notwithstanding these limitations, the study certainly does not indicate any hazard from smokeless tobacco as regards cardiovascular disease.

3.6 Summary of the evidence relating to mortality or incidence of MI

The overall data came from four epidemiological studies, two case-control studies of MI in males conducted in Northern Sweden[30,51], one prospective study of male Swedish construction workers[34] and one prospective study of a representative sample of the non-institutionalized male and female US population[53]. All have some limitations, as discussed in the preceding sections, but none of the studies seem so weak as to deserve exclusion from consideration or so strong as to deserve particular weighting when evaluating the combined evidence. It seems appropriate to carry out some meta-analyses to determine what the overall evidence tells us.

Table 1 summarizes the relevant data, comparing the three groups of major interest, (A) non-users of tobacco, (B) users of smokeless tobacco only and (C) smokers only. Results are shown for the relative risk of B to A, C to A and C to B, this final estimate being derived, where necessary, from the material presented by applying the method of Fry *et al*[45]. Note that the definitions of the three groups vary somewhat from study to study:

Huhtasaari 1992[30]

A. Never used tobacco

B. Current snuff, no current smoking - unclear if past smoking included

C. Current smoking, no current snuff - unclear if past smoking included.

Bolinder 1994[34]

A. Never used tobacco

B. Current snuff, never tobacco

C. Current cigarettes, never snuff

Huhtasaari 1999[51]

A. Never used tobacco

B. Current snuff, no current smoking

C. Current smoking, no current snuff

Accortt 2002[53]

A. Never used smokeless tobacco or smoked cigarettes

B. Ever used smokeless tobacco, never cigarettes

C. Ever cigarettes, never smokeless tobacco

(Note that pipe and cigar smoking were ignored in this study, and that information collected on smokeless tobacco related to current use in NHANES1 and to ever use in NHEFS.)

As indicated in Table 1, the relative risks also vary in the extent to which they have adjusted for factors other than age.

Despite these variations, it still seems useful to consider combined estimates based on these data.

**Smokeless tobacco use as compared no tobacco use**

There are 17 estimates in the table, not all independent as they overlap in respect of age (e.g. result 3 is the combination of results 1 and 2) and disease (e.g. results 4 and 5 are both subsets of result 6). Of the 17 estimates, ten are greater than 1.0 (two significantly and two marginally significantly at $p<0.05$, all in the Bolinder 1994[34] study), two are equal to 1.0 and five are less than 1.0 (one significantly). The general impression is of some heterogeneity, with only the Bolinder 1994[34] study providing evidence of a higher risk of smokeless tobacco users.

Table 2 provides the results of varying meta-analyses of these data, all based on independent estimates, and the choice of studies included depending on disease definition, sex or age. For disease, results are shown for three endpoints (i) MI or IHD, (ii) Stroke and (iii) Fatal MI, all cardiovascular disease (CVD) or all circulatory disease (CID), the final definition including the maximum number of fatal occurrences for which data are available. For sex, results are shown for males or for both sexes, very limited data being available for females. For age, most analyses are based on results for all ages for which data are available, while some are restricted to age groups 35-54 or 55-64.

The table presents results of both fixed-effects and random-effects meta-analyses, as well as providing information on between-study heterogeneity. With one exception, MI/IHD results for men aged 35-54 where the RR estimate is 1.60 (95% CI 1.18-2.16), all the fixed effects meta-analyses give a relative risk estimate of about 1.2, and many are statistically significant at $p<0.05$. However, statistical significance is only present when there is significant heterogeneity between estimates. There, random-effects estimates are arguably more appropriate, and though relative risk estimates remain elevated, they are never significant. The most relevant results are probably all ages both sexes random-effects estimates for MI/IHD, where the RR is 1.09 (CI 0.80-1.49), and for All CVD/All CID/Fatal MI, where it is 1.30 (CI 0.95-1.77).

Even ignoring the presence of potential biases present in the studies, it is evident that an increased risk of cardiovascular disease in smokeless tobacco users has not been established. The results suggest, but do not prove, the existence of a modest association.

**Smoking as compared to no tobacco use**

Of the 12 estimates in Table 1, all for males, all are greater than 1.0 and six are greater than 2.0, with 10 statistically significant at $p<0.05$. It is clear that the data demonstrate a marked increase in risk associated with smoking. Inasmuch as the association is clear and merely confirms what is known from numerous other studies, there seems no point in carrying out meta-analyses of these data.

**Smoking as compared to smokeless tobacco use**

Of the 12 estimates in Table 1, all for males, 11 are greater than 1.0 and nine are statistically significant. Table 3 presents the results of varied meta-analyses (not as extensive as in Table 2 as there are no results for females). With the exception of the results for stroke, which are based on limited data, all the estimates show a higher risk in smokers which is generally statistically significant. The overall data, both for MI/IHD and for All

CVD/All CID/Fatal MI, are heterogeneous and provide random-effects estimates that are significantly ($p<0.05$) increased, at 2.14 (CI 1.31-3.49) and 1.51 (CI 1.09-2.09), respectively. The first of these two estimates is based on data from all four of the studies considered.

Overall, the data clearly show that the risks of MI /IHD in smokeless tobacco users are lower than those in smokers, with the relative risk estimated (by inverting the estimate in Table 2) equal to 0.47 (0.29-0.76).

TABLE 1 Relative risks comparing (A) non-users of tobacco, (B) users of smokeless tobacco only and (C) smokers only

| Result set | Study: Sex | Age | Disease | Relative risk (95% CI): B : A | C : A[a] | D : B |
|---|---|---|---|---|---|---|
| | Huhtasaari 1992[30] | | | | | |
| 1 | M | 35-54 | MI | 0.96 (0.56-1.67) | 3.11 (2.09-4.63) | 3.22 (1.82-5.70) |
| 2 | M | 55-64 | MI | 1.24 (0.67-2.30) | 1.35 (0.87-2.10) | 1.09 (0.55-2.16) |
| 3 | M | 35-64 | MI | 0.89 (0.62-1.29) (Unadjusted) | 1.87 (1.40-2.48) | 2.09 (1.39-3.15) |
| | Bolinder 1994[34] | | | | | |
| 4 | M | 35-54 | IHD | 2.0 (1.4-2.9) | 2.91 (2.36-3.59) | 1.46 (1.03-2.05) |
| 5 | M | 35-54 | Stroke | 1.9 (0.6-5.7) | 2.85 (1.58-5.13) | 1.50 (0.52-4.33) |
| 6 | M | 35-54 | All CVD[2] | 2.1 (1.5-2.9) | 2.96 (2.47-3.56) | 1.41 (1.04-1.93) |
| 7 | M | 55-65 | IHD | 1.2 (1.0-1.5) | 1.59 (1.39-1.83) | 1.33 (1.08-1.63) |
| 8 | M | 55-65 | Stroke | 1.2 (0.7-1.8) | 1.07 (0.72-1.59) | 0.89 (0.54-1.48) |
| 9 | M | 55-65 | All CVD[2] | 1.1 (1.0-1.4) (Adjusted for age and region) | 1.50 (1.34-1.68) | 1.36 (1.16-1.61) |
| | Huhtasaari 1999[51] | | | | | |
| 10 | M | 35-64 | MI | 0.58 (0.35-0.94) | 3.53 (2.48-5.03) | 6.09 (3.66-10.13) |
| 11 | M | 35-64 | Fatal MI | 1.50 (0.45-5.03) (Adjusted for age and country of residence as matching factors and for hypertension, diabetes, cholesterol, family history of early death from MI, education and marital status) | 8.57 (2.48-30.3) | 5.71 (1.64-19.95) |
| | Accort 2002[53] | | | | | |
| 12 | M | 45+ | IHD | 0.6 (0.3-1.2) | 1.5 (1.1-2.1) | 2.50 (1.27-4.93) |
| 13 | M | 45+ | Stroke | 0.7 (0.2-2.0) | - | - |
| 14 | M | 45+ | All CID[d] | 1.0 (0.7-1.5) | - | - |
| 15 | F | 45+ | IHD | 1.4 (0.8-2.2) | - | - |
| 16 | F | 45+ | Stroke | 1.0 (0.3-2.9) | - | - |
| 17 | F | 45+ | All CID[d] | 1.2 (0.7-1.9) (All analyses adjusted for age, race and poverty index; stroke and IHD analyses also adjusted for alcohol, exercise, fruit/vegetable intake, systolic blood pressure; IHD analyses also adjusted for serum cholesterol and body mass index) | - | - |

[a] For Bolinder 1994[34] estimates for smoking <15 and 15+ cigs/day were combined using the method of Fry and Lee[45]

[b] For Bolinder 1994[34], Huhtasaari 1999[51] and Accord 2002[53] estimates of C:B were obtained from estimates of B:A and C:A using the method of Fry and Lee[45]

[c] CVD = cardiovascular disease

[d] CID = circulatory disease

TABLE 2 Meta-analyses of relative risks relating to smokeless tobacco use as compared to non-use of tobacco

| Disease | Sex | Age | Results included | Relative risk (95% CI) Fixed effects | Random effects | Heterogeneity Chisq (DF) | p |
|---|---|---|---|---|---|---|---|
| MI/IHD | M | All | 1,2,4,7,10,12 | 1.17 (1.00-1.36) | 1.04 (0.73-1.49) | 20.24 (5) | 0.001 |
| | M+F | All | 1,2,4,7,10,12,15 | 1.18 (1.03-1.37) | 1.09 (0.80-1.49) | 20.70 (6) | 0.002 |
| | M | 35-54 | 1,4 | 1.60 (1.18-2.16) | 1.43 (0.70-2.92) | 4.80 (1) | 0.03 |
| | M | 55-64 | 2,7 | 1.20 (0.99-1.46) | 1.20 (0.99-1.46) | 0.01 (1) | >0.1 |
| Stroke | M | All | 5,8,13 | 1.19 (0.79-1.79) | 1.19 (0.79-1.79) | 1.48 (2) | >0.1 |
| | M+F | All | 5,8,13,16 | 1.17 (0.80-1.71) | 1.17 (0.80-1.71) | 1.56 (3) | >0.1 |
| All CVD,[a] All CID or fatal MI | M | All | 6,9,11,14 | 1.22 (1.06-1.40) | 1.33 (0.91-1.95) | 13.04 (3) | 0.005 |
| | M+F | All | 6,9,11,14,17 | 1.22 (1.07-1.40) | 1.30 (0.95-1.77) | 13.05 (4) | 0.01 |

[a] CVD = cardiovascular disease, CRD = circulatory disease.

TABLE 3 Meta-analyses of relative risks relating to smoking as compared to smokeless tobacco use (in males)

| Disease | Age | Results included | Relative risk Fixed effects | Random effects | Heterogeneity Chisq (DF) | p |
|---|---|---|---|---|---|---|
| MI/IHD | All | 1,2,4,7,10,12 | 1.69 (1.45-1.97) | 2.14 (1.31-3.49) | 38.02 (5) | <0.001 |
| | 35-54 | 1,4 | 1.80 (1.34-2.42) | 2.10 (0.97-4.54) | 5.41 (1) | 0.02 |
| | 55-64 | 2,7 | 1.31 (1.07-1.59) | 1.31 (1.07-1.59) | 0.30 (1) | >0.1 |
| Stroke | All | 5,8 | 0.98 (0.62-1.54) | 0.98 (0.62-1.54) | 0.76 (1) | >0.1 |
| All CVD,[a] All CID, or fatal MI | All | 6,9,11 | 1.40 (1.21-1.61) | 1.51 (1.09-2.09) | 4.99 (2) | 0.08 |

[a] CVD = cardiovascular disease, CRD = circulatory disease.

## 4. Summary of evidence relating smokeless tobacco use to hypertension

### 4.1 Case reports

In 1980, Blackley and Knochel[54] reported the case of an 85 year old man who chewed tobacco containing 8.3 per cent (wt/wt) licorice paste and had the classical features of exogenous mineralocorticoid excess: hypokalemia, hypertension, renal potassium wasting, metabolic alkalosis, sodium retention and depressed renin. Natural licorice contains glycyrrhizinic acid, a compound with well-documented mineralocorticoid activity, and the symptoms resolved rapidly on withdrawal of the tobacco and reappeared on resumption of it.

In 1984, McPhaul *et al*[24] described the case of a 69 year old woman with an adrenal phaeochromocytoma in which snuff dipping rapidly provoked paroxysmal hypertension that induced myocardial ischaemia, relieved by an $\alpha$-adrenergic antagonist. After resection of the tumour, she continued to dip snuff and remained totally asymptomatic. The authors note that "cigarette smoking is known to induce paroxysmal hypertension in patients with pheochromocytoma, presumably by nicotine's stimulation of epinephrine release from the adrenal medulla."

In 1986, in a letter to Anaesthesiology, Wells *et al*[55] described the case of an obese 49 year old women admitted for a hysterectomy. Prior to surgery her blood pressure had been consistently reported as about 140/80 mm.Hg but on arrival in the operating room it rose to 210/115 mm.Hg, despite an apparent lack of anxiety or apprehension. It was then discovered that the patient had a large mass of snuff between the cheek and gum and when this was removed her blood pressure returned to 150/85 mm.Hg over the next 15 minutes. The authors attribute the increase to the nicotine in snuff, but offer no explanation as to why her blood pressure had been consistently lower earlier when it seems quite likely she would then have been using snuff.

In 1987, in a letter to Pediatrics, Adelman[56] described the case of a 16-year-old boy with a one-year history of severe hypertension, who gave a history of heavy chewing tobacco use since the age of 9. In hospital, his blood

pressure was noted to be significantly higher when chewing than when not chewing tobacco, and became normal and his symptoms (headaches, shortness of breach and chest pain) disappeared when chewing was stopped.

While the elevation in blood pressure in the study by Wells *et al*[55] cannot clearly be concluded to be a consequence of smokeless tobacco, the other three case histories seem to show quite strong evidence that the hypertension arose because of its use. Such limited data do not, however, exclude the possibility that the hypertension was a rare reaction, perhaps related to some unusual characteristic of the subject (e.g. presence of disease, allergic sensitivity or specific gene), and do not allow inferences to be drawn for the population at large. Note that all four of the case reports emanated from the USA.

4.2 Experimental studies

In 1960, Simon and Iglauer[27] summarized the results of three experimental studies in which the acute effects of smoking cigarettes, chewing tobacco or smoking pipes and cigars on cardiac output (as measured by the ballistocardiogram), pulse, blood pressure and skin temperatures were measured. The individual studies had been reported on earlier[57-59].

In 17 young men (mean age 27.2) who habitually smoked, no significant changes in cardiac output were seen after smoking low-nicotine filtered or regular cigarettes, and no significant change in pulse rate was seen following the smoking of low-nicotine cigarettes. However the pulse rate was significantly ($p<0.01$) increased following the smoking of regular cigarettes and a drop in skin temperature was seen following smoking of both types of cigarette. Results for blood pressure in the smokers were not reported.

In the 24 habitual users of chewing tobacco (mean age 51.1), the chewing of standard commercial tobacco produced changes in cardiac output in 23. While no rise in pulse rate was seen following chewing placebo gum, pulse increased by 6.5 beats/min on average after chewing low-nicotine tobacco and by 13.4 beats/min after chewing commercial tobacco. After chewing commercial tobacco, a rise in blood pressure was seen in all subjects tested, the mean rise being 17.9 mm.Hg systolic and 11.8 mm.Hg diastolic. In one subject where a 15/15 mm.Hg rise was seen, no rise after chewing the placebo gum was seen. Changes in skin temperature were similar to those seen with smoking. [Results for pipes and cigars are not summarized here.]

In 1977, Bordia *et al*[60] described the results of an experimental study conducted in India involving subjects who were all in the habit of both smoking and chewing tobacco. 15 were coronary artery disease patients and 10 were normal controls. At each of three attendances, each subject first abstained for 24 hours from use of tobacco, then had blood taken and pulse, blood pressure and ECG recorded and then either smoked two cigarettes, smoked two biris (often referred to as bidis) or chewed tobacco, followed by a further collection of blood and monitoring of pulse, blood pressure and

ECG. Following smoking cigarettes or biris or following tobacco chewing, there was a significant increase in the pulse rate and blood pressure, more markedly on the coronary artery disease patients than on the normal patients. From the results presented, the increases and also the duration of the increases following tobacco use appear to be somewhat higher following biri smoking than following either cigarette smoking or tobacco chewing. However, although the authors present results of significance tests of the rises themselves and of the differences between the two groups of patients, they do not test the significance of the differences between tobacco types or present the data in a way that allows this to be estimated.

The authors also presented results of a study in which patients with mild hypertension who were habituated to tobacco chewing were persuaded to discontinue tobacco for 5 to 7 days. Blood pressure tended to decline during the period of abstinence, though not in all patients, and then go up again on restarting chewing (see also section 5 for further results from this study).

In 1984, Squires *et al*[20] described the results of a study on 20 healthy non-smoking male athlete volunteers conducted in Texas, ten of whom used oral tobacco and ten of whom did not. After a pre-test period of 5 minutes, 2.5 g of snuff was placed in each man's mouth and then removed 20 minutes later. During the pre-test period, the experimental period and a 5 minute post-test period, heart rate and blood pressure were measured every minute. Between the pre-test and the experimental period, mean heart rate increased from 69 to 89.3 beats per minute ($p<0.05$), while mean blood pressure values rose from 118/72 to 129/79 mm.Hg ($p<0.05$). Both heart rate and blood pressure reduced somewhat, to 84.6 beats per minute and 126/76 mm.Hg after the tobacco was removed. Changes occurring during the experiment were similar for men who normally used oral tobacco and those who did not. Squires *et al*[20] also described a similar study in 10 anaesthetized dogs where significant increases in heart rate and blood pressure were also seen.

In 1984, Glover *et al*[61] described the results of studies in Oklahoma of the acute effects of smokeless tobacco on the motor performance of college

age males. Each study involved ten subjects administered a specific perceptual motor task - a Reaction Time/Movement Time task, a Pursuit Rotor Task or a Pegboard test. Following a five minute pre-test period, five of the ten subjects ingested a pinch of smokeless tobacco in the manner and quantity to which he was accustomed, and the motor performance tests were then repeated over a 25 minute period. "No substantive difference" was noted between the five subjects given smokeless tobacco and the five control subjects in any of the motor performance tasks, but smokeless tobacco was noted to lead to haemodynamic changes including increased heart rate and blood pressure which were apparent within 3 to 5 minutes. No significance tests of these changes were reported.

In 1986, Ksir *et al*[62] described the results of an experimental study conducted in Wyoming, USA on five college baseball players who regularly chewed moist snuff. Each subject attended for two days having not eaten, drunk or chewed tobacco beforehand in the morning. On the tobacco day, the subject inserted snuff in his mouth at the start of the procedure, and on the non-tobacco day he did not. Blood pressure and heart rate were measured in the resting state, then after three four-minute periods on a bicycle ergometer with progressively increasing resistance, and then during a recovery period. When chewing tobacco, there was a significantly higher resting heart rate ($p<0.01$) and resting systolic blood pressure ($p<0.05$) but no change in resting diastolic blood pressure. Heart rate and systolic blood pressure (but not diastolic blood pressure) increased during exercise, but remained higher on tobacco than on non-tobacco days. Following exercise, heart rate recovered more slowly on tobacco days for four of the five subjects, but there was no difference between tobacco and non-tobacco days in the decline in systolic blood pressure.

In an abstract in 1986, Gapter and Noble[63] described an experimental study involving 24 male athletes in two body weight strata. In each stratum, half of the athletes chewed tobacco and half did not. The athletes sat for 15 minutes, rode a bicycle ergometer for 15 minutes at three intensities and recovered for 15 minutes. The subjects who chewed showed significantly

higher systolic blood pressure during and after exercise and lower perceived exertion than those who did not, regardless of body weight. Results for diastolic blood pressure were not presented.

In 1987, Edwards *et al*[64] described the results of two studies carried out in Oklahoma. One was the study previously reported by Glover *et al*[61] (*vide supra*). The other was a study involving groups of 30 male athletes, and 30 male non-athletes, each group consisting of 20 smokeless tobacco users and 10 non users of tobacco. The non users were the control subjects, the tobacco users being randomly assigned to appear for testing under one of two conditions – normal use of tobacco (i.e. without abstaining from usual tobacco use before testing), and having abstained from tobacco use for 12 hours before testing. Each of the six groups of ten subjects (athletes/non athletes x non use/regular use/temporary abstinence) rested for 15 minutes during which demographic information was obtained, the heart rate monitoring equipment was attached and the testing procedures explained. They then underwent 50 30 second trials on a Reaction/Movement Timer test, after 10 of which each smokeless tobacco user placed one pouch of tobacco in his mouth and kept it there for the remaining 40. Although reaction times were significantly ($p<0.05$) faster for athletes than non-athletes, neuromuscular performance was not significantly enhanced as a result of smokeless tobacco use. Heart rates were lower in athletes than non-athletes ($p<0.01$). The use of smokeless tobacco results in a significant ($p<0.01$) elevation in heart rate, the effects becoming apparent after the first five minutes in both the tobacco-using groups. Blood pressure seems not to have been determined.

In 1988, Benowitz *et al*[6] reported the results of a nicotine absorption study in 10 healthy men who were habitual cigarette smokers and had prior experience of oral snuff and chewing tobacco. In the study subjects were studied under four conditions; (i) smoking their usual brand of cigarettes, at one puff every 45 seconds for 9 minutes, resulting in smoking on average one and a third cigarettes, (ii) holding 2.5 gm of oral snuff between the lip and the gum for 30 minutes, (iii) chewing tobacco, in a dose selected by the subject, for 30 minutes and (iv) chewing two pieces of nicotine gum for 30 minutes.

No significant differences between cigarettes, snuff or chewing tobacco were seen in systolic or diastolic blood pressure or in heart rate, whether maximal increases from baseline or the area under the curve up to two hours were considered. The area measures tended to be greater for the two smokeless tobacco conditions.

In 1989, Benowitz *et al*[7] described the results of a crossover study in San Francisco of 8 healthy men who regularly smoked cigarettes and had previous experience with the use of both oral snuff and chewing tobacco. Subjects were studied over four 3- or 4-day blocks during which they used oral snuff, chewing tobacco, or cigarettes *ad libitum* or abstained from all tobacco. Concentrations of nicotine and cotinine, cardiovascular effects and urine sodium, catecholamine and mutagenicity were measured over the 24 hours at the end of each treatment block. Nicotine and cotinine concentrations were similar while smoking or using snuff or chewing tobacco. Heart rate was increased while using tobacco at all times of day except 0700 hours compared with abstinence, but no significant difference was noted between the three types of tobacco. Blood pressure was similar during cigarette smoking and smokeless tobacco use and tended to be higher than during abstinence, although not significantly so. No significant difference was seen between cigarette smoking and smokeless tobacco use as regards urinary catecholamine excretion or urinary mutagenicity. Sodium excretion was significantly ($p<0.05$) higher (and potassium excretion tended to be higher) using smokeless tobacco than smoking cigarettes. The increase in sodium excretion, reported the year before in a letter to the New England Journal of Medicine[65], was believed to be due to absorption of sodium from the smokeless tobacco. The authors note that "sodium may be added to smokeless tobacco both for flavor and as part of an alkaline buffer to facilitate buccal absorption of nicotine."

In a crossover study in Texas reported in 1992 and described in more detail in section 5, Van Duser and Raven[66] compared the effects of oral smokeless tobacco and placebo on the cardiorespiratory response to exercise. Heart rate was increased at rest as a result of the smokeless tobacco (82 vs 64

bpm, $p<0.001$), but the difference from the placebo decreased at 60% maximal exercise (164 vs 153 bpm, $p<0.05$) and became non significant at 85% maximal exercise (177 vs 171 bpm).

Of the ten experimental studies summarized,[6,7,20,27,60-64,66], five of which were of crossover design[6,7,60,62,66], none were conducted in Sweden. All those studies that provided relevant data reported an acute rise in blood pressure following use of smokeless tobacco, and all reported an acute rise in heart rate. The three studies[6,7,60] that compared the acute effects of smoking and of smokeless tobacco found them to be quite similar in respect of effects on heart rate and blood pressure. Some of the studies refer to the possibility that sodium or liquorice in the smokeless tobacco may contribute to the effects on blood pressure, but information was not available from the material reviewed as to whether they are present in Swedish snuff.

Although it seems clear enough that smokeless tobacco (at least as used in the US) has an acute effect on blood pressure and heart rate, and although smoking is associated with the same acute effects and with an increased risk of cardiovascular disease, it does not necessarily follow that use of smokeless tobacco will necessarily have the same effect on risk of cardiovascular disease. The acute effects have been linked to nicotine and, as noted earlier, pipe smokers have high nicotine exposure but not the increased risk of cigarette smokers.[67]

4.3 Cross-sectional studies

In a study of male college students in Texas, reported in an abstract in 1982[68], 22 tobacco chewers had mean systolic and diastolic blood pressure respectively, 9 and 4 mm.Hg higher than 69 non chewers of tobacco ($p<0.01$). (As cited by Friedman *et al*[69], the source reference being so far unobtainable.)

In 1985, in a letter to the New England Journal of Medicine, Schroeder and Chen[23] reported results of a study of 710 male and 923 female subjects aged 18 years or older. Among men aged 18 to 25, the mean blood pressure of the 19 current smokeless tobacco users was 143.7/80.7 mm.Hg as compared with 127.7/70.0 for the 23 cigarette smokers and 131.6/72.8 for the non users. The mean difference in diastolic blood pressure between smokeless tobacco users and non users, 7.9 mm.Hg, was noted to be significant ($p\leq0.01$). Since results were only reported for men aged 18 to 25 and not for older men, or for women, the statistical significance cited may be misleading due to "data-dredging."

In another letter in the same issue of the Journal, Hampson[26] presented data from 16 brands of smokeless tobacco showing a mean sodium level of 1.76 per cent by weight, comparable in magnitude to foods such as dill pickles (1.43 per cent sodium) and cured, fried bacon (1.09 per cent sodium), which are "traditionally considered extremely high in sodium." The article did not actually refer to the known effects of salt on blood pressure, but noted that smokeless tobacco products "may pose a potential threat to patients who must restrict their sodium intake."

According to Eliasson *et al*,[12] smokers and snuff users have been shown by Benowitz *et al*[7] to have increased rates of urinary excretion of catecholamines, which might explain an increased blood pressure due to sympathetic stimulation.

Westman and Guthrie,[70] in a study conducted in Kentucky reported in 1990, compared the blood pressure of 27 men who did not use smokeless tobacco, 25 who chewed up to one pouch of tobacco per day, 7 who chewed

more than one pouch per day and 15 who used snuff. The most relevant findings are summarized below as means (SDs).

| | Non users | Chewers ≤1 pouch/day | Chewers >1 pouch/day | Snuff users |
|---|---|---|---|---|
| N | 27 | 25 | 7 | 15 |
| Systolic blood pressure (mmHg) | 124.2 (13.5) | 122.9 (10.9) | 139.3 (25.1) | 125 (9.8) |
| Diastolic blood pressure (mmHg) | 74.0 (13.6) | 79.3 (9.0) | 83.1 (16.1) | 74.3 (6.8) |
| Plasma renin activity (ng/litre.sec) | 0.40 (0.30) | 0.34 (0.25) | 0.24 (0.12) | 0.56 (0.32) |
| Plasma aldosterone (pmol/litre) | 119 (111) | 119 (78) | 97 (97) | 144 (100) |
| Sodium (mmol/litre) | 134 (61) | 130 (58) | 171 (44) | 130 (50) |
| Potassium (mmol/litre) | 45 (27) | 34 (21) | 55 (29) | 44 (22) |

The authors noted the higher blood pressure, lower plasma renin activity and aldosterone concentrations and higher urinary sodium and potassium levels in heavy chewers and concluded that their survey supports the association between smokeless tobacco and hypertension seen in the general population. They considered that their observations of relative renin-aldosterone suppression "suggest that the mineralo-corticoid effect of the licorice contained in chewing tobacco ... may have a causative role in tobacco chewers' hypertension," noting that previous attempts to account for this relation have focused on the nicotine and salt content of smokeless tobacco.

The study has some limitations that should be taken into account. First, it is based on small numbers; second, no potential confounding variables have been taken into account, including tobacco smoking or age. It should be noted that the heavy chewers were of average age 37.3, almost 10 years older than the non users, who were of average age 27.5. Finally, with the exception of the difference in renin activity, none of the differences are statistically significant at $p<0.05$. The authors state that the difference in systolic blood pressure is significant ($p<0.007$) but simple calculation based on the means and SDs presented suggests this is not correct.

Morris *et al*[71] noted in 1990 that, in some persons, long-term ingestion of liquorice, which contains glycoside derivatives of glycyrrhetinic acid, produces a number of symptoms including hypertension. They also noted that

glycyrrhetinic acid inhibits hepatic 5$\beta$-reductase activity, an enzyme which inactivates mineralocorticoids and may lead to hypertension as a result. They found that chewing tobacco, most brands of which contain liquorice, and also saliva from tobacco chewers inhibits hepatic 5$\beta$-reductase activity. The possibility was therefore raised that it was the liquorice present in some brands of chewing tobacco that might be the risk factor for hypertension.

In a study in Sweden reported in 1991 and described in more detail in section 5, Wennmalm *et al*[14] found that the mean blood pressure (mmHg) in 18-19 year old men was no higher in the 127 who used snuff only (systolic 122, diastolic 65.3) than in the 377 who were non-tobacco users (systolic 122, diastolic 66.4). Smokers of cigarettes only had significantly reduced systolic blood pressure (118; $p<0.05$) but similar diastolic blood pressure to the non-tobacco users.

In 1991, Eliasson *et al*,[12] in a study conducted in young men in Sweden, compared cardiovascular risk factors in 18 non-tobacco-users, 21 habitual snuff users (five of whom were ex smokers) and 19 cigarette smokers (one of whom used to use snuff). The three groups were similar in age and body mass index. The mean diastolic blood pressure was 72.8 mm.Hg for non-tobacco-users, 70.9 mm.Hg for snuff users and 77.5 mm.Hg for smokers ($p<0.05$ vs non-tobacco-users). No differences between groups were seen for systolic blood pressure or pulse rate (see also section 5 for further results).

In the study of Swedish construction workers introduced in section 3.2, Bolinder *et al*[39] also reported results for blood pressure and heart rate. First, they noted that the odds ratio for having a disability diagnosis of hypertension was increased, as compared to non-tobacco users, in those who used smokeless tobacco but did not smoke (OR = 3.0, CI = 1.9-4.9) but not in those who smoked but did not use smokeless tobacco (OR = 0.9, CI = 0.4-1.9). Second, based on measurements made at the time of interview, they found that the odds ratio of having a diastolic blood pressure >90 mm.Hg was significantly increased at every age in the smokeless tobacco users (ORs 1.3,

1.3, 1.8 and 1.3 for age groups 16-35, 36-45, 46-55 and 56-65), but decreased, significantly for all age groups except the first, for smokers of 15+ cigarettes/day (ORs 0.9, 0.8, 0.8 and 0.7 for the same four age groups). Similar conclusions were reached for systolic blood pressure >160 mm.Hg. The probability of having a heart rate >80 beats/min was similarly raised in both smokeless tobacco users and smokers, at age 45+, but was only increased in smokers at younger ages.

In 1992, Siegel *et al*[15] reported the results of a study conducted among 1061 US professional baseball players who were not current smokers of cigarettes. 584 were current non users of smokeless tobacco, while 477 were users, 75% of which used primarily oral snuff, the rest chewing tobacco. The smokeless tobacco users tended to be more often white and drink more alcohol and have higher serum caffeine levels than non users. After adjustment for age, race, alcohol use and serum caffeine, there was no significant difference in systolic or diastolic blood pressure, in pulse or in total or HDL cholesterol levels between non users or users of smokeless tobacco or between users of snuff or chewing tobacco. Thus, for example, mean diastolic blood pressure (mm.Hg) was 72.1 in non users, 71.9 in snuff takers and 70.9 in tobacco chewers. There was, however, a tendency (p=0.02) for higher mean serum nicotine levels to be associated with higher diastolic blood pressure levels. The authors concluded that "smokeless tobacco has at most a modest effect on cardiovascular risk factors in young physically fit men."

In 1995, Eliasson *et al*[13] reported results from a study conducted in Northern Sweden comparing blood pressure in groups of men aged 25-64 subdivided by their tobacco use. As seen from the Table below, there was no indication that current snuff dipping was associated with increased blood pressure. Results were noted to be unchanged by age adjustment. The proportion of men who used antihypertensive agents was noted to be the same (4.5%) in snuff dippers and non-tobacco users, but higher (12.2%) in smokers (see also section 5 for further results).

| | | Diastolic BP (mm.Hg) Mean (95% CI) | Systolic BP (mm.Hg) Mean (95% CI) |
|---|---|---|---|
| Non-tobacco users[a] | 220 | 82.4 (80.9-83.8) | 130 (127-132) |
| Ex cigarette smokers (no snuff) | 130 | 84.0 (82.2-85.9) | 132 (129-135) |
| Cigarette smokers (no snuff) | 124 | 82.1 (80.1-84.0) | 130 (127-133) |
| Snuff dippers (no smoking) | 92 | 82.9 (80.6-85.2) | 129 (126-133) |
| Snuff and cigarette users | 38 | 82.6 (78.8-86.4) | 129 (124-135) |

[a] Did not use tobacco and never been regular tobacco users. Pipe and cigar smokers not included in analysis.

In their 1997 review, Ahlbom *et* al[36] cite a personal communication by Wilhelmsen as not finding increased blood pressure in long-term snuff dippers.

In 1998, Bolinder and de Faire[11] conducted ambulatory 24-hour blood pressure monitoring in 135 healthy, normotensive, middle aged (35 to 60 years) male firefighters in the Stockholm City Fire Brigade, comparing 47 habitual smokeless tobacco users, 29 smokers and 59 nonusers of tobacco, with adjustment for age, body mass index, waist-hip ratio, physical training level and alcohol consumption. With the exception of an increase ($p<0.05$) in mean daytime values in smokers, no significant differences were seen between the three groups in respect of diastolic blood pressure, whether mean levels or variability over the whole 24-hour period, day-time or night-time were considered. Nor was there any difference in diastolic blood pressure based on a single measurement a day later. Systolic blood pressure showed rather more evidence of a difference, with mean 24-hour and mean daytime values increased ($p<0.05$) to a similar extent in both smokeless tobacco users and smokers, though night-time variability increased only in smokers. Heart rate was increased ($p<0.05$) in both smokeless tobacco users and smokers in both day-time and night-time as well as over the whole 24-hour period. When results were restricted to the 75 men aged 45+, much more evidence was seen of a between-group difference in blood pressure, with systolic blood pressure clearly increased in smokers ($p<0.001$ for the day-time period), and less clearly increased in smokeless tobacco users ($p<0.05$ at two time points) and diastolic blood pressure clearly increased in both smokers and smokeless

tobacco users (again $p<0.001$ for the day-time period). It seems rather surprising that the differences in blood pressure seen in the older group were so marked, given that they formed over half the subjects and little evidence of an effect was seen in the total group.

Two previous papers by Bolinder *et al*[9,10] also gave some blood pressure data for the same group of firemen. In one,[10] concerned with effects on atherosclerosis, no significant differences between the same three groups were seen in respect of systolic or diastolic blood pressure, but a significant ($p<0.01$) increase in heart rate was seen in smokers. In the other,[9] concerned with effects on physical performance, no significant differences were seen in respect of blood pressure or heart rate when measured at rest, but significant ($p<0.05$) increases in systolic blood pressure and heart rate at a workload of 190W were seen in smokers, but not smokeless tobacco users.

In 2001, Wallenfeldt *et al*[72] described the results of a study conducted in Gothenburg involving 391 clinically healthy men all 58 years old, of which 48 currently and 33 formerly used snuff. Systolic blood pressure was found, in univariate analysis, to be significantly ($p<0.05$) associated with increasing cigarette-years but not with increasing snuff-years. Analyses were not reported comparing blood pressure in current snuff only users, current cigarette only users and current non users (see also section 5 for further results).

In his review "Does smokeless tobacco cause hypertension," Westman[33] regards experimental studies as providing evidence on acute effects of smokeless tobacco use and cross-sectional studies as providing evidence on chronic effects. He states that smokeless tobacco contains three ingredients known to elevate blood pressure, nicotine which has an acute cardiovascular effect, and sodium and liquorice which possibly have a chronic cardiovascular effect. It is beyond the scope of this review to consider all the evidence relating to nicotine, sodium and liquorice, but it is important to point out that there are problems in interpreting cross-sectional studies as necessarily providing evidence on chronic effects. While subjects are unlikely

to be smoking while their blood pressure is being taken, it seems eminently possible that, unless instructions have been given to the contrary, some may be using smokeless tobacco at the time, or have used it shortly before, when its acute effects are still occurring.

Of the studies considered in this section only four, all in Sweden, appear to have attempted to have avoided acute effects. In their 1991 study, Eliasson *et al*[12] carried out their examination after overnight abstention from tobacco, while in their 1995 study, they[13] instructed subjects not to use tobacco for the hour before examination. In their 1992 study, Bolinder *et al*[39] did not allow smoking or use of smokeless tobacco in the waiting room or during examination, while in their 1998 study, Bolinder and de Faire[11] required at least eight hours abstention from tobacco.

The results of these four studies were rather conflicting. In their 1995 study Eliasson *et al*[13] found no difference between the blood pressure of smokers, snuff users or non-tobacco users, while in their earlier study,[12] in young men, a blood pressure increase (diastolic only) was seen in smokers, but not in snuff users. Nor, in the 1998 study of Bolinder and de Faire,[11] was there any significant difference in blood pressure measured, following abstention from tobacco, between smokers, smokeless tobacco users and non-tobacco users, though some increases were seen later in smokers and smokeless tobacco users during the 24-hour ambulatory recordings when subjects were instructed to consume tobacco *ad libitum* according to their usual habits. In contrast to the lack of effect of smokeless tobacco on blood pressure measured after abstention, in the study of Swedish construction workers[39] clear increases were seen in smokeless tobacco users but not in smokers, not only in blood pressure but also in having a disability diagnosis of hypertension. It is interesting to note that, as for the results on cardiovascular mortality and MI incidence summarized in section 3, this study produces results which differ from the others.

Of the remaining studies, it is interesting to note that, in those conducted in Sweden[9,10,14,36,72] there is little suggestion of an increased blood pressure in snuff users. In contrast, three studies in the USA report an increase in smokeless tobacco users,[23,69,70] though one does not.[15] Although, as discussed earlier, some of the increases noted are of dubious statistical significance, the possibility arises that US smokeless tobacco may have effects that Swedish snuff does not. It is important to note that all the evidence cited in sections 4.1 and 4.2 on case reports and experimental studies, which clearly suggests an acute effect of smokeless tobacco, comes from the USA. What is missing is evidence from experimental studies conducted using Swedish snuff.

5. Summary of evidence relating smokeless tobacco use to other endpoints of possible relevance to cardiovascular disease

In 1965, Sogani and Joshi[73] described the results of a study in India in which the effects on blood coagulation and fibrinolytic activity were compared in three groups, each of 11 males - cigarette smokers, biri smokers and tobacco chewers. The study was carried out in the morning after overnight abstinence. An initial blood sample was taken and then the subjects smoked two cigarettes, two biris or chewed a betel containing flavoured tobacco, a final blood sample being taken five minutes after completion of smoking or 20 minutes after the start of chewing. In all the three groups, whole blood clotting time and recalcified plasma clotting time decreased between the two blood samples, while prothrombin time, platelet adhesiveness, fibrinogen and fibrinolytic activity increased. Platelet count did not materially change. Changes were always less marked for chewing than for cigarette smoking, although this was statistically significant only for fibrinolytic activity ($p = 0.001$).

In the 1977 experimental study reported in section 4, Bordia *et al*[60] also reported a number of acute effects of tobacco use, decrease in whole blood coagulation time, prothrombin time, partial thromboplastin time and plasma recalcification time and an increase in euglobine lysis time and platelet adhesive index, more marked in the coronary artery patients than in the normal controls. The changes were seen to an apparently fairly similar extent in response to smoking cigarettes, smoking biris or chewing tobacco, though, as noted earlier, it was not possible to assess the significance of differences between types of tobacco use from the material presented. The authors did, however, claim that the haemodynamic changes following biri smoking and tobacco chewing were more pronounced than those following cigarette smoking. The authors also noted that the daily nitroglycerine requirement of 10 coronary artery disease patients having frequent anginal attacks was reduced after stopping chewing.

In 1985, Ekenvall and Lindblad[74] studied the effects of nicotine on vibration induced Raynaud phenomena in 111 patients, 49 smokers, 16

snuffers and 46 non-tobacco users. A cold provocation test (measurement of systolic finger blood pressure after local and general cooling) was performed. More patients with advanced disease than patients with early disease used nicotine, and, given disease severity, test results were more often pathological among nicotine users than among non users. The authors noted that "since snuffers had at least as severe symptoms and as many pathological cold provocation tests as smokers, nicotine seems to be responsible for the effects." However, no statistically significant differences between smokers and snuffers were seen.

In 1986, Khandelwal *et al*[75] reported summary results in an abstract of a study in India involving 120 men, 40 current non users of tobacco, 40 current smokers and 40 current chewers, aimed at comparing the effects of cigarette smoking and chewing on high density lipoprotein (HDL) cholesterol status. Exclusion criteria included diabetes, hypertension, obesity, endocrinometabolic and renal disorders and taking of beta-blockers or lipid lowering drugs. HDL levels were "significantly" low in light, moderate, and heavy smokers and in moderate to heavy chewers, but ex smokers and ex chewers had almost normal levels. Results of significance tests comparing smokers and chewers were not reported and could not be calculated from the limited information provided.

In 1987, O'Dell *et al*[76] presented a case report of a 38-year old man with Buerger's disease considered to be clearly associated with the use of chewing tobacco. The man had smoked only briefly in college but had chewed tobacco during the day for the previous four years. His medical history was negative for diabetes, hypertension, hypercholesterolaemia, heart disease and frostbite. Following treatment with nifedipine and anti-platelet therapy, and complete abstinence from tobacco, his symptoms and pain resolved. Most, and in some series all, patients with Buerger's disease have been found to have a history of heavy cigarette smoking.

In 1988, Lie[77] described the case of a 34 year old white man with evidence of the intermediate stage of Buerger's disease who complied with the

recommendation of abstinence from the use of chewing tobacco and, in the two-year period that followed, experienced no recurrence of symptoms or new signs of peripheral vascular insufficiency.

In 1988, Bahrke *et al*[78] described the results of three studies of tobacco use and exercise performance on the US Army Physical Fitness Test. The first two studies compared smokers and non smokers, whilst the third study compared smokeless tobacco users and non users. It was unclear from the paper whether the non smokers in the first two studies included smokeless tobacco users or whether the non users in the third study included smokers, though smokeless tobacco was noted to be the only form of tobacco used by the users in this study. Smokers did significantly worse than non smokers as regards numbers of push-ups ($p<0.001$) and sit-ups ($p<0.001$) and time taken to do a two mile run ($p<0.05$), with a dose response evident for push-ups and sit-ups ($p<0.05$). In contrast, the performance of smokeless tobacco users and non users was similar. However, within the users, years of use was significantly ($p<0.05$) associated with worse performance on all three markers.

In 1989, Tucker[79] reported the results of a study in 2840 US adult males, 93 of whom were regular users of smokeless tobacco, 568 were cigarette smokers and 10 reported use of both products. After adjustment for the potential confounding effects of age, education, physical fitness, body fitness and other tobacco use, the risk of hypercholesterolaemia, as assessed by a serum cholesterol level of 6.2 mmol/$\ell$ or greater, relative to non users of tobacco, was 2.51 (95% CI 1.47-4.29) in users of smokeless tobacco, 1.98 (95% CI 1.29-3.03) in smokers of 20+ cigarettes daily and 1.51 (95% CI 1.14-2.00) in smokers of 1-20 cigarettes daily. It is interesting to note that, before adjustment, the relative risk in users of smokeless tobacco was only 1.08 (95% CI 0.63-1.85) and not significant. It is not readily apparent why adjustment should have had such a large effect. The smokeless tobacco users were younger, and younger men were much less likely to have hypercholesterolaemia than older men, but from the data presented in Table 1 of the paper, the relative risk adjusted only for age can be calculated as a non-significant 1.46 (95% CI 0.83-2.56). The relative risk adjusted only for

education, the only other factor noted to be correlated with smokeless tobacco use, is only 1.14 (95% CI 0.65-1.98). One must wonder whether the multiply-adjusted relative risk estimate cited of 2.51 is in fact correct.

In 1991, Wennmalm *et al*[14] described the results of a study in Gothenburg in which, *inter alia*, the 2,3-dinor metabolites of thromboxane $A_2$ and prostacyclin (Tx-M and PGI-M, respectively) were measured in 577 randomly sampled 18-19 year old men. Thromboxane $A_2$ is noted to be "a powerful platelet aggregatory and adhesive agent and a strong vasoconstrictor," while "increased formation of prostacyclin in the vascular endothelium may indicate increased interaction between the platelets and the vessel walls." The study included 377 non-tobacco users, 43 who smoked cigarettes only, 127 who used snuff only and 30 who both smoked and used snuff. Median Tx-M (pg/mg creatinine), 128 in non-tobacco users, was significantly ($p<0.001$) increased in cigarette only smokers (180) and in those who both smoked and used snuff (187), but not increased at all in snuff only users (126). PGI-M (pg/mg creatinine) did not vary significantly by group and was slightly lower in snuff users (121) than in non-tobacco users (129), with median levels 140 in cigarette only smokers and 122 in the mixed group. Urinary catecholamine concentrations did not vary by group. During a bicycle ergometer test, the maximal work load was significantly reduced in both cigarette only smokers and the mixed group, but not in snuff only users.

In the 1991 study in Swedish young men described in section 4, Eliasson *et al*[12] reported that, compared to non-tobacco users, coffee intake and alcohol consumption was significantly ($p<0.001$) higher and physical activity was significantly ($p<0.01$) lower in smokers. Smaller, but still significant ($p<0.01$ for coffee and alcohol, $p<0.05$ for exercise) differences were also seen in snuff users. Smokers also had a significantly higher haemoglobin ($p<0.01$), white cell count ($p<0.01$), fibrinogen ($p<0.05$), serum insulin ($p<0.01$), serum cholesterol ($p<0.01$) and serum triglycerides ($p<0.001$), but did not differ significantly as regards platelet count, blood glucose, LDL cholesterol, HDL cholesterol, LDL/HDL ratio, serum lipoprotein, tissue plasminogen activator or plasminogen activator inhibitor.

In contrast, the only significant difference noted in the snuff users was an increase in serum insulin, though of a smaller magnitude than that seen in smokers. Though fibrinogen also showed some evidence of an increase, it seemed reasonable to conclude that "the use of snuff by young men appears to have less impact than smoking on cardiovascular risk factors."

As noted in section 3.2, Bolinder *et al*[39] reported, in 1992, an increased incidence of Raynaud-like symptoms, indicating traumatic vasospastic disease, in both smokers and smokeless tobacco users.

In 1992, Van Duser and Raven[66] carried out a crossover trial in Texas involving 15 symptomatic male current oral smokeless tobacco users. Following a 5 minute rest period, pre-treatment measures of oxygen uptake ($VO_2$), cardiac output ($Q_c$), heart rate (HR), stroke volume (SV = $Q_c$/HR), plasma lactate concentrations ($L_c$) and plasma nicotine concentrations ($N_c$) were made after which the subject was instructed to put the treatment sample (smokeless tobacco or placebo) in his buccal mucosal space, while further measurements of $VO_2$, $Q_c$, HR, SV, $L_c$ and $N_c$ were made every five minutes for 30 minutes. The sample was then removed and the subject then performed graded exercise tests on a treadmill, with further measurements taken. Comparing the response to the test and placebo, no significant differences were seen in $VO_2$ or $Q_c$. However, HR increased more with smokeless tobacco ($p<0.0005$) and SV decreased ($p<0.05$). $N_c$ ($p<0.0001$) and $L_c$ ($p = 0.01$) were also increased. The authors concluded that "these data indicate that the increased $N_c$ incurred by OST [= oral smokeless tobacco] usage increases anaerobic energy production and produces an increased tachycardiac response to a given relative submaximal workload."

In 1983, Stegmayr *et al*[80] described the results of a study of 40-49 year old Swedish men, in which plasma levels of antioxidant vitamins were compared in 17 regular users of oral snuff, 26 regular smokers and 54 non tobacco users. Regular smokers had significantly lower plasma levels of ascorbate ($p<0.001$), lipid-standardized $\alpha$-tocopherol ($p = 0.032$), $\alpha$-carotene ($p<0.001$) and $\beta$-carotene ($p = 0.014$) than non tobacco consumers. However,

plasma levels of these vitamins were very similar in regular snuff dippers and non tobacco users. Smokers had significantly lower levels of ascorbate than snuff dippers ($p = 0.0011$), other differences between smokers and snuff dippers not reaching statistical significance. Comparisons were also made on food intake, based on a rather larger number of men with such data available. The intake of fruit and vegetables tended to be lower and fat consumption higher in smokers than in snuff dippers or non users of tobacco. Smokers, but not snuff dippers, had plasma levels of ascorbate significantly below those expected from their ascorbic acid intake, "indicating enhanced expenditure of ascorbate in smokers but not in snuff dippers."

In 1995, Eliasson *et al*[13] reported results from a study of a randomly selected population sample of 604 men aged 25-64 in Northern Sweden, there being too few snuff users in women for their results to be relevant to this review. Comparisons were made between non-tobacco users, ex cigarette smokers (no snuff), cigarette smokers (no snuff), sniff dippers (no smoking) and those who used both snuff and cigarettes. There was no significant difference between groups as regards blood pressure (see also section 4), total or HDL cholesterol or triglycerides. Compared to non-tobacco users, plasma fibrinogen levels ($g/\ell$) were significantly increased in current smokers, 3.58 (95% CI 3.45-3.71) vs 3.24 (95% CI 3.14-3.33), and also somewhat increased in former smokers, 3.45 (95% CI 3.32-3.58), but were not increased at all in snuff users who did not smoke, 3.16 (95% CI 3.01-3.31). In men, tissue plasminogen activator (tPA) activity, plasminogen activator inhibitor type 1 (PAI-1) and glucose levels did not vary significantly by smoking or snuff use. The authors noted that snuff dippers have a higher daily tobacco exposure and plasma cotinine than smokers. Nevertheless, "the use of smokeless tobacco, as moist oral snuff, does not appear to affect these cardiovascular risk factors."

In their 1997 review, Ahlbom *et al*[36] cite a personal communication by Wilhelmsen as one of a number of studies that indicated that snuff dipping "does not have pronounced effects on the levels of blood lipids, fibrinogen or other biochemical risk factors for cardiovascular disease."

In their study of Stockholm firefighters, Bolinder *et al*[10] compared biochemical risk factors for cardiovascular disease and atherosclerosis, as determined by ultrasonographic measurement of carotid intima media thickness, in 40 men who had never used tobacco, 28 who had used smokeless tobacco and had never smoked and 29 who smoked (including 5 who used smokeless tobacco also). After adjustment for age, smokeless tobacco users did not show any significant differences from never users in any of the blood measurements taken. Smokers, however, showed significant differences (many at $p<0.001$) in all of them – increased total cholesterol, LDL cholesterol, triglycerides, fibrinogen, apolipoprotein B and apolipoprotein B/apolipoprotein A-I ratio, and decreased HDL cholesterol and apolipoprotein A-I. Smokeless tobacco users also showed no evidence of any difference from never users in any of the intima media wall measurements or lumen diameters of the common carotid or bulb area. Smokers showed evidence of an increase in wall thickness, more clearly in the bulb area, but not in lumen diameter. The authors conclude that "on the basis of these data, it appears most likely that the increased occurrences of atherosclerosis in smokers is caused by other components of tobacco smoke than nicotine."

Based on the same population of firefighters, Bolinder *et al*[9] also carried out a study of physical fitness and cardiovascular response to exercise. Smokers were found to have an increased odds (compared to non users) of having a sedentary occupation (OR = 5.7, CI = 2.0-16.2), low physical training (OR = 7.0, CI = 2.6-18.5) and medium/high alcohol consumption (OR = 6.5, CI = 1.4-29.5). In contrast, no such increase was seen for smokeless tobacco users, where the odds ratios were, respectively, 0.4 (CI = 0.1-1.8), 0.7 (CI = 0.2-2.3) and 1.3 (CI = 0.6-3.0). Blood cotinine levels were higher, at 347 ng/ml, in smokeless tobacco users than in smokers, 253 ng/ml ($p<0.001$). After adjustment for age, body mass index, waist/hip ratio, alcohol consumption, level of physical training and physical demands of the job, maximal oxygen uptake and maximal work during the exercise test was similar in non-users and smokeless tobacco users but significantly ($p<0.001$) decreased in smokers. The authors concluded that "the findings indicate that

long-term use of smokeless tobacco does not significantly influence exercise capacity in healthy, physically well-trained subjects."

In 2000, Khurana *et al*[81] described the results of a study conducted in Jaipur, India involving 30 smokers, 30 tobacco chewers and 30 controls who neither smoked nor chewed. The subjects were selected from hospital outpatients and volunteers and alcoholics, as well as those with diabetes, hypertension, various other medical conditions or taking lipid lowering drugs, beta-blockers, oral contraceptives or thiazide diuretics were excluded. Blood samples were taken and lipid analyses performed. No differences were seen between smokers and tobacco chewers. Compared to the controls, both groups had significantly higher concentrations of VLDL-cholesterol ($p<0.001$) and triglycerides ($p<0.001$) and lower concentrations of HDL-cholesterol ($p<0.01$). They also had higher total cholesterol and LDL-cholesterol, but not significantly. No adjustment was made in analysis for age, sex or diet, so the comparisons must be regarded as rather crude.

In the 2001 study in Gothenburg referred to previously in section 4, Wallenfeldt et *al*[72] carried out multiple regression analyses to investigate the joint effect of smoking or snuff use (each coded as 1 = never user, 2 = ex user and 3 = current user) on various endpoints studied in a sample of healthy 58 year old men. Cigarette smoking but not snuff taking was highly significantly ($p<0.001$) associated with increased intima-media thickness of both the femoral artery and the carotid bulb, and with increased C-reactive protein levels. In univariate analysis cigarette smoking was significantly associated with increased body mass index ($p<0.01$), waist circumference ($p<0.001$) and waist-hip ratio ($p<0.001$), reduced HDL cholesterol ($p<0.01$), increased triglycerides ($p<0.001$) and increased plasma insulin ($p<0.05$). Correlations with snuff use were always weaker than with cigarette smoking and only significant for waist-hip ratio ($p<0.05$) and triglycerides ($p<0.01$). Interpretation of the univariate results for snuff are not straightforward as 95% of the snuff users were current or past smokers and compared with only 55% of those who had never used snuff. If would have been better if all analyses relating to possible effects of snuff had been adjusted for cigarette smoking.

The data summarized above relate to a relatively small number of studies conducted in India and in the US and quite a large number conducted in Sweden. The four studies from India, two on acute haemodynamic changes,[60,73], two on lipids[75,81], both report effects of smokeless tobacco that are comparable to those seen in smokers. The material from the US consists of two case reports of Buerger's disease associated with the use of chewing tobacco[76,77], one study which reported that smoking but not smokeless tobacco was associated with reduced exercise performance[78], one study which reported an increased plasma lactate concentration and decreased stroke volume associated with smokeless tobacco use[66], and one study[79] which reported that risk of hypercholesterolaemia was increased in both smokers and smokeless tobacco users, though, as noted above, some doubt exists about the magnitude of the claimed increase in smokeless tobacco users.

The studies in Sweden concern a wide range of endpoints, but generally show a very similar pattern of response. Apart from two reports[39,74] of a similar increase in prevalence of Raynaud-type symptoms in both smokeless tobacco users and smokers, and reports of increased levels of insulin[12] and of triglycerides[72] in smokeless tobacco users that are less marked than that seen in smokers, the studies all show no adverse effect of smokeless tobacco use for endpoints that are virtually all associated with smoking. This conclusion applies to endpoints such as atherosclerosis,[10,72] response to exercise,[9,14] cholesterol levels,[10,12,36,72] triglycerides,[10,12,36] fibrinogen,[10,12,13,36] markers of platelet activity[14] and levels of antioxidant vitamins.[80] Exceptionally, one study[13] reported no effects of either smokeless tobacco use or smoking on cholesterol levels and triglycerides. Overall the data from the studies in Sweden summarized in this section show that effects of Swedish snuff have not been convincingly demonstrated and if they exist are clearly less than those associated with smoking.

## 6. Discussion and Conclusions

It is clear that the use of smokeless tobacco, whether as typically used in the USA or Sweden, involves an exposure to nicotine that is quite comparable to that from cigarette smoking. Since cigarette smoking is associated with an increased risk of cardiovascular disease and since nicotine has been implicated in several processes related to the disease,[17] there is some concern that the use of smokeless tobacco also might increase risk. Although, in view of the lack of increased heart disease risk in pipe smokers,[18] such concern might not be fully justified, it was decided to review the available evidence relevant to this concern.

Four epidemiological studies have been conducted. These include two case-control studies of MI in Northern Sweden,[30,51] one prospective study of Swedish construction workers[34] and one prospective study of a representative sample of the US population.[53] All involve moderately large numbers of cases of cardiovascular disease and, though all have some potential limitations, they all provide some useful information. Endpoints considered vary from study to study, and include all MI, fatal MI and mortality from IHD, stroke, all cardiovascular disease and all circulatory disease, and the results predominantly relate to men.

As expected, the evidence of an increased risk in smokers (compared to non-users of tobacco) is generally clear. The evidence of an increased risk in smokeless tobacco users is much less compelling. The two studies in Northern Sweden[30,51] and the US study[53] show no significant increase in risk, and it is only the study of Swedish construction workers[34] where a significant increase is seen, which even then is less than that seen in smokers. Combining estimates of the relative risk of smokeless tobacco users compared to non-tobacco users for MI from the two case-control studies[30,51] and for IHD from the two prospective studies[34,53] by random-effects meta-analysis gives an estimate of 1.09 (CI 0.80-1.49) for the sexes combined which is not significant. Similarly combining estimates for fatal MI from one of the Swedish case-control studies[51] with those for all cardiovascular disease death from the Swedish construction workers study[34] and for all circulatory disease

death from the US prospective study[53] gives an estimate of 1.30 (CI 0.95-1.77) for the sexes combined. These two estimates are little changed if attention is restricted to males (1.04, CI 0.73-1.49 and 1.33, CI 0.91-1.95 respectively).

Combining estimates of the relative risk of smokers to smokeless tobacco users (here only available for males), in contrast, shows significant results, with RRs of 2.14 (CI 1.31-3.49) for MI/CHD and of 1.51 (CI 1.09-2.09) for fatal MI/cardiovascular disease/circulatory disease.

Overall the epidemiological data do not demonstrate the existence of an association between smokeless tobacco use and risk of cardiovascular disease. If some increase in risk does exist, and this cannot be ruled out with the relatively limited data, it will clearly be weaker than that with smoking.

Evidence has also been reviewed relating to the association of smokeless tobacco use with hypertension and other risk factors for cardiovascular disease. Here the conclusions to be drawn seem quite different for US smokeless tobacco and for Swedish snuff.

For US smokeless tobacco the evidence consists of:

(i) a number of case reports[24,54-56] suggesting an acute hypertensive effect of smokeless tobacco;

(ii) a number of experimental studies[6,7,20,27,61-63,66] which generally found an acute rise in blood pressure and/or heart rate;

(iii) a number of cross-sectional studies,[15,23,68,70] all but one of which[15] report an increased blood pressure in smokeless tobacco users;

(iv) two case reports[76,77] of Buerger's disease associated with smokeless tobacco;

(v) one report[78] that increasing years of smokeless tobacco use was associated with reduced exercise performance;

(vi) one report[66] of an increased tachycardiac response to a given relative submaximal workload, following smokeless tobacco use; and

(vii) one report[79] of increased hypercholesterolaemia in smokeless tobacco users.

Though some of the cross-sectional studies fail to distinguish possible acute and chronic effects of smokeless tobacco, there certainly seems to be adequate evidence of an effect of US smokeless tobacco on the cardiovascular system. Some of the evidence allows comparison of effects in smokers and in smokeless tobacco users, with some studies on blood pressure[23,69] and on cholesterol levels[79], suggesting the possibility that effects might be greater in smokeless tobacco users. However, the evidence here is inconclusive.

Limited data from studies in India[60,73,75,81] also suggest an effect of smokeless tobacco on cardiovascular variables.

For Swedish snuff the evidence of any effect on cardiovascular risk factors is very limited. Most cross-sectional studies[9,10,12-14,36,72] found no real suggestion of an increased blood pressure in snuff users, and though one[34] found clear increases in smokeless tobacco users in both blood pressure and a disability diagnosis of hypertension, this was the same study of construction workers which unusually found an association with cardiovascular mortality. Similarly, although there are two reports[39,74] of an increase in Raynaud-like symptoms in smokeless tobacco users, the evidence generally[9,10,12-14,36,72,80] shows little or no association with cardiovascular risk factors, including levels of fibrinogen, cholesterol and other lipids or antioxidant vitamins, sonographic evidence of atherosclerosis, markers of platelet activity, and response to exercise.

While one would certainly like to have an explanation of the unusual results from the study of Swedish construction workers[34], the overall data in relation to Swedish snuff provides little evidence that it has any effect at all on risk of cardiovascular disease or on factors that are generally associated with an increased risk. Even if it does have some effects, they are likely to be substantially less than those from smoking.

While the one US study of cardiovascular mortality[53] did not find an increased risk in smokeless tobacco users, there is clear evidence of an effect on blood pressure and possibly also other endpoints related to vascular disease.

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