

# Smokeless Tobacco and Cardiovascular Disease

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Various forms of smokeless tobacco (mainly snuff and chewing tobacco) cause an immediate increase in heart rate and blood pressure, but regular users of smokeless tobacco do not have permanent changes of heart rate or blood pressure when not exposed to tobacco. Cardiac output during workload and maximal working capacity are unaffected. Users of smokeless tobacco usually do not have the biochemical stigmata that regular smokers have. Thus, the scientific literature suggests that they are similar to nontobacco users in terms of levels of hemoglobin/hematocrit, leukocytes, antioxidant vitamins, fibrinogen, components of the fibrinolytic system, C-reactive protein, and thromboxane A<sub>2</sub> production. Two studies have found that snuff users, as opposed to smokers, do not have increased intima-media thickness or atherosclerotic lesions when investigated by ultrasound. Results on the risk for myocardial infarction have provided conflicting evidence, 2 case-control studies showing the same risks as in nontobacco users and one cohort study showing an increased risk for cardiovascular death. In all, the use of smokeless tobacco (with snuff being the most studied variant) involves a much lower risk for adverse cardiovascular effects than smoking does. Whether or not the apparent risk reduction is a useful strategy to help inveterate smokers to quit is a matter of debate, as are the public health effects of a high prevalence of snuff use in some populations.

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Whereas cigarette smoking is pandemic, the use of smokeless tobacco can best be described as endemic, restricted to particular populations or countries. Smokeless tobacco use is quite common in North America, some of the Scandinavian countries, Saudi Arabia, India, Bangladesh, Southeast Asia, and parts of Africa. It often is used in certain subsets of a population, such as athletes, male adolescents and young adults, and people in

professions in which smoking is not allowed. In rich countries, a large proportion of adult users of smokeless tobacco are former smokers.

## Many Forms of Smokeless Tobacco

Globally, there is a plethora of smokeless tobacco products, homemade as well as commercially available. Some of the products and the main user groups are described in Table 1. The complexity of smokeless tobacco composition makes it difficult to make general statements about the effects of all forms of smokeless tobacco on the cardiovascular system. Nearly all scientific studies on the health effects, including those on the cardiovascular system, have been performed in the United States and Sweden, and concerned the use of moist snuff. The results should therefore be regarded as representative only of moist snuff available commercially in these countries.

Snuff is pulverized tobacco that, when it was first introduced in Europe in the 17th century, was inhaled in dry form through the nostrils (sniffed). Today, most snuff is moist and taken orally, either in a loose form or in tea-bag-like small packages (sachets). The United States and Sweden dominate the commercial snuff market.

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Supported by grants from the Strategic Research Foundation, the Swedish Research Council, the Heart and Chest Foundation, the Council for Worklife and Social Research, and the Västerbotten and Norrbotten county councils.

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0033-0620/03/4505-0001\$30.00

doi:10.1053/pcad.2003.00102

**Table 1. Selected Smokeless Tobacco Products**

Product	Typical Use Pattern	Characteristics
Moist snuff, US type	Adolescents, athletes in the United States	Pulverized tobacco, fermented, portion packed
Moist snuff, Swedish type	Men of all ages, increasing in women, Sweden, and Norway	Pulverized tobacco, nonfermented, semisterile, available in loose form or sachets, marketed as snus
Dry snuff	Women in parts of southern United States	Pulverized dry tobacco, taken orally or sniffed
Snuff, South-African type	South Africa, more prevalent in women than in men	Ground tobacco mixed with other plant products, mostly homemade but also commercially available, sniffed or taken orally
Chewing tobacco, US type	Adolescents, athletes in the United States	Air-cured tobacco, loose leafs (shredded), plugs, or twists, mixed with flavoring solutions
Toombak	Sudan	Tobacco mixed with natron powder, usually prepared manually by toombak vendors
Betel quid	South and Southeast Asia	Prepared from tobacco, betel leaves, areca nut, and slaked lime

Data from Rodu and Cole,<sup>46</sup> Johnson,<sup>51</sup> Idris et al,<sup>52</sup> and Peltzer.<sup>53</sup>

The manufacturing process and the composition of snuff differs somewhat between the 2 countries. In the United States, snuff production involves a fermentation process, whereas Swedish snuff (locally called *snus*) is prepared by a heating process without traditional smoke drying, yielding a semisterile product with a lower content of toxic substances such as tobacco-specific nitrosamines than previously.<sup>1</sup> It must be noted that, even within a country, there are wide variations in the content of nicotine and tobacco-specific nitrosamines, and the physiologic effects vary considerably between different brands of moist snuff.<sup>2</sup> Various blending ingredients are added to make the brands of snuff taste differently. In the United States, snuff usually is placed between the lower gum and the chin, whereas in Sweden it is placed under the upper lip.

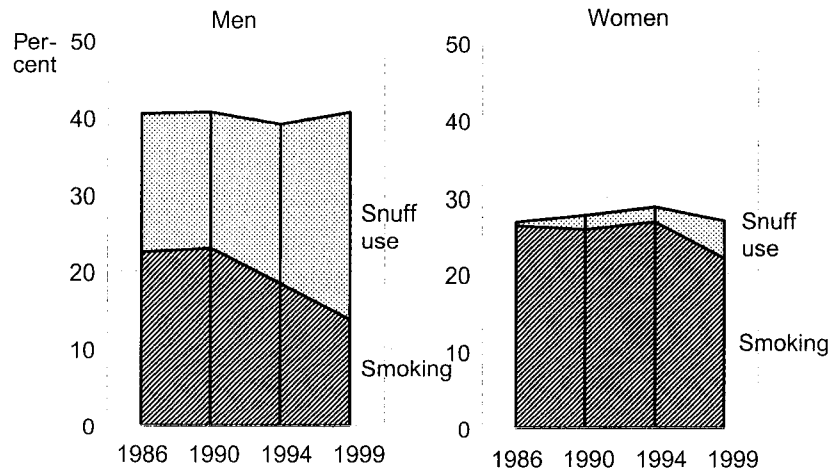
### **The Epidemiology of Snuff Use in the United States and Scandinavia**

In the United States, the use of snuff and other forms of smokeless tobacco shows a distinct geographic and social pattern. Nationwide interview data from the Centers of Disease Control and Prevention show that 32% of US men and 3% of US women have ever used smokeless tobacco.<sup>3</sup> About a quarter of these are current users, yielding a prevalence rate of 8% in men and well below 1% in women across the country (calculated from data from the National Center

for Chronic Disease Prevention & Health Promotion<sup>3</sup>). There are, however, large regional variations ranging in men from 1% in New York State to 18% in West Virginia.<sup>3</sup> Smokeless tobacco is used as frequently by students as by the US population in general. Thus, a national survey performed in 1999 showed 8.7% of male and 0.4% of female college students to be current users of smokeless tobacco.<sup>4</sup> The prevalence was much higher among white students than among other ethnic groups, with the highest rates in the South and the lowest in the Northeast.<sup>4</sup> Athletes are more likely than nonathletes to use smokeless tobacco.<sup>4,5</sup> For example, in the late 1980s and the beginning of the 1990s, as many as 39% to 45% of professional baseball players were using smokeless tobacco.<sup>5,6</sup> Concomitant use of cigarettes and smokeless tobacco is not uncommon in men, being present in a sixth of all users of smokeless tobacco, but virtually nonexistent in women.<sup>7</sup>

The use of moist snuff is traditional in Scandinavian countries. The European Union ban on sales of smokeless tobacco has more or less eradicated the snuff consumption in Denmark and Finland, but in Sweden (exempted from the ban) and Norway (not a member of the European Union) snuff is still sold. Sweden has the world's largest sales of snuff per capita. As the consumption of snuff has been increasing considerably in recent years, cigarette use has been declining. The widespread use of snuff has been implicated in the

**Fig 1. Prevalence of smoking and snuff use among randomly selected 24- to 74-year-old men and women in northern Sweden during the years 1986 to 1999. Subjects with concomitant use of cigarettes and snuff are assigned to a group of smokers. Data from 4 risk factor surveys performed within the framework of the Northern Sweden MONICA Project.**



development toward Europe's lowest prevalence of cigarette smoking in Swedish men.<sup>8</sup> Swedish women, in whom snuff use is much less common than in men (Fig 1), have a relatively high prevalence of smoking in an international perspective.<sup>8</sup> Even within a small country such as Sweden, there are large regional variations in the use of snuff, and this is related inversely to smoking rates. In northern parts of the country, 11% of middle-aged men smoke cigarettes and 27% use snuff regularly.<sup>9</sup> In the south, the prevalence of smoking is 22% and of snuff use is 7%.<sup>10</sup> In neighboring Norway, as many as 20% of teenage boys and 4% of teenage girls use snuff regularly, compared with a prevalence of regular smoking of 14% and 16%, respectively.<sup>11</sup>

### Gateway To or Exit From Smoking?

There is a fierce debate on the public health impact of smokeless tobacco. Is it a safer alternative to smoking to be used by inveterate nicotine addicts and thus reduce the impact of smoking on public health? Or does snuff use involve important health hazards per se and does it serve as a gateway to smoking among young people?

There are indeed indications supporting the gateway hypothesis. Studies among US Air Force recruits<sup>12</sup> as well as among Swedish boys<sup>13</sup> have shown an increased risk for beginning cigarette smoking among those who have experimented with smokeless tobacco. Switching from smokeless tobacco to smoking is quite frequent in US college students.<sup>14</sup>

There are, however, several problems in interpreting these results. Young people who take up smoking often have a drug- and risk-seeking lifestyle, and experimenting with snuff may be yet another expression of this lifestyle. The Swedish experience is also that the prevalence of smoking is higher among teenage girls than among boys, despite boys having experimented with snuff much more frequently. The issue of snuff as a gateway to smoking is extremely difficult to explore scientifically, at least by the use of quantitative research.

In countries where snuff dipping is endemic, it is commonly used to quit smoking. Again, the situation in Sweden is particularly illustrative. About half of middle-aged snuff users are ex-smokers.<sup>15,16</sup> When a large national sample of Swedish ex-smokers were asked about how they succeeded in quitting, 50% stated that they had stopped without help, 33% had used snuff, and 17% had used some form of nicotine replacement therapy (L Ramström, personal communication). In people who continue to smoke, cigarette consumption is considerably lower in those who concomitantly use snuff compared with those who are exclusive smokers.<sup>7,16</sup>

### What Types of Scientific Evidence on Cardiovascular Health Hazards Are Available?

The research on potential health hazards of smokeless tobacco has focused on the risks for cardiovascular disease, cancer, oral diseases, and

addiction. Increased risks for diabetes and osteoporosis also have been discussed. Cardiovascular diseases are the main topic of this review. Current knowledge about the other disorders also is summarized briefly.

In the great majority of investigations on cardiovascular disease, the use of moist snuff has been studied, whereas studies on the possible impact of other forms of smokeless tobacco are virtually nonexistent.

Most published studies concern the impact of smokeless tobacco on intermediate end-points and established cardiovascular risk factors, such as blood pressure levels, serum lipid levels, fibrinolytic variables, and antioxidant vitamin levels. Studies on major cardiovascular end-points (myocardial infarction and stroke) are few and have been performed exclusively in Sweden; the results are thus applicable only to the Swedish type of moist snuff. There is a dearth of studies that have explored the risk for peripheral artery disease or venous thromboembolism in users of smokeless tobacco.

### **Impact of Smokeless Tobacco on Cardiovascular Risk Factors and Other Intermediate End-Points**

#### *Blood Pressure*

Because of the sympathoadrenal-activating properties of nicotine,<sup>17,18</sup> and the relatively high content of sodium and sometimes licorice,<sup>19,20</sup> smokeless tobacco has the potential to affect blood pressure. Numerous studies have reported on blood pressure levels of tobacco users and on acute effects of smokeless tobacco (Table 2). Three early studies (data collection before the mid-1980s) showed higher resting blood pressure levels among users of smokeless tobacco than among nonusers of tobacco. However, none of the more recent studies have been able to confirm any adverse effects of smokeless tobacco on resting blood pressure levels during nonexposure to tobacco, or prevalence of hypertension (Table 2). This is in line with the absence of sustained hypertension in smokers.<sup>21</sup> It may be speculated that the change in sodium content of snuff could partly explain the discrepant observations in early and later studies.

However, like smoking, smokeless tobacco

causes an immediate increase in blood pressure levels, confirmed in a number of studies (Table 2). As reviewed by Westman,<sup>20</sup> the increase is in the order of 10 to 20 mm Hg systolic and 6 to 12 mm diastolic. This seems to be a direct effect of nicotine because (1) the increase in blood pressure is related to the amount of nicotine absorbed,<sup>22</sup> and (2) nicotine replacement therapy causes a similar increase in blood pressure.<sup>19</sup>

#### *Other Hemodynamic and Physiologic Effects*

Smokeless tobacco causes an immediate increase in heart rate but seems to affect resting heart rate only a little, if at all (Table 3). During physical exercise, maximal working capacity and maximal oxygen uptake is not different from that in nontobacco consumers, but during exposure to snuff the pulse rate is higher at submaximal workload. Snuff does not involve lower body mass index or higher waist-hip ratio the way smoking does (Table 3).

#### *Biochemical Variables*

The characteristic laboratory pattern of smokers cannot be replicated in users of smokeless tobacco (Table 4). Thus, smokeless tobacco does not cause elevated hemoglobin or hematocrit levels, an increase in leukocyte counts, increased high-sensitivity C-reactive levels, high fibrinogen levels, impairment of the fibrinolytic system, or reduction of circulating levels of antioxidant vitamins. Smokers often have a less favorable lipid profile than nontobacco consumers. This is at least partially because smokers are more likely to have a diet high in saturated fats. In this regard, snuff users resemble nontobacco users rather than smokers.

Diabetes is an important risk factor for myocardial infarction, stroke, and peripheral artery disease and, recently, smokeless tobacco has been implicated in the causation of insulin resistance and type 2 diabetes. Long-term use of nicotine replacement (gums, patches, nasal sprays, and so forth) has been associated with insulin resistance and hyperinsulinemia.<sup>23</sup> Because insulin resistance often precedes the development of diabetes, it could well be that snuff has the same effects as nicotine gums and patches. Indeed, in a population-based cross-sectional study, an increased risk for type 2 diabetes (odds ratio, 2.7) was observed

**Table 2. Effects of Smokeless Tobacco on Blood Pressure Levels**

Study	Study Population, Type of Smokeless Tobacco	Effect on Resting Blood Pressure	Effects on Other Measures of Blood Pressure
Simon, 1960 <sup>54</sup>	US 34- to 71-year-old male users of chewing tobacco	—	Immediate increase in SBP and DBP
Bordia, 1977 <sup>55</sup>	Indian male users of chewing tobacco, with and without coronary artery disease	—	Immediate increase in SBP and DBP in both patients and healthy men
Squires, 1984 <sup>56</sup>	Young US men, snuff users and nontobacco users	Significantly higher resting SBP and DBP	Immediate increase in SBP and DBP
Clover, 1984 <sup>57</sup>	US male users of smokeless tobacco	—	No significant immediate effect on SBP or DBP
Schroeder, 1985 <sup>58</sup>	18- to 25-year-old US men	Higher SBP and DBP than in smokers and nontobacco users (not clear if this was during exposure to tobacco or not)	—
Ksir, 1986 <sup>59</sup>	Snuff users among US male college students	—	No significant immediate effect on SBP or DBP
Benowitz, 1988 <sup>39</sup>	Healthy 24- to 61-year-old US men, all smokers	—	Immediate increase in SBP and DBP, both snuff and chewing tobacco
Westman, 1990 <sup>60</sup>	US men using snuff and chewing tobacco, mean age 26-37 years	No effect on SBP or DBP in snuff users but increased SBP in heavy users of chewing tobacco	—
Ernster, 1990 <sup>5</sup>	US professional baseball players, both snuff and chewing tobacco	No effect on SBP or DBP	—
Eliasson, 1991 <sup>35</sup>	Young Swedish men, mean age 24 years	No effect on SBP or DBP	—
Wennmalm, 1991 <sup>25</sup>	Young healthy men in Sweden, snuff users	No effect on resting SBP or DBP	—
Siegel, 1992 <sup>6</sup>	US professional baseball players	No effect on SBP or DBP	—
Bolinder, 1992 <sup>33</sup>	Snuff users among Swedish construction workers	Increased prevalence of elevated blood pressure (SBP >160 mm Hg and/or DBP >90 mm Hg)	—
Hirsch, 1992 <sup>21</sup>	Swedish healthy volunteers, mean age 27 years, regular snuff users	No significant difference in SBP or DBP	Immediate increase in SBP and DBP, similar increase as in controls during physical exercise
Eliasson, 1995 <sup>36</sup>	Randomly selected Swedish 25- to 64-year-old men and women	No effect on SBP or DBP	—
Bolinder, 1997, 1998 <sup>37,61</sup>	Swedish middle-aged firemen, snuff users	No significant effect on SBP or DBP	No effects on SBP or DBP during workload. Ambulatory daytime DBP higher than in nontobacco users (related to cotinine levels), no effect on nighttime DBP
Fant, 1999 <sup>22</sup>	US male volunteers, mean age 32 years, regular users of smokeless tobacco	—	Immediate increase in SBP and DBP
Wallenfeldt, 2001 <sup>30</sup>	Swedish randomly selected 58-year-old men	No effect on SBP or DBP	—

SBP, systolic blood pressure; DBP, diastolic blood pressure

**Table 3. Effects of Smoking and Use of Smokeless Tobacco (Snuff or Chewing Tobacco) on Physiologic Risk Factors for Cardiovascular Disease**

Variable (Reference)	Effect of Smokeless Tobacco
Heart rate at rest <sup>5,6,21,35,61,62</sup>	No effect
Heart rate during exposure to smokeless tobacco <sup>6,19-22,54-56,61,62</sup>	Immediate increase, typically 10-20 beats per minute, and significant increase during daytime (mean 6 beats per minute)
Cardiac output at rest and during workload <sup>62</sup>	Same during exposure to oral smokeless tobacco as when exposed to placebo
Work capacity <sup>21,25,37,62</sup>	Same maximal workload and maximal oxygen uptake as in nontobacco users, but increased tachycardiac response to submaximal workload during exposure to smokeless tobacco
Body weight, body mass index <sup>30,35,36,56,63,64</sup>	Same as in nontobacco users (and higher than in smokers) in 5 reports but significantly higher in one study
Waist-hip ratio <sup>30,36,64</sup>	Same as in nontobacco users

in high consumers of snuff compared with nontobacco users.<sup>24</sup> These results are, however, hampered by the small number of events (12 newly diagnosed cases among high consumers of snuff) and the fact that the prevalence of impaired glucose tolerance was not increased among snuff users. As shown in Table 4, there are several studies that have failed to show elevated levels of insulin in snuff users. The finding of an excess risk for diabetes in snuff dippers needs to be confirmed (or refuted) in independent studies.

The data available on cardiovascular risk factors thus suggest that snuff does not activate inflammatory processes, antioxidant consumption, or hemoconcentration as smoking does. Also, the few markers of endothelial function (von Willebrand factor and plasminogen activator inhibitor-1) and platelet activation (thromboxane A2

production) that have been studied, seem to be unaffected. Together, these observations suggest little, if any, activation of biochemical processes involved in the pathogenesis of atherothrombotic disorders. The possible impact of smokeless tobacco on insulin sensitivity, impaired glucose tolerance, and type 2 diabetes needs to be explored further.

As a caveat, it should be mentioned that nicotine itself has been shown to accelerate several biochemical and physiologic processes that are involved in the development of atherosclerosis. Most of these effects have been shown in animal models and tissue culture systems.<sup>25</sup> Nicotine may cause delayed wound healing<sup>26</sup> and it may, by analogy, be reasoned that endothelial repair also could be affected. High doses of oral nicotine given to cholesterol-fed rabbits result in extensive

**Table 4. Effects of Smoking and Snuff Use on Biochemical Risk Factors for Cardiovascular Disease**

Variable (Reference)	Effect of Smokeless Tobacco
Antioxidant vitamins <sup>65</sup>	Serum levels of vitamin C (ascorbic acid), carotene, and vitamin E (tocopherol) similar as in nontobacco users, higher than in smokers
Fibrinogen <sup>30,36,64</sup>	Same as in nontobacco users, lower than in smokers
Fibrinolytic system <sup>36,64</sup>	Same levels of plasminogen activator inhibitor-1 and tissue plasminogen activator activity as in nontobacco users
Thromboxane A2 production (probably reflecting platelet activation) <sup>25</sup>	Same levels as in nontobacco users, lower than in smokers
C-reactive protein <sup>30</sup>	Same as in nontobacco users, lower than in smokers
Fasting blood glucose <sup>24,30</sup>	Same as in nontobacco users, in some reports lower than in smokers
Fasting serum/plasma insulin <sup>30,36,64</sup>	Same as in nontobacco users
Hemoglobin, hematocrit <sup>35,64</sup>	Same as in nontobacco users, lower than in smokers
Serum lipids <sup>5,6,30,36,64</sup>	Same levels of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, lipoprotein(a), and other lipid fractions as nontobacco users; usually more favorable lipid profile than in smokers
Leucocytes <sup>5,6,64</sup>	Same as in nontobacco users, lower than in smokers

endothelial damage and enhance the development of aortic and carotid atherosclerosis.<sup>26</sup> In animal models, nicotine adversely affects cholesterol metabolism, resulting in high low-density lipoprotein and low high-density lipoprotein cholesterol levels. Nicotine, by releasing catecholamines, induces lipolysis and releases plasma free fatty acids.<sup>26</sup> The applicability of the animal models of atherosclerosis used in these studies has been questioned, and the doses of nicotine used are often very high compared with what is achieved by using smokeless tobacco. Nevertheless, nicotine in itself may cause endothelial dysfunction in humans, although to a lesser extent than smoking a cigarette of the same nicotine yield.<sup>27</sup> The clinical significance of this observation is not clear because nicotine replacement therapy does not seem to increase the risk for myocardial infarction in high-risk individuals.<sup>28</sup>

If nicotine is confirmed to be a culprit in the atherosclerotic process in humans, this would seriously caution against the long-term use of both snuff and nicotine replacement therapy. However, the evidence available today suggests that the observations in animal models and tissue culture systems cannot be applied to the human setting without severe reservations.

### **Atherosclerosis in Snuff Users**

Two studies, both conducted in Sweden (and thus reflecting the effects of the Swedish type of moist snuff), have used ultrasound to measure endothelium-media thickness and to detect atherosclerotic changes among smokers, snuff users, and nontobacco users. In the first study, middle-aged firemen were investigated.<sup>29</sup> Those who smoked regularly had consistently higher measures of endothelium-media thickness and more atherosclerotic lesions when compared with nontobacco users. However, their fellow firemen who were regular snuff dippers had the same mean endothelium-media thickness and no more atherosclerotic changes in the carotid artery than nontobacco users had.

In the second study, both the femoral and carotid arteries were investigated by ultrasound in a random sample of middle-aged men.<sup>30</sup> Regular smokers, but not snuff users, had much more atherosclerotic carotid or femoral lesions compared with men who had never used tobacco.

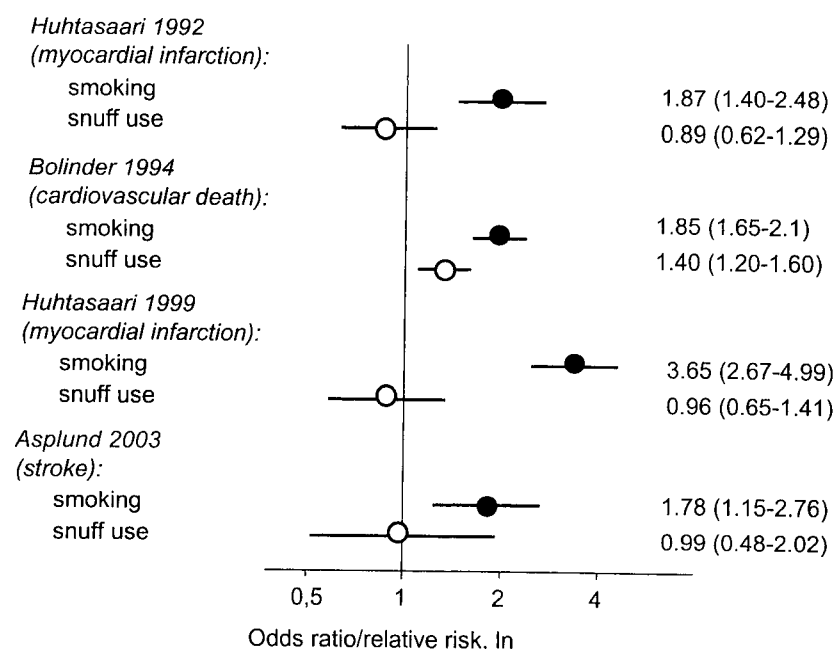
Thus, the limited scientific evidence available suggests that atherosclerotic processes are not accelerated in regular users of snuff.

### **Myocardial Infarction and Stroke in Snuff Users**

As reviewed in other articles in this issue, smoking markedly increases the risk for myocardial infarction, sudden death, stroke, and peripheral artery disease. The possible relationship between snuff use and cardiovascular disease has been explored much less. In fact, there are only 3 studies that have studied the relationship between snuff and risk for myocardial infarction<sup>16,31,32</sup> and one not yet published study on the risk for stroke. All were performed in Sweden. Three of the studies have been performed by our own research group and, although the study populations have been entirely independent, the results need confirmation by independent researchers.

The first study (published in 1992) that explored the relationship between snuff use and risk for myocardial infarction was performed within the framework of the Northern Sweden centre of the World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project, which is a very large multinational study of cardiovascular diseases and their risk factors.<sup>31</sup> Patients who had suffered a myocardial infarction were interviewed about their tobacco habits and other risk factors and they were compared with people who had not had a myocardial infarction (classic case-control study).<sup>32</sup> If the patient had died, a family member was interviewed. As shown in Figure 2, smokers had a nearly 2-fold increase in the risk for myocardial infarction, whereas snuff users did not appear to have any excess risk. The absence of a relationship between snuff use and risk for myocardial infarction remained after adjustment for a number of possible biologic and social confounders.<sup>32</sup>

The next study investigating the relationship was performed among 135,000 construction workers in Sweden.<sup>33</sup> From 1971 to 1974 they underwent a health examination and they were asked about tobacco habits, including the use of snuff. Twelve years later, the Swedish cause-of-death register was checked to record deaths and, if so, the cause of death. Thus, this was a straight-



**Fig 2.** Results from studies that have explored the risk for myocardial infarction and sudden cardiac death and stroke in regular smokers (●) and regular snuff users (○). The risk among non-users of tobacco is set at 1. Horizontal lines represent 95% confidence intervals. The 4 studies are described in the text. Note that the results of the Asplund 2003 study on stroke are preliminary.

forward cohort design. Compared with nontobacco users, those who used snuff in the beginning of the 1970s were found to have a relative risk of 1.4 for dying of any cardiovascular disorder during the 12-year follow-up period, whereas the relative risk in smokers was 1.8-1.9 (Fig 2). The relative risk was much higher in younger cohorts, being 2.1 in snuff users who were 35 to 54 years of age at entry into the study and 1.1 in 55- to 65-year-old snuff users. When subdivided into different manifestations of cardiovascular disease, the relative risks associated with snuff were very similar for death from ischemic heart disease and stroke. Adjustment for potentially confounding variables had little impact on the risk estimates.

The Northern Sweden MONICA research group have performed 2 additional studies on possible adverse effects of snuff use on the risk for cardiovascular disease, one with myocardial infarction and one with stroke as an end-point. In a case-referent study involving a population-based sample of 687 subjects with myocardial infarction (fatal and nonfatal) and 687 closely matched referents, detailed information on tobacco habits was obtained.<sup>16</sup> As shown in Figure 2, this study failed to show an increased risk for myocardial infarction in snuff users compared with men who had never used tobacco (odds ratio, 0.96). Cigarette smokers had an odds ratio of 3.65 for myocardial

infarction. After adjustment for multiple cardiovascular risk factors, the odds ratio remained essentially unchanged for smoking and was reduced to well below 1 for use of snuff. If restricting the analyses to fatal cases of myocardial infarction (including sudden death), there was a tendency toward increased risk associated with snuff use but with very wide confidence intervals owing to few deaths overall (odds ratio, 1.50; 95% confidence interval, 0.45-5.03).

Preliminary results are available from our ongoing analyses of the risk for stroke in snuff users as compared with smokers and nonusers of tobacco. This study has a nested case-control design (ie, data collection [including information on tobacco habits] has been prospective but subjects who have suffered a stroke and subjects free of cardiovascular events have been compared in conventional case-control pairs). With nontobacco users as referents, the odds ratio for stroke, all subtypes together, was observed to be very close to 1 in snuff users, whereas regular smokers had an odds ratio of 1.78 (Fig 2). The latter is very close to the odds ratio of 1.8 found in a meta-analysis of the risk for stroke in smoking men.<sup>34</sup>

As is evident from Figure 2, the results of the 4 studies agree on one point: the risk for a severe cardiovascular event is much smaller in snuff users than in smokers. But in the comparison be-



tween snuff users and nontobacco users the results are discrepant. The cohort study on construction workers showed an increased risk whereas the ensuing 3 case-control studies did not. There are several possible explanations for this discrepancy. The construction worker study was based on deaths in an official vital statistics database. As discussed earlier, nicotine has immediate sympathoadrenal activating properties. This mediates its effects on heart rate and there is a possibility that smokeless tobacco may initiate arrhythmias and that this could enhance the risk for sudden death. None of the 3 studies performed in the Northern Sweden MONICA Center were designed to explore the risk for sudden death, and they did not have sufficient statistical power to detect a small increase in this risk.

Also, there has been a change in snuff use among Swedish men during the past few decades, with the high-prevalence groups gradually shifting from elderly low-educated men to young and middle-aged men with a high level of education. In the construction worker study, snuff users had, as a group, an unfavorable risk factor profile at the health survey in the beginning of the 1970s, with higher body mass index and higher resting blood pressure levels than nontobacco users.<sup>33</sup> Several studies performed during the 1990s were not able to confirm that snuff users had elevated resting blood pressure or increased body weight.<sup>5,6,35-37</sup> Because a large proportion of adult snuff users in Sweden today are former smokers, it could be argued that they constitute the most health-conscious part of the population of tobacco consumers. Possibly, they have other more favorable health behaviors as well, not present among snuff users 30 years ago. On the other hand, it may be argued that the admixture of ex-smokers in the group of snuff users would tend to increase the risk for cardiovascular events. This potential confounder has not been addressed sufficiently in any of the 4 studies.

A third possible explanation for the apparent discrepancies between the results of the construction worker study and the more recent studies is that the composition of moist snuff has changed over the years. The content of some of the toxic products (eg, tobacco-specific nitrosamines) was reduced by half in Swedish snuff from 1983 to

1992,<sup>1,38</sup> and this could perhaps be associated with reduced health hazards of snuff.

### Composition of Cigarette Smoke as Compared With Snuff

All of the 4 earlier-mentioned studies on snuff and hard cardiovascular end-points agree in that there is a marked difference in risk between cigarette smoking and snuff use. This occurs despite the fact that nicotine content, nicotine absorption, nicotine levels in the blood, and the risk for nicotine addiction is about the same with cigarettes and snuff.<sup>39</sup> It seems that tobacco constituents other than nicotine account for the differences in risk for myocardial infarction, stroke, and carotid and femoral atherosclerosis.

Many of the components of tobacco smoke are produced when tobacco is burned and inhaled, and are not present in snuff or other forms of smokeless tobacco. This may help to explain the different effects in the causation of cardiovascular disease. The effects of the complex constituents of tobacco smoke are reviewed extensively in other articles in this issue. Only a few important characteristics of tobacco smoke, as compared with smokeless tobacco, are summarized here<sup>1,40,41</sup>:

- The process of burning tobacco produces toxic substances, for instance, through endogenous nitrosation;
- Among the approximately 2,500 chemical substances identified in tobacco smoke, several moieties (eg, tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, and a wide variety of oxidant gases) have been implicated as agents causing cardiovascular disease;
- A specific chemical compound, 1,3 butadiene, that accelerates atherosclerotic plaque formation has been identified in environmental tobacco smoke;
- The elevated circulating levels of carbon monoxide in cigarette smokers have been implicated in the pathogenesis of smoking-related cardiovascular disease, however, the clinical and experimental evidence to support this hypothesis is not very robust;
- Some tobacco components are better absorbed through the airways than through the mucous membranes of the mouth.

### Possible Implications for Public Health

Because the use of moist snuff seems to affect the cardiovascular system much less than cigarette smoking, would it be reasonable to promote it, for instance, to be used in inveterate smokers who have failed to quit by other means?

Before answering this question, other health hazards implicated in the use of snuff have to be considered. Tobacco-specific nitrosamines and other carcinogens can be absorbed from snuff to a considerable extent, and snuff dippers have as high levels of hemoglobin and DNA adducts as cigarette smokers have. In an analogy with cigarette smoking, smokeless tobacco has been implicated as a causative factor in cancer of the mouth, pharynx, esophagus, stomach, and urinary bladder according to a 1988 report by the US Surgeon General.<sup>42</sup> Several studies published in recent years have, however, failed to confirm the suspicion that commercially available moist snuff causes cancer.<sup>1,33,43-45</sup> On the other hand, dry snuff used in parts of the United States and betel quid used in South Asia seems to increase the risk for cancer in the upper respiratory tract considerably.<sup>46-48</sup> As a reflection of the changing scientific evidence, Swedish health authorities have decided recently to remove the label "Snuff causes cancer" that has been compulsory on moist snuff packages for many years.

What other health hazard may be involved in the use of snuff? At the site where the tobacco is placed, for instance, under the upper lip in Sweden or between the lower gum and the chin in the United States, leukoplakia (local tissue reactions with thickening and whitening) is common.<sup>49</sup> The changes usually are reversible after cessation of snuff use. Snuff users also often have gingival recessions that seem to be irreversible.<sup>49</sup>

The most obvious adverse effect of snuff dipping is that of addiction. Soon after placing smokeless tobacco in the mouth, nicotine peaks in the circulation at high levels,<sup>39</sup> and snuff seems to be at least as addictive as cigarette smoking.<sup>19,22</sup> Some snuff users replace the portion more or less continuously throughout the day and they constantly have high blood levels of nicotine. The success rate among people who try to quit using snuff is no better than that among cigarette smokers.<sup>50</sup>

Thus, established health hazards as a result of the use of snuff involve heavy addiction and oral lesions. Other risks are either small or poorly explored in clinical studies.

It is evident that the use of snuff involves much lower risks for cardiovascular disease and cancer than cigarette smoking does. Proponents of snuff have applied the concept of *harm reduction*. The Swedish experiences would indicate that, in men, snuff is very frequently used as an aid to quit smoking and that this has helped to keep the prevalence of smoking and of smoking-related disorders low in international comparisons.

People involved in the fight against tobacco intuitively refute the idea of treating cigarette smoking with smokeless tobacco as being flawed. From a medical and moral point of view, the only reasonable norm is nonuse of tobacco. In many countries, governmental decisions reflect the view that the goal of a tobacco-free society means that smokeless tobacco should be fought as vigorously as smoking. For instance, the European Union, acting on a World Health Organization recommendation, has prohibited the sale of snuff in all its member states except Sweden<sup>51</sup> (it is somewhat paradoxical that the European Union subsidizes tobacco production to be used for manufacturing cigarettes). The US Congress has banned the advertising of smokeless tobacco on radio and television and required health warnings on packages and printed advisements.<sup>51</sup>

### Unresolved Issues

As is evident from this article, the hazards of snuff and other forms of smokeless tobacco are only partially known. Among the issues that need to be resolved are:

- Can the results of the Swedish studies on the risk for myocardial infarction, sudden death, and stroke be applied to all commercially available snuff brands, or are the hazards different?
- Does homemade smokeless tobacco used in many poor countries of the world involve risks for cardiovascular disease that are different from those of snuff used in rich countries?
- Does smokeless tobacco cause disturbances of the heart rhythm and, if so, does this increase the risk for sudden death?
- Does the immediate increase in blood pressure

and heart rate on intake of snuff have any long-term deleterious effects on the heart and the vascular tree?

It emerges from this list of unresolved issues that it is wise to be cautious when discussing the health hazards of snuff use and their impact on health policy—there is still much room for improved knowledge.

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