Institute of Environmental Medicine,
Karolinska Institutet, Stockholm, Sweden

Swedish moist snuff and the risk of cardiovascular diseases

Maria-Pia Hergens

Karolinska Institutet

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To my mother Eva

ABSTRACT

The snuff consumption in Sweden has increased substantially during recent decades and today more than every fifth male adult uses snuff daily. However, the evidence on health effects from long-term use of snuff is limited, especially regarding cardiovascular diseases.

The overall objective of this thesis was to study the association between snuff use and cardiovascular diseases. Two epidemiological materials were used and both were restricted to men only. One material included a population based case-control study with 1 437 cases of myocardial infarction and 1 810 matched controls, aged 45-70 years and living in Stockholm or Västernorrland county between 1992 and 1994. The second material was a large nationwide cohort based on construction workers who attended at least one health check-up between 1978 and 1993. We found that snuff use was highly correlated with smoking and some cardiovascular risk factors. Furthermore, snuff users were generally younger than the non snuff users and there were geographical differences with a higher prevalence of snuff use in northern Sweden.

To avoid confounding from smoking the main analyses were restricted to never smokers. We found no evidence that the snuff use increased the overall risk of myocardial infarction. In the large prospective cohort, consisting of more than 100 000 non-smoking construction workers, we observed an increased risk of fatal myocardial infarction among current snuff users compared to never users, the risk being even higher among heavy users, with relative risk estimates of 1.32 (95% CI, 1.08-1.68) and 1.96 (95% CI, 1.08-3.58), respectively. Furthermore, no increased overall risk of stroke was observed among the snuff users. However, the relative risk for fatal cases was 1.38 (95% CI 0.99-1.91) among current snuff users and for fatal ischemic stroke the relative risk was 1.72 (95% CI 1.06-2.78). For those who suffered non-fatal myocardial infarction or non-fatal ischemic stroke we found an increased mortality both overall and in cardiovascular diseases among snuff users compared to never tobacco users. We also found associations between snuff use and high blood pressure as well as hypertension. The prevalence of high blood pressure was significantly higher among snuff users than non-users at the time of first blood pressure measurement. During follow-up, snuff users who were normotensive at the first blood pressure measurement, had an increased risk of developing hypertension or high blood pressure at a subsequent measurement with relative risks of 1.36 (95% CI, 1.07-1.72) and 1.39 (95% CI 1.08-1.79), respectively.

In conclusion, snuff use does not seem to increase the risk of myocardial infarction or stroke. However, an increased risk of fatal diseases was observed among snuff users, both for myocardial infarction and stroke, suggesting that snuff use could influence the severity of these outcomes. Snuff use was also associated with an increased risk for high blood pressure and hypertension.

Key words: Snuff, cardiovascular diseases, myocardial infarction, stroke, hypertension, case-control study, cohort study

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LIST OF PUBLICATIONS

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III. **Hergens M-P**, Lambe M, Pershagen G, Terent A, Ye W. Use of smokeless tobacco and the risk of stroke among Swedish men. *Submitted 2007*

IV. **Hergens M-P**, Lambe M, Pershagen G, Ye W. Hypertension among male snuff users - a prospective study from Sweden. *Submitted 2007*

LIST OF ABBREVIATIONS

BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Confidence Interval
CPS	Cancer Prevention Program
CT	Computed Tomography scan
CVD	Cardiovascular Diseases
ECG	Electrocardiogram
IARC	International Agency for Research on Cancer
ICD	International Classification of Disease
IPR	Inpatient Register
IHD	Ischemic Heart Disease
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NBHW	National Board of Health and Welfare
NRN	National Registration Number
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
RR	Relative Risk
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SHEEP	Stockholm Heart Epidemiology Program
VHEEP	Västernorrland Heart Epidemiology Program

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of death in developed countries today [1, 2]. In 2002 CVD accounted for 45% of all deaths in Sweden among men and 44% among women [3]. However, the mortality from CVD has decreased in Sweden during the last 30 years due to preventive measures and lifestyle changes as well as improved medical care [4, 5].

Besides high age and sex, the most well known risk factors for CVD include smoking, diet, physical inactivity, high blood pressure, diabetes and high cholesterol [6]. Smoking has been the number one preventable risk factor for cardiovascular diseases in Sweden. Smokeless tobacco, including the Swedish moist snuff, has been proposed as an alternative to smoking, for harm reduction [7, 8]. However, the evidence regarding health effects from long-term use of snuff is limited and the literature is inconclusive [9-18]. The uniquely high prevalence of snuff use in Sweden and the integrated health care system makes it possible to perform epidemiological studies for estimating the risk of snuff on cardiovascular diseases. In paper I and II included in the thesis, the risk for myocardial infarction among snuff users was estimated and in Paper III the main objective was to estimate whether snuff is a risk factor for stroke. In paper IV we investigated the effect of snuff use on blood pressure and hypertension, a well known risk factor for cardiovascular diseases.

BACKGROUND

Cardiovascular disease: pathology, occurrence, and risk factors

Myocardial infarction

Ischemic heart disease occurs when there is a reduction of the coronary blood flow, which leads to an imbalance between the oxygen supply and the demand of the myocardium [19]. The blood flow reduction is usually due to progressive atherosclerosis with extensive occlusion of the coronary arteries. Myocardial infarction (MI) is the rapid development of myocardial necrosis, usually a result from plaque rupture with thrombus formation in a coronary vessel, leading to an acute reduction of blood supply to a part of the myocardium. The blood flow could further decrease due to additional events such as vasospasm, thrombosis or circulatory changes. Diagnosis is usually based on symptoms described by the patient, electrocardiogram (ECG) and measurement of specific heart enzymes in blood samples.

The incidence of MI increased until 1980 [5, 20] but has declined ever since [21, 22]. During this period a decrease in several traditional risk factors for myocardial infarction was observed [23]. There are clear differences in occurrence between the sexes; the incidence is approximately four times higher among men younger than 60 years compared to women of the same age. The incidence of myocardial infarction increases steadily with age and in the ages older than 75 years the difference between men and women has decreased to one and a half. Totally for all ages over 20 years, the incidence among men is twice as high as among women [3].

More than 200 risk factors for myocardial infarction have been described [24] and the most established risk factors include smoking, diet, physical inactivity, high blood pressure, diabetes and high cholesterol [6]. Some of these factors are modifiable, such as tobacco use, physical activity and diet.

Stroke

Stroke is a general name for ischemic stroke and hemorrhagic stroke [25]. An ischemic stroke occurs when either extra- or intracranial blood vessels are occluded, causing hypoxemia in parts of the brain. These occlusions could be caused by blood clots from the heart “traveling” to the brain or by clots from the carotis artery. Blood clots from the heart are often due to pathologic heart rhythms and clots from the carotis artery could be caused by atherosclerosis. Strokes that are a result of emboli are referred to as cardioembolic strokes and account for approximately 20% of all strokes. Ischemic stroke could be followed by a hemorrhage but the etiology differs from hemorrhagic stroke, which is caused by rupture of intracranial blood vessels often due to high blood pressure or a deformity of the blood vessels. Diagnosis should be based on a full neurological and cardiovascular assessment, electrocardiogram, urinalysis, and brain imaging including computed tomography (CT) scan or magnetic resonance imaging (MRI).

In 2002, stroke accounted for 20 % of all cardiovascular deaths among men and 27 % among women. Stroke is the second most common cause of death after myocardial infarction [26]. Every year approximately 30 000 persons are diagnosed with stroke. The proportions of subtypes are 85% for ischemic, 10% for hemorrhagic and 5% for unspecified strokes. The occurrence of stroke has been relatively stable during the period 1987-2001 although the survival rate has increased. The risk of getting stroke increases with age and approximately 80 percent of all cases occur among persons older than 65 years [26].

Ischemic stroke and hemorrhagic stroke have different pathological etiology and therefore they differ to some extent regarding risk factors. Besides high age and male sex, hypertension, hyperlipideamia and diabetes are important for all types of stroke [27]. Tobacco smoking is also a risk factor for all types of stroke with the strongest effect observed for subarachnoid hemorrhage and ischemic stroke [28-30]. Heart diseases such as arrhythmias are risk factors for ischemic stroke [31] while extensive alcohol consumption is an important risk factor for hemorrhagic stroke [29].

Hypertension

Persistently increased blood pressure is required for a clinical diagnose of hypertension. High blood pressure may be harmful to the cardiovascular system through an increased workload on the heart and has an effect on the coronary, renal and cerebral arteries. However, hypertension often lack symptoms and many people could therefore have hypertension without knowing it [19, 32].

The blood pressure varies both between individuals and within individuals at different times [32]. Within an individual it can change with physical activity, stress and age. Anxiety and pain can also temporarily increase the blood pressure. For this reason hypertension is not diagnosed from one blood pressure measurement only, but should be based on several measurements [32]. In epidemiological studies hypertension can be defined in several ways, for example by using different cut-points of systolic and diastolic blood pressure, information on medication and self reports of diagnoses [33]. The definition of hypertension has been subject to much debate, partly based on diverging views on how and when it should be treated [33].

The prevalence of hypertension in a population depends on the definition, including cut-points on systolic and diastolic blood pressure. In guidelines from 1999, WHO defines a blood pressure of 140/90 mm Hg or above, in untreated subjects, as hypertension. Further, according to WHO's guidelines a blood pressure of 140-159/90-99 mm Hg is defined as "mildly increased blood pressure", 160-179/100-109 mm Hg as "moderately increased blood pressure" and >180/>110 mm Hg as "seriously increased blood pressure". Before these guidelines were introduced higher cut-points were often used to decide whether or not treatment was necessary. In Sweden 160/95 mm Hg was used, leading to a lower prevalence [34].

Using the WHO guidelines from 1999, more than a quarter of the population had hypertension worldwide in 2000 and the number is estimated increase to 29% by 2025 [35]. The prevalence varies widely in the world but is generally between 20-50 % in developed countries [36]. The prevalence among people older than 20 years is 27%, of them 60% have mildly increased blood pressure, 30% have moderately increased blood pressure and 10 % have seriously increased blood pressure [32].

Smokeless tobacco

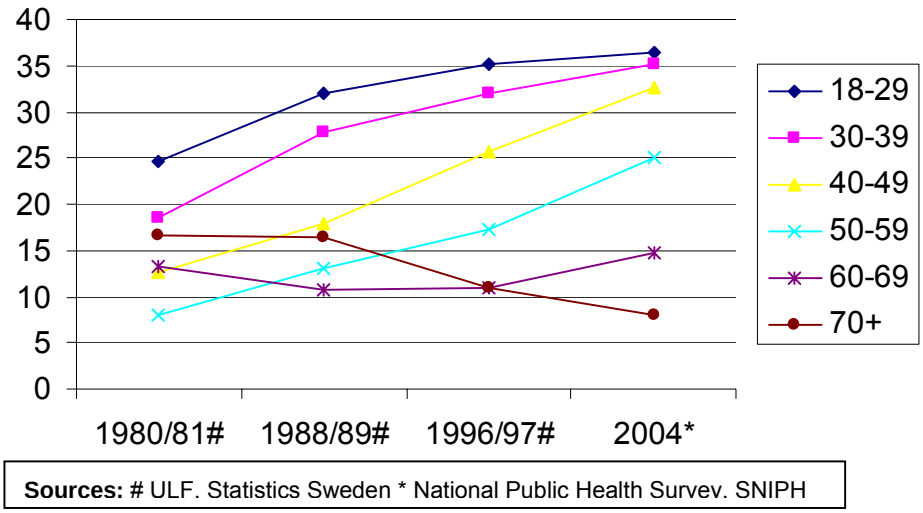
Smokeless tobacco

Smokeless tobacco is mostly used orally, while nasal use has become rare. Chewing tobacco and snuff are the two dominant products used in Europe and North America [17, 37]. The various types of snuff and smokeless tobacco differ in their formulation and composition, partly as a consequence of how the tobacco is refined. In other parts of the world, including Central and South-East Asia, parts of East-Africa and South-America smokeless tobacco is used either by itself or in combination with other products, such as betel nut quid, slaked lime and areca nut [38-40]. In most countries smokeless tobacco constitutes only a small proportion of the total tobacco market, except for Sweden where snuff (snus) constitutes approximately 50% of the total tobacco sold. Both in USA and in Sweden the use of snuff has increased in recent decades whereas smokeless tobacco is prohibited in the European Union since 1992.

Occurrence of snuff in Sweden

In 1920, 70 % of the total tobacco sales in Sweden consisted of snuff, after that the proportion decreased substantially. In recent decades the sales increased and in 2000, 53% of all tobacco sold in Sweden was snuff [9, 11]. The prevalence of snuff use has increased steadily since the 1970s and according to data from 2004, more than 20% of the men between 18-84 years were daily snuff users with the highest prevalence in the lower age groups (18-29 years), shown in figure 1.

Figure 1. Prevalence (%) of daily or occasional snuff use among men, by age groups.
(Reprint from "Hälsorisker med svenskt snus" Stockholm: National Institute of Public Health, 2005 with permission from the publisher)



Since the 90s the largest increase has been seen among well educated men and women leading to decreasing socioeconomic differences among snuff users [3, 9]. Approximately 3% of the women (18-84 years) were daily snuff users in 2004 but in the ages 15-16 years 8% of the girls used snuff. Both among men and women there are great regional differences in snuff use with the highest proportion in northern Sweden [9, 41-44]. The use of snuff is often combined with smoking and approximately 50% of the snuff users are also ever smokers although it is rare that daily snuff use is combined with daily smoking [9, 45].

Table 1 Percentage of adults (18-24) using snuff and/or smoking, daily or occasionally, by sex (Reprint from "Hälsorisker med svenskt snus" Stockholm: National Institute of Public Health, 2005 with permission from the publisher)

Tobacco consumption	1988-89#		1996-97#		2004*	
	Men	Women	Men	Women	Men	Women
None	53.4	66.1	58.6	69.1	58.3	70.1
Smoking only	25.5	32.4	17.9	28.9	15.0	24.0
Snuff only	10.8	0.5	14.0	0.9	15.8	2.9
Both smoking and snuff	10.3	1.0	9.5	1.2	10.9	3.0

Chemical composition of Swedish moist snuff (snus)

Since 2005 the tobacco industry is forced by law to declare the constituents in their products. The chemical composition and the nicotine content in snuff depend on the tobacco as well as the cultivation, harvest, production process and storage [12], [46]-[47]. More than 3 000 chemical substances are found in tobacco such as amino acids, carbohydrates, lignin, fatty acids, chlorophyll and their breakdown products [48] as well as heavy metals, such as lead and cadmium [9]. Secondary metabolites include alkaloids, nicotine being the predominant (85-95% of total alkaloids) but also tobacco specific nitrosamines, flavonoids, polyphenols and aromatic substances [12], [49, 50].

Snuff is manufactured from the Nicotiana Tabaccum plant, using dark chlorophyll-rich tobacco grounded into flour and then pasteurized through a heating process. The contents in Swedish moist snuff are presented in table 2 [9].

Table 2. Contents in Swedish moist snuff.

Chemical substance	**Percent (%)**
Tobacco	40-50%
Water	45-60%
Sodium	1.5-3.5%
Bicarbonate	1.5-3.5%
Moisturizing agents (glycerol and propylene glycol)	1.5-3.5%
Aroma additives	< 1%

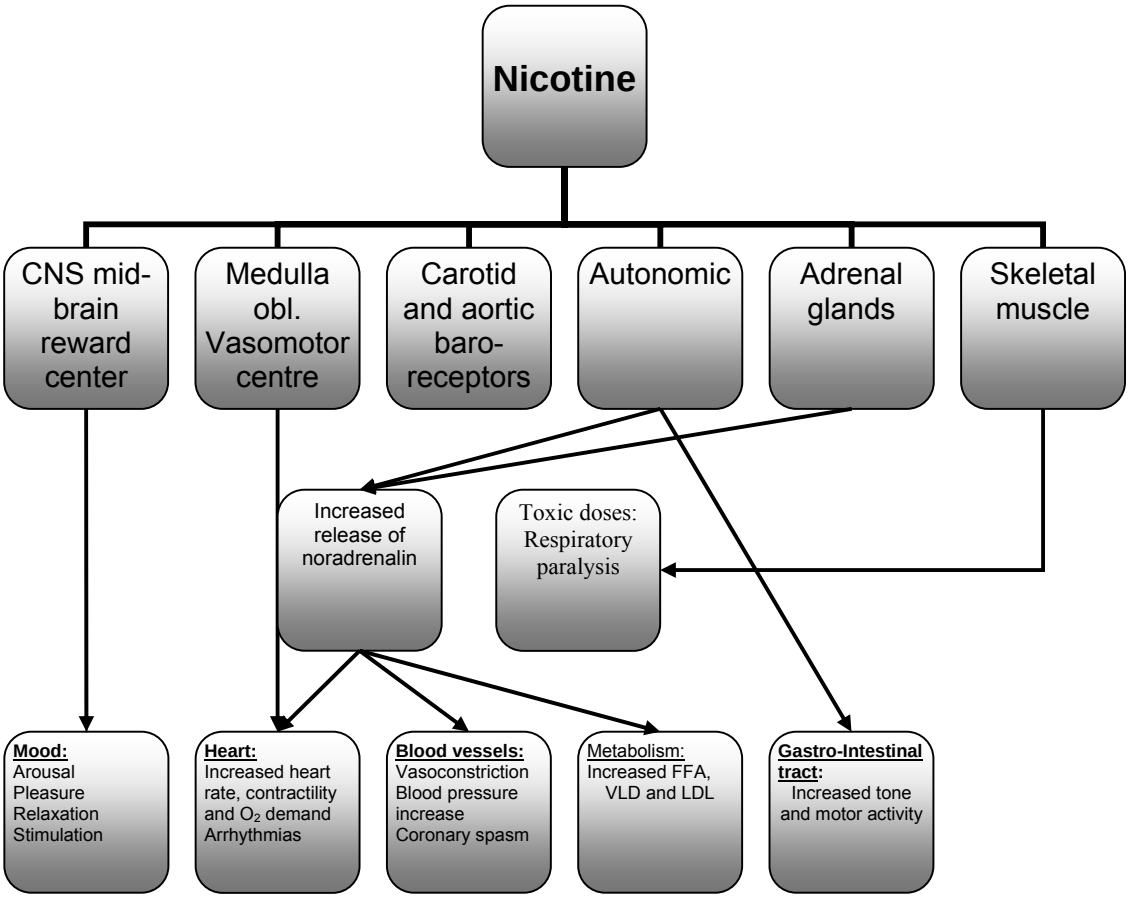
Nicotine is the most important addictive substance in smokeless tobacco [51] and the nicotine content in snuff varies between 0.5-1.3% depending on the type of snuff. Snuff also contains several chemical compounds that are known or suspected to be carcinogenic, such as the tobacco-specific N-nitrosamines (TSNA). The levels of TSNA varies between different types of smokeless tobacco and the levels have declined in moist snuff used in Sweden and in USA since the 1980s. It is also important to mention that snuff contains substances, such as antioxidants and nitrate, which could partly neutralize the hazardous effects from nicotine and TSNA [12], [9].

Nicotine

The absorption of nicotine from snuff through the oral mucosa is slower than when the tobacco is smoked [52, 53]. The levels of unionized nicotine increases with higher pH, which facilitate the absorption of nicotine [54]. Previous studies on smokeless tobacco reported that the pH ranged from 5.39 to 7.99 and the proportion of unionized nicotine varied between 0.23%-48.3% [12] where moist snuff had the highest mean pH. The nicotine levels found in snuff users are equivalent to those found in smokers, and due to the slow absorption the levels remain higher among snuff users during a longer period [52, 55, 56] Unionized nicotine can cross the cell membranes and bind to receptors at the autonomic ganglia, the adrenal medulla and the central cholinergic synapse. Exposure to nicotine results in effects that work through the activation of several central nervous

system pathways , the cardiovascular effects are mainly due to stimulation of the sympathetic ganglia and the adrenal medulla whereas a parasympathetic stimulation leads to gastrointestinal effects (Figure 2) [57]-[58]. The increase in blood pressure through activation of the sympathetic nervous system is observed at relatively low blood levels of nicotine. These effects reach a maximum even if the nicotine level in the blood is further increased; and persist as long as the nicotine levels are moderate, including overnight [59, 60]. This means that a snuff user can have a sympathetic activation 24 hours per day [60].

Figure 2 Major pharmacological actions of nicotine (Reprint from Bolinder G. Long-term Use of Smokeless Tobacco- cardiovascular mortality and risk factors: Karolinska Institutet, 1997. with permission from author)



Cardiovascular and metabolic effects from nicotine and snuff

Studies in animals

Increases in blood pressure and heart rate as a result of nicotine exposure have been observed in several animal studies, both after intravenous injections [61-63] and after 2 weeks of exposure from subcutaneous pellets [64]. Studies on snuff and cardiovascular effects in animals confirmed these results [65-67]. However, the levels of nicotine measured in blood exceeded those found in humans after exposure from the same type of snuff [56, 66]. Further, studies showed that injections of nicotine could induce cardiac arrhythmias in dogs [68] and increase the sensitivity to arrhythmias and induce ventricular fibrillation in hearts with healed myocardial infarction [69]. Two studies found poorer myocardial healing after infarction and larger tissue damage in hearts after myocardial infarction in animals exposed to nicotine [70, 71].

The results on metabolic effects in animals exposed to nicotine are inconclusive. Some did not observe any effects on insulin and glucose intolerance in rats exposed to nicotine [64, 72] while others found increased blood sugar levels, decreased HDL and increased LDL levels [73, 74], as well as more extensive plaque formation in blood vessels [75] and increased endothelial damage [76].

Studies in humans

Physiological and metabolic effects

Exposure to nicotine can cause a release of free fatty acids which, through the formation of lipoproteins, could increase the risk of arteriosclerosis [77]. This is confirmed in one study from USA, where hypercholesterolemia among those who used smokeless tobacco was twice as great as among those not using any tobacco [78]. Other cross-sectional studies did not observe an effects on blood fats, fibrinogen, C-reactive protein or other biochemical factors which can affect the risk of cardiovascular diseases, after long-term use of snuff [79-84]. Neither does snuff seem to have any effect on the occurrence of atherosclerosis and arteriosclerosis of the carotid [81, 85]. However, a more recent study observed damages in the endothelial cells in the brachial artery 35 min after exposure to snuff. This was not observed after exposure to placebo. It is suggested that this type of damage in the endothelial cells could lead to atherogenic changes and cardiovascular disease [86].

A Swedish study compared insulin resistance between snuff users and never snuff users. No difference was observed between the groups in fasting insulin, fasting glucose or glucose after an Oral Glucose Tolerance Test (OGTT) [80]. Another study showed an increase in insulin resistance and hyperinsulineamia among subjects with long-term use of nicotine substitutes. However, causality regarding the role of nicotine could be questioned in this study since the group of nicotine users were all former smokers and snuff users, compared to never tobacco users [87].

Two Swedish epidemiological studies have observed a higher prevalence of type-2 diabetes among snuff users compared to never users [88, 89], but only one saw significant differences [88] and after further follow-up, no increased risk of type-2 diabetes was observed among snuff users [89]. An increased risk of diabetes mortality was reported in one American cohort (Cancer Prevention Study-II), while no such increase was observed in another cohort (Cancer Prevention Study-I) [90]. All studies regarding snuff use and the risk of diabetes are based on few cases, which make the results unreliable.

Circulatory effects

The literature regarding acute cardiovascular effects from snuff use and smokeless tobacco is more or less consistent and reports on effects such as increase in pulse rate, a rise in the systolic blood pressure, an increase in the cardiac output, as well as vascular constriction [55, 56, 65, 83, 91, 92]. The elevations observed in blood pressure range from 10-20 mm Hg in systolic blood pressure and 6-12 mm Hg for diastolic blood pressure [55, 91, 92]. One study found a 5-10% higher heart rate and blood pressure, both at rest and at work load, among those exposed to snuff within 2 hours prior to measurement [93]. Another study found no differences during work load between snuff users and non-snuff users, although a continued increase in pulse rate after physical activity was observed in snuff users [94].

Studies on the long-term effects on blood pressure are more inconclusive. Two Swedish studies show an increased prevalence of high blood pressure or a higher daily mean blood pressure, among snuff users compared to those who do not use snuff [95, 96] while others have failed to see any association between long-term use of snuff or smokeless tobacco and hypertension [79-81, 93, 94, 97]. Results from American studies are also inconclusive, some showing a higher prevalence of high blood pressure among smokeless tobacco users [98, 99], while others found no association [82, 83]. So far, all studies on smokeless tobacco and snuff use and the effect on blood pressure are based on cross-sectional methodology which makes it difficult to assess causality.

Epidemiological studies on myocardial infarction and stroke

Four Swedish studies have been carried out within the WHO MONICA- project in Norrbotten and Västerbotten County [100-103]. Three studies examined the effect of snuff on myocardial infarction [100, 101, 103] and overall, no increased risk of myocardial infarction was observed. Two of the studies divided the cases into non-fatal and fatal cases. In the first, an increased risk was observed for fatal cases among snuff users, however not statistically significant [101]. The second could not confirm these results. In this study fatal cases were further divided into groups of survival time after symptom debut (<28 days , < 24 hours and < 1 hour) but no analyses were made for all fatal cases together [103]. The fourth study within the MONICA-project is a nested case-control study assessing the risk of stroke among snuff users [102]. No increased risk of stroke, fatal and non-fatal, was observed among snuff users compared to non tobacco users. Neither did another case-control study find any evidence that snuff use increased the risk of subarachnoid hemorrhage [104]. Three Swedish cohort studies have

investigated snuff use and the risk of cardiovascular disease (CVD) [105-107]. In one study the outcome was presented as mortality from CVD, with separate analysis for ischemic heart disease (IHD) and cerebrovascular disease [105], in the second, mortality and incidence of coronary heart disease was used as outcome and analyzed together [106]. Significant risks of death from CVD, IHD and cerebrovascular diseases were observed in the first study and the second found an increased risk of CHD among snuff users, although the estimates were not statistically significant. The third study presented outcome as incidence or mortality in IHD or stroke. Analyses were made for fatal cases separately. No increased risk was observed for IHD or stroke. However, for fatal IHD a small increase in risk was suggested [107]. American studies on snuff and smokeless tobacco and CVD mortality are inconclusive. One found no increased risk of death from CVD and cerebrovascular disease in the group which used smokeless tobacco compared with those who had never consumed tobacco [108] and another, based on two cohorts (CPS-I and CPS-II), observed a 10-60% increased risk of death from CVD or cerebrovascular diseases among those who used smokeless tobacco compared to never users [90]. Separate analyses for exclusive snuff use showed no increased risk of stroke compared to those who never used any tobacco.

Other health outcomes

Cancer

Smokeless tobacco and the risk of cancer has been evaluated thoroughly in several reports [9, 10, 12, 16, 109]. Both the international Agency for Research on Cancer (IARC) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) concluded that smokeless tobacco is associated with an increased risk for several types of cancer, such as oral cancer and pancreatic cancer. These results are based on epidemiological studies of all types of smokeless tobacco and supported by experimental animal studies. The evidence for the risk of oral cancer from use of Swedish moist snuff is not as strong but could not be ruled out [9, 10, 16].

Oral lesions

All oral use of smokeless tobacco causes mucosal changes in the mouth. These damages are called snuff-induced lesions and there is some evidence that these lesions could be precancerous and potentially malignant [110, 111]. The damage is more severe when using snuff with high pH or high nicotine content [112, 113]. However most lesions usually disappear after cessation [9].

Pregnancy outcome

So far the evidence on the effect of snuff use on reproductive outcomes is limited. Only one study has been conducted suggesting that snuff use could increase the risk for pre-eclampsia and premature birth. Snuff also seems to inhibit fetal growth [114].

AIMS

The main aim of this thesis was to investigate whether long-term use of Swedish moist snuff increases the risk of cardiovascular diseases, using two large epidemiological materials. The specific aims were:

- To asses the risk of fatal and non-fatal myocardial infarction among men who use snuff but have never smoked (I and II).

- To compare the probability of all deaths and cardiovascular death among snuff users and non snuff users among subjects who suffered from a myocardial infarction or ischemic stroke (II and III)

- To study whether snuff use affects the risk of fatal and non-fatal stroke among never smoking men (III)

- To investigate if there is a difference in risk from snuff use between subtypes of stroke, such as ischemic, hemorrhagic and unspecified stroke.

- To compare the prevalence of high blood pressure among snuff users and non snuff users among never smoking men (IV).

- To study whether snuff use increases the risk of hypertension among never smoking men with normal blood pressure at start of follow-up (IV).

MATERIAL AND METHODS

This thesis uses data from two epidemiological materials; a regional case-control study and a nationwide cohort study. The Stockholm Heart Epidemiology Program (SHEEP) and the Västernorrland Heart Epidemiology Program (VHEEP) are population based studies on risk factors for myocardial infarction. The Construction Workers Cohort is based on materials from health examinations provided to all employees in the construction industry.

Table 3 An overview of the materials and methods used in the four papers in the thesis.

	Paper I	Paper II, III and IV
Design	Case-control	Cohort
Study population	Native Swedes, aged 45-70 years living in Stockholm or Västernorrland counties between 1992-1994	All employees within the construction industry in Sweden between 1969-1993
Participants	1432 men with myocardial infarction and 1810 controls	Paper II: 118 395 never smoking men with no prior myocardial infarction Paper III: 118 465 never smoking men with no prior stroke Paper III: 120 930 never smoking men with blood pressure measurements
Follow-up		1978-2003/4 through register linkage 1978-1993 health check-ups
Outcomes	Myocardial infarction	Paper II: Myocardial infarction Paper III: Stroke Paper IV: High blood pressure and Hypertension
Exposure	Current snuff users Former snuff users Questionnaires	Current snuff users -Groups according to amount g/day Former snuff users Questionnaires
Matching variables	Age, hospital catchment area	
Adjustments	Age, hospital catchment area, smoking	Age, Body Mass Index, area of domicile
Statistical Analyses	Odds ratio, unconditional logistic regression model	Hazard ratio, Cox regression model Odds ratio, unconditional logistic regression model. Generalized Estimation Equations (GEE)

Paper 1: The SHEEP and VHEEP material

The Stockholm heart epidemiology program (SHEEP) is a population based case-control study with the objective to study risk factors for myocardial infarction and the Västernorrland heart epidemiology program (VHEEP) is linked to the SHEEP study. The study design in SHEEP and VHEEP is identical, except for the regional catchment area. The study base in SHEEP consists of Swedish citizens without previous myocardial infarction aged 45-70 years living in Stockholm County between 1992-1993 (men) or 1992-1994 (women). In the VHEEP study Swedish citizens living in Västernorrland County between 1993-1994 and aged 45-65 years defined the study base [115].

Case and control identification, data collection and major risk factors for myocardial infarction in the SHEEP and VHEEP study have been described in detail previously [115-119]. Since the prevalence of snuff use among women is very low, less than 1%, the present study is restricted to men only.

Case identification

Three sources were used for identification of cases; 1) coronary and intensive care units at the internal medicine departments of all emergency hospitals within Stockholm and Västerbotten County, 2) the computerized Inpatient Register in the two counties and 3) death certificates from the national Causes of Death Register, both held at Statistics Sweden. The diagnose criteria were identical at all the medical units and certain criteria had to be fulfilled; 1) case history and information of specific symptoms, debut and duration of symptoms, 2) blood samples with increased levels of specific heart enzymes, i.e. kinase (CK and CK-MB) and lactate dehyrdogenase (LD and LD1) with maximal values 15-18 hours and 36-48 hours after symptom debut, respectively, 3) specific ECG-changes and 4) myocardial necrosis on autopsy findings, corresponding to the date of symptom debut. For diagnose of myocardial infarction at least two of criteria 1-3 or criteria 4 had to be met. These criteria were accepted by the Swedish Association of Cardiologists in 1991. Through linkage to the Inpatient Register each case was checked for myocardial infarctions between 1975 (1985 in VHEEP) and date of inclusion in the study. This way subjects with earlier myocardial infarction were excluded and only first time events were included. Cases still alive after 28 days after symptom debut were classified as non-fatal cases and those who died within 28 days were considered fatal cases.

In total, the SHEEP study consists of 1 485 male cases, aged 45-70, who had suffered either a fatal or a non-fatal myocardial infarction during the years 1992-1994 and who had never suffered from myocardial infarction before, and their matched controls (n=2 088). The VHEEP study consists of 275 male cases, aged 45-70, identified during 1993-1994 and their matched controls (n=337).

Control identification

The controls were randomly selected from the study base through linkage to a computerized register of the population in Stockholm and Västerbotten counties. One master referent per case was selected within two days of case incidence and matched on age, sex and hospital catchment area. The hospital catchment area was linked to the residence address and not related to the hospital where the case was treated. Five candidate controls per case were identified simultaneously so that potentially non-responding controls could be replaced by another control that was part of the study base at the time of the case identification. All controls were alive, regardless of whether the matched case survived the myocardial infarction or not [117]. Sometimes both the initial and the substitute control responded which made the controls more numerous than the cases. Each control was checked for prior myocardial infarction through linkage to the Inpatient Register in the same way as the cases.

Questionnaire

Information on exposure and potential risk factors was collected by self administered questionnaires which were sent out to all cases and their matched controls. To minimize the non-response, an introduction letter was sent out prior to the questionnaire. The returned questionnaires were checked and an additional interview was made through telephone to fill in missing data. If the additional information suggested previous myocardial infarction the subject was excluded from the study. For deceased cases, exposure information was gathered through a self administered questionnaire completed by the next-of-kin, sent out within 6 month after the death.

The hospital treated cases and their matched controls were offered an additional health examination including measurements of blood pressure, height and weight as well as blood sampling, 3 months after inclusion in the study. The total participation rate was 88% among the non-fatal cases, 62% for the fatal cases and 74% among the controls in the SHEEP study. The corresponding figures were 89%, 67% and 82% in the VHEEP study.

Covariate exposure

Through the questionnaires, information on both well known and potential risk factors is available [117]. Several of these risk factors were controlled for in the present study, such as diabetes, hyperlipideamia (6.46 mmol/l), hypertension (=>170/95 mmHg), overweight (BMI=>30), physical inactivity and work related stress. Smoking status was categorized as never smokers, former smokers and current smokers. Amount of cigarettes was used and stated as cigarettes/day. Daily smokers who stopped smoking one year prior to inclusion were defined as former smokers and those who smoked daily within one year was categorized as current smokers.

Snuff exposure

The information on snuff used was based on questions regarding daily usage, age when starting to use snuff, amount used (measured in boxes/week) and age at cessation. In the analyses snuff use was divided into three categories, never used snuff, former snuff users and current users. Subjects who used snuff daily but stopped more than two years before inclusion were regarded as former snuff users whereas daily snuff users within the two years prior to inclusion were categorized as current snuff users. Due to lack of power the information on duration and amount was not used in the risk assessments.

Paper II-IV: The Construction Workers Cohort

Together with trade unions and the Swedish Employers Association, the Construction Workers Health Services (BYGGHÄLSAN) offered free out-patient medical services between 1969 and 1993 to all employees (blue collar and white collar) in the building industry. Personal invitations and advertisements at almost all major building sites in Sweden were used to reach the workers and approximately 75% of the employees in the industry are registered in the Construction Workers Cohort. There is no information on whether the non-attendants did not get an invitation or if they were unwilling to participate. At stationary or mobile clinics, staffed by nurses and physicians, preventive health check-ups were offered every second year during the first years and every third year thereafter. The total number of visits in the register is over 1 150 000 among 386 000 individuals. The mean number of visits was three and some individuals had up to 13 visits. More than 200 000 men had more than one visit.

Due to limited exposure information prior to 1978, the present studies are restricted to subjects with at least one registration after January 1 1978. In all, 300 637 individuals had a health check-up between 1978 and 1993 and 77 844 of them were also registered prior to 1978. These subjects overlap to some extent with a previous study on snuff use and cardiovascular diseases based on the construction worker cohort with men registered between 1971 and 1975 [105]. The present studies are based on more than 200 000 new subjects. Approximately five percent of the employees were women (n=14 982) and considering the low prevalence of snuff use in this group, the present studies were restricted to men.

Snuff use and smoking are closely correlated and to avoid confounding all former or current tobacco smokers were excluded. For subjects with multiple health visits, all information available on smoking habits was used during the period 1971 through 1993. In a previous quality control of smoking among individuals registered between 1971 and 1975 four percent reported being both current and ex-smokers [120]. Inconsistencies over time were found in 2.6% among those with more than one health check-up. In all, more than 160 000 men were excluded due to ever smoking. For detailed information of inclusion and exclusion criteria in the final cohort, see figure 3

Questionnaire

Exposure information was collected at the health check-up through a self-administered questionnaire with approximately 200 items, self reported environmental exposure at the workplace, detailed information on tobacco status and various health symptoms as well as drug consumption. To avoid misunderstandings and inconsistencies a nurse verified the answers together with the employee. Blood pressure, height and weight were registered at the health check-ups in a form called the LS-form. From 1975 the self administered questionnaire was no longer in use and no tobacco information is available during the period 1975 to 1978. However, the LS-form was continuously in use and was extended in 1978 with more detailed information on tobacco habits.

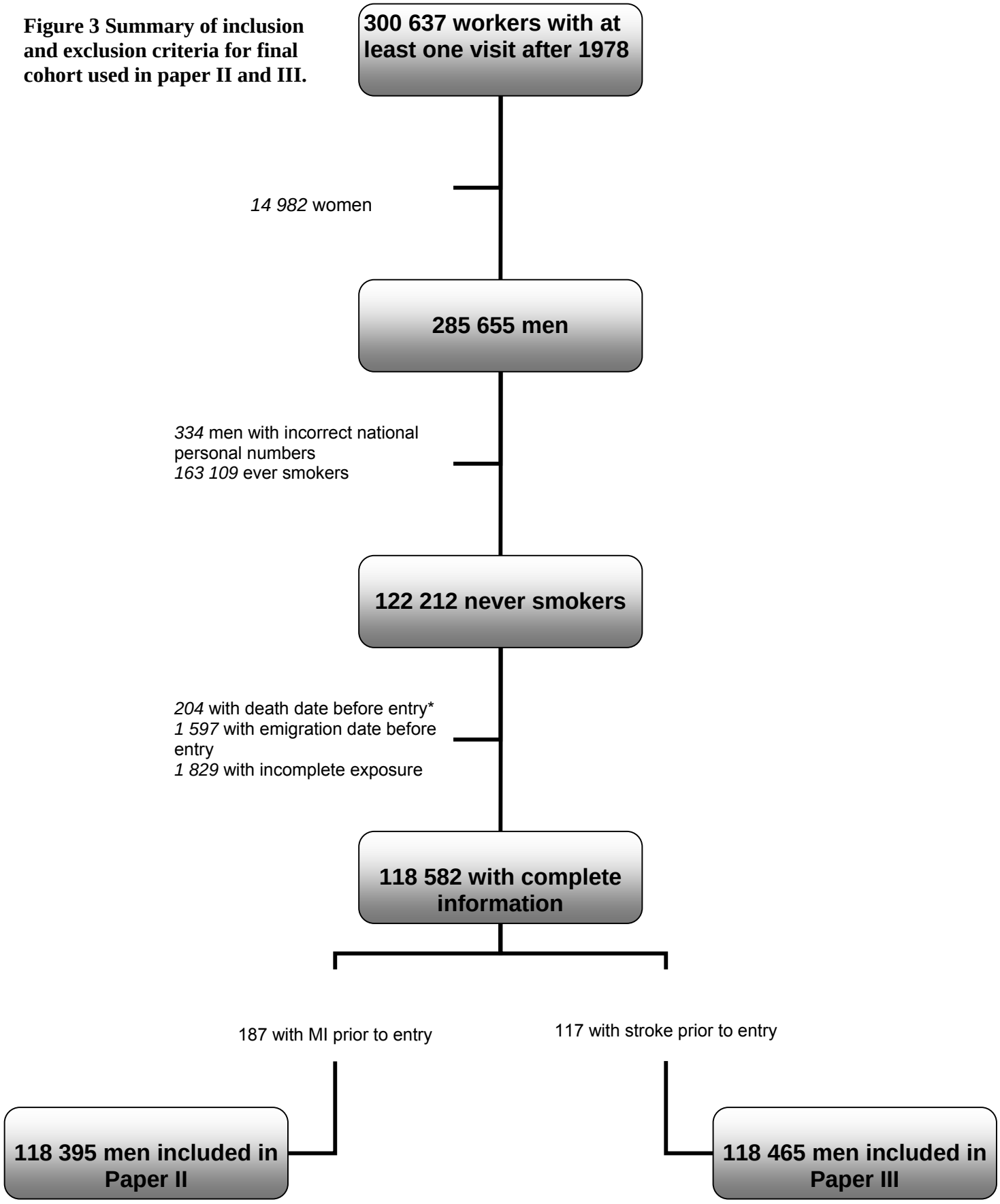
Covariates exposure

Blood pressure was measured after 5 minutes of rest in a supine position. A standard mercury manometer was used and the blood pressure was recorded to the nearest 2 mm Hg. Some of the individuals have two measurements at one health visit. When this is the case the mean of the two measurements was used. Less than 0.2% lacked information on blood pressure. Height and weight was used to calculate the Body Mass Index (BMI). The variation in length over time was less than 1 cm in 79% of the study subjects and less than 4 cm among 98.5%. BMI was divided into four categories; <20, 20-24.9, 25-29.9 and ≥30. From 1971 and onwards we had access to information on residence county, through linkage to the Register of Total Population. The regions were further divided into three categories; northern, middle and southern Sweden.

Snuff exposure

Detailed information regarding duration of snuff fuse, amount used in grams/week and time since cessation (in years) was available. Current snuff use was defined as using at least 1 gram of snuff per day for at least 1 year. Subjects who had stopped using snuff more than 1 year before enrolment were classified as former snuff users. In paper II, current users were divided into four groups according to amount of daily snuff intake: less than 12.5 gram/day, 12.5-24.9 gram/day, 25-49.9 gram/day, and 50 or more gram/day.

Figure 3 Summary of inclusion and exclusion criteria for final cohort used in paper II and III.



* The entry dates were redefined to the date for complete coverage of the Inpatient Register

Follow-up

The national registration number (NRN), a unique personal identifier assigned to all Swedish residents, enabled follow-up through record linkages to the nationwide Causes of Death Register, the Inpatient Register, the Myocardial Infarction Register (study II), the Total Population Register and the Migration Register. In this way a complete follow-up was possible, from entry into the cohort until the date of emigration, death or diagnosis, whichever came first. Subjects with NRNs which were not to be found in any of the mentioned registers were excluded from the study. In all, approximately 1.4% of the subjects were lost to follow-up due to incorrect NRN. For subjects who lived in a county without coverage or with incomplete Inpatient Register coverage, cohort entry dates were reset to the date when the Inpatient Register became complete in that county.

Inpatient Register, Causes of Death Register and Acute Myocardial Infarction Register

In Sweden, there are virtually no private inpatient care services, and residents usually use regional hospitals within the county of their domicile, except for unusual emergency situations. In 1965 the National Board of Health and Welfare (NBHW) established the Inpatient Register. However, counties started reporting to the Swedish Inpatient Register in different calendar years and in 1969 the coverage was 60%, in 1983 it was 85% and since 1987 the Register achieved 100% nationwide coverage [121]. In addition to the patient personal registration number, the Inpatient Register also contains date of admission and discharge, one primary discharge diagnose and up to seven differential diagnoses. From 1961 the National Board of Health and Welfare administer a complete register for causes of death, with information on the date of death, underlying cause of death and differential diagnoses coded according to the International Classification of Diagnoses (ICD7-ICD10) The Acute Myocardial Infarction Register, founded in 1987, was established by combining information from the Inpatient and Causes of Death Registers [22].

Case identification

Detailed information on the International Classification of Diseases used in paper II-IV is presented in Table 4

Paper II: Myocardial infarction

Acute myocardial infarction was coded according to the Swedish revision of International Classification of Diseases 9th (1987-1997) and 10th edition (from1997) (ICD-9:410; ICD-10:I21:I22). Cases of myocardial infarction before 1987 were identified from both the Inpatient Register and Causes of Death Register and were coded according to the Swedish revision of ICD-7 before 1969 and ICD-8 from 1969 through 1986 (ICD-7:420.10:420.17; ICD-8:410). Since the death certificates in 2004 were not yet computerized, they were examined and coded by one of the authors who was blinded to

snuff use status of the dead subjects. Incident cases were defined as the first event of myocardial infarction registered as main diagnose in the Inpatient Register or as underlying cause if death in the Causes of Death Register. Subjects found in the IPR who died within 28 days were considered fatal cases. Subjects with myocardial infarction registered as a bi-diagnosis prior to a myocardial infarction were excluded.

Paper III: Stroke

Cases of stroke, (ischemic, hemorrhagic and unspecified), were identified from the Inpatient Register (as main diagnosis) and the Causes of Death Register (as underlying cause). The definitions of stroke and subtypes are specified in detail in table 4. Ischemic stroke included those with occlusion in both precerebral and cerebral arteries, cerebral thrombosis and cerebral embolism as well as transient cerebral ischemia. Hemorrhagic stroke included both non-traumatic intracranial hemorrhage and subarachnoid hemorrhage. Unspecified stroke represented ill-defined cerebrovascular diseases. Some cases were registered with two different subtypes of stroke in the Inpatient Register within 28 days. When this was the case the latest diagnose was used or the most specified definition. Incident cases that died within 28 days were considered fatal cases. Subjects identified with stroke as bi-diagnosis prior to main diagnosis were excluded.

Paper IV: Hypertension

Cases of hypertension were identified through the Inpatient Register using both main diagnosis and co-morbidity. The definition was broad and included malignant and benign hypertension with or without heart and kidney failure coded according to the International Classification of Diseases (ICD-7: 440-447, ICD-8:400-404, ICD-9: 401-405 and ICD-10:I10-I15). High blood pressure at the health visits was not regarded as hypertension and was analyzed separately. A systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at the health visit was classified as high blood pressure. A“healthy” cohort was created for the follow-up analyses including only those with systolic blood pressure <140 mmHg and diastolic blood pressure < 90 mmHg at the first visit along with those never registered with hypertension in the Inpatient Register prior to baseline (Figure 3).

Figure 4 Summary of inclusion and exclusion criteria for final cohort used in paper IV

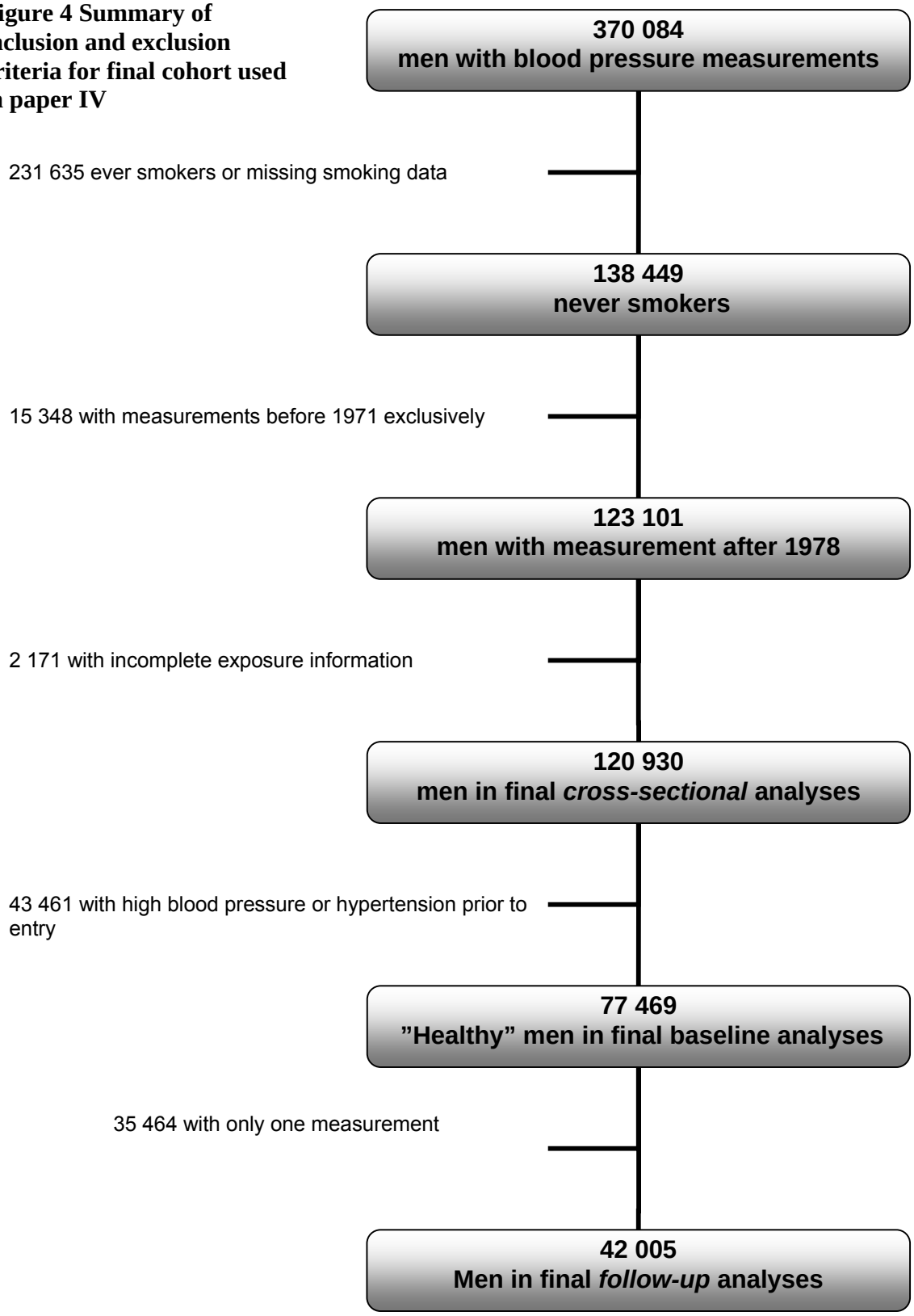


Table 4. International Classification of Disease (ICD) codes and definition of subtypes of outcomes in paper II-IV

ICD 7	(-1968)	ICD 8	(1968-1986)	ICD 9	(1987-1996)	ICD 10	(1997-2003)
			Myocardial Infarction				
420.10	Myocardial infarction	410	Acute myocardial infarction	410	Acute myocardial infarction	I21	Acute myocardial infarction
420.17	Myocardial infarction					I22	Reinfarction within 28 days of first diagnosed myocardial infarction
			Ischemic stroke				
332	Cerebral embolism Cerebral thrombosis	432	Occlusion of precerebral arteries	433	Occlusion and stenosis of precerebral arteries	G45	Transient cerebral ischemia
333	Transient cerebral ischemia	433	Cerebral thrombosis	434	Occlusion of cerebral arteries	G46	Vascular syndromes of brain in cerebrovascular diseases
		434	Cerebral embolism	435	Transient cerebral ischemia	I63	Cerebral infarction
		435	Transient cerebral ischemia				
		437	Generalized ischemic cerebrovascular disease				
			Hemorrhagic stroke				
330	Subarachnoid hemorrhage	430	Subarachnoid hemorrhage	430	Subarachnoid hemorrhage	I60	Subarachnoid hemorrhage
331	Cerebral hemorrhage	431	Cerebral hemorrhage	431	Intracerebral hemorrhage	I61	Intracerebral hemorrhage
				432	Other and unspecified intracranial hemorrhage	I62	Other non-traumatic intracranial hemorrhage
			Unspecified stroke				
334	Other and ill-defined cerebrovascular disease	436	Acute, but ill-defined cerebrovascular disease	436	Acute, but ill-defined cerebrovascular disease	I64	Stroke, not specified as hemorrhage or infarction
		438	Other and ill-defined cerebrovascular disease	437	Other and ill-defined cerebrovascular disease	I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
				438	Late effects of cerebrovascular disease	I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
						I67	Other cerebrovascular diseases
			Hypertension				
440	Benign essential hypertension with heart disease	400	Malign hypertension	401	Essential hypertension	I10	Essential hypertension
441	Malign essential hypertension with heart disease	401	Benign essential hypertension	402	Hypertension with heart disease	I11	Hypertension with heart disease
442	Hypertension with heart and kidney disease	402	Hypertension with heart disease	403	Hypertension with kidney disease	I12	Hypertension with kidney disease
443	Other hypertension	403	Hypertension with kidney disease	404	Hypertension with heart and kidney disease	I13	Hypertension with heart and kidney disease
444	Benign essential hypertension without heart or kidney disease	404	Hypertension with heart and kidney disease	405	Secondary hypertension	I15	Secondary hypertension
445	Malign essential hypertension without heart or kidney disease						
446	Hypertension with kidney disease						
447	Other hypertension						

Statistical analysis

All analyses were conducted in SAS statistical software, (Cary, NC, USA).

Paper I

Odds ratios (OR), with 95% confidence intervals (95% CI) were calculated as estimates of the relative risks. The model used was unconditional logistic regression, where the case-control pairs were split. The subjects were divided into 9 groups according to combinations of smoking and snuff habits, with never smoking, never snuff users as reference group. The study design required that the matching variables, age (5-year groups) and hospital catchment area were controlled for in all logistic models [122]. Further analyses were made including potential confounders such as diabetes, hyperlipideamia, hypertension, overweight, physical inactivity, and job strain. However, the point estimates did not change substantially and these variables were not included in the final analyses.

Paper II-IV

Hazard ratios (HR) with 95% confidence intervals (95% CI) were calculated using the Cox regression model featuring calculations of risk over a time period. Attained age (as time scale) [123], BMI and region of residence were controlled for in all analyses. To test the assumption of proportional hazards for snuff dipping and covariates we used the method of Shoenfeld´s partial residuals and there was no indication of violation of the assumption of proportionality for any of the variables checked in the regression models [124].

Each cohort member contributed person-years from the entry date until the date of first case diagnosis (myocardial infarction, stroke or hypertension), death, emigration out of Sweden, the date for moving into a county without or with an incomplete inpatient register, or the end of year 2004 (2003 for paper III and IV), whichever occurred first. In paper II the cohort was also stratified into two age groups (35-45 and 55-65) to enhance comparability with a previous study [105]. To assess selection bias a sensitivity analysis was performed by excluding the first five years of follow-up.

In paper II and III, the incidence rate was standardized to the total person-years experienced by all participants using 5-year categories. In addition, Kaplan Meir cumulative mortality curves among those who had experienced a non-fatal myocardial infarction or ischemic stroke were plotted for ever snuff users and never users with follow-up through 2003. To compare the groups, the Log-rank test was used.

We were interested in changes in the rates of high blood pressure and the influence by snuff use. The repeated observations of blood pressure on individuals were used to study the change over time. In this type of studies the repeated observations are usually correlated and to adjust for this within variability we used Generalized Estimation Equations (GEE). In the model blood pressure was defined as a binary variable, and age at entry was considered as a potential confounder and included in the analyses [125]-[126].

RESULTS

Paper I: Snuff use and myocardial infarction

In all, there were 1432 cases (1173 nonfatal and 259 fatal) and 1810 controls, included in the final analyses. Among those with complete tobacco information, 492 men were former or current snuff users but only 57 of them had never smoked. Approximately 10% of the men were current snuff users both among the cases, and among the controls and 5% were former snuff users. There were no differences in smoking habits between non-fatal and fatal cases, where approximately 40% were current smokers and 9 % were former users.

The distribution of snuff users differed markedly between the age groups. The proportion of snuff users was greater in the younger age groups (Table 5).

Table 5. Snuff consumption in different age groups in the SHEEP and the VHEEP study. All subjects are included, both cases and controls.

	<=55 years	**56-60 years**	**61-65 years**	**61-65 years**	**>65 years**
	N (%)	N (%)	N (%)	N (%)	N (%)
Never used snuff	341 (77%)	416 (80%)	596 (85%)	708 (86%)	689 (91%)
Former snuff users	32 (7%)	39 (8%)	30 (4%)	43 (5%)	19 (3%)
Current snuff users	73 (16%)	64 (12%)	73 (11%)	70 (9%)	49 (6%)
Total	446 (100%)	519 (100%)	699 (100%)	821 (100%)	757 (100%)

A geographic difference was also observed where subjects from northern Sweden (VHEEP) had a larger proportion of snuff users than Stockholm (SHEEP), with 15% and 9% snuff users, respectively (Table 6).

Table 6. Snuff consumption in Stockholm (SHEEP) and northern Sweden (VHEEP) divided into never and ever smokers.

	SHEEP		**VHEEP**	
	Never smoked	Ever smoked	Never smoked	Ever smoked
Never used snuff	747 (96%)	1615 (83%)	144 (87%)	244 (71%)
Former snuff users	10 (1%)	110 (6%)	9 (6%)	34 (10%)
Current snuff users	26 (3%)	226 (12%)	12 (7%)	65 (19%)
Total	783 (100%)	1951 (100%)	165 (100%)	343 (100%)

Snuff use and smoking were strongly associated, among the controls. Mixed users tended to smoke less than those who exclusively smoked, with a mean consumption of 16.4 and 18.6 cigarettes/day, respectively. Snuff use was also associated with hypertension and obesity, two other known risk factors for myocardial infarction. These associations appeared stronger among current snuff users than among former snuff users (Table 7).

Table 7. Associations between snuff use and certain risk factors for myocardial infarction among the controls in the SHEEP study. The associations are expressed as odds ratios with 95% confidence intervals.

		Snuff Use				
		Never (n=1538)	Former (n=90)		Current (n=90)	
			%		%	
				OR* (95% CI)		OR* (95% CI)
Hypertension‡	1810	26	23	0.98 (0.58–1.6)	35	1.8 (1.3–2.5)
Overweight (BMI≥30 kg/m2)	1809	10	14	1.5 (0.79–2.8)	18	1.9 (1.2–2.9)
Former smoker	1810	31	73	8.1 (4.3–15.4)	52	4.4 (2.8–6.9)
Current smoker	1810	30	13	1.2 (0.50–2.7)	33	2.5 (1.6–4.1)

*Odds ratios adjusted for age group, hospital catchment area, and smoking.
‡170/95 mm Hg at examination or hypertension in questionnaire.
¶Stopped smoking 1 year before inclusion.

After adjustment for age and hospital catchment area no increased risk of myocardial infarction was observed among former and current snuff users. Increased risks (not statistically significant) were observed for fatal myocardial infarction, both among former and current snuff users (Table 8). Further adjustment for diabetes, hyperlipideamia, hypertension, overweight, physical inactivity, and job strain in the analyses had negligible influence on the results.

Table 8. Associations between snuff use and myocardial infarction among never smoking men in the SHEEP study. The associations are expressed as odds ratios with 95% confidence intervals.

	Controls	All Cases		Non –fatal cases		Fatal cases	
Snuff use	**N**	**N**	**OR* (95% CI)**	**N**	**OR* (95% CI)**	**N**	**OR* (95% CI)**
Never	598	293	1.0§	248	1.0§	45	1.0§
Former†	12	7	1.2 (0.46–3.1)	6	1.2 (0.43–3.2)	1	1.7 (0.21–13.6)
Current	28	10	0.73 (0.35–1.5)	7	0.59 (0.25–1.4)	3	1.7 (0.48–5.5)

†Stopped using snuff more than 2 years before inclusion.
*Adjusted for age, hospital catchment area
§Reference category.

Paper II and III: Snuff use and myocardial infarction and stroke

In paper II and III more than 118 000 male workers who had never smoked were included in the final analyses contributing with more than 2 million person years. Current snuff users had a lower mean age at enrolment compared to never snuff users, 26.7 years and 33.3 years, respectively. Approximately 30 percent of the men were ever snuff users. In table 9 the baseline characteristics are presented.

In total, 3 651 (2 810 non-fatal, 841 fatal) cases of myocardial infarction and 3 249 (2 968 non-fatal, 281 fatal) cases of stroke were identified during follow-up. When dividing stroke into subtypes, ischemic stroke was most common, constituting 70% of the cases. Hemorrhagic stroke and unspecified stroke represented 17% and 13%, respectively. The proportion of unspecified stroke changed over time, from 16% in 1987 to 8% in 2003. The average age at diagnosis was 66.1, 59.4 and 65.6 years among patients with ischemic, hemorrhagic and unspecified stroke, respectively.

Compared to non-tobacco users, no overall increased risk of acute myocardial infarction or stroke was observed among snuff users. However, an excess risk of fatal disease was observed both for myocardial infarction and stroke (all types and ischemic) among snuff users (Figure 5 and 6). For myocardial infarction this excess risk was most evident among heavy users (50 grams or more per day) (relative risk, 1.96, 95% CI 1.08-3.58). Sensitivity analyses excluding the first 5 years of follow-up did not change the results.

Table 9. Baseline characteristics of never-smoking male workers in the Swedish Construction Workers Cohort, registered from 1978 to 1993.

Characteristics	Paper II[1]				PaperIII[2]			
			Snuff use (%)				Snuff use (%)	
	N	(%)	Never	Ever	N	(%)	Never	Ever
Age at entry (years)								
<35	80 685	(68.0)	63.7	36.3	80 667	(68.0)	63.7	36.3
35-44	17 635	(14.9)	81.6	18.4	17 628	(14.9)	81.6	18.4
45-55	11 161	(9.5)	89.3	10.7	11 184	(9.5)	89.3	10.7
55+	8 914	(7.6)	88.4	11.6	8 986	(7.7)	88.4	11.6
BMI* (weight/height^2)								
<20	7 605	(6.4)	70.6	29.4	7 610	(6.4)	70.7	29.3
20-24	71 647	(60.5)	71.6	28.4	71 647	(60.5)	71.6	28.4
25-30	34 102	(28.8)	69.1	30.9	34 148	(28.9)	69.1	30.9
30+	5 041	(4.5)	68.0	32.0	5 060	(4.3)	68.0	32.0
Region								
North	32 768	(27.7)	68.3	31.7	32 815	(27.8)	68.3	31.7
Middle	61 669	(52.0)	70.7	29.3	61 682	(52.0)	70.8	29.2
South	23 958	(20.3)	73.6	26.4	23 968	(20.3)	73.6	26.4
Total	**118 395**	**(100)**	**70.6**	**29.4**	**118 465**	**(100)**	**70.6**	**29.4**

*Adjusted for age distribution at entry

[1] Paper II: Snuff use and myocardial infarction

[2] Paper III: Snuff use and stroke

Figure 5. Adjusted relative risk* (RR) with 95% confidence interval (95% CI) for myocardial infarction (MI) and stroke among ever snuff users

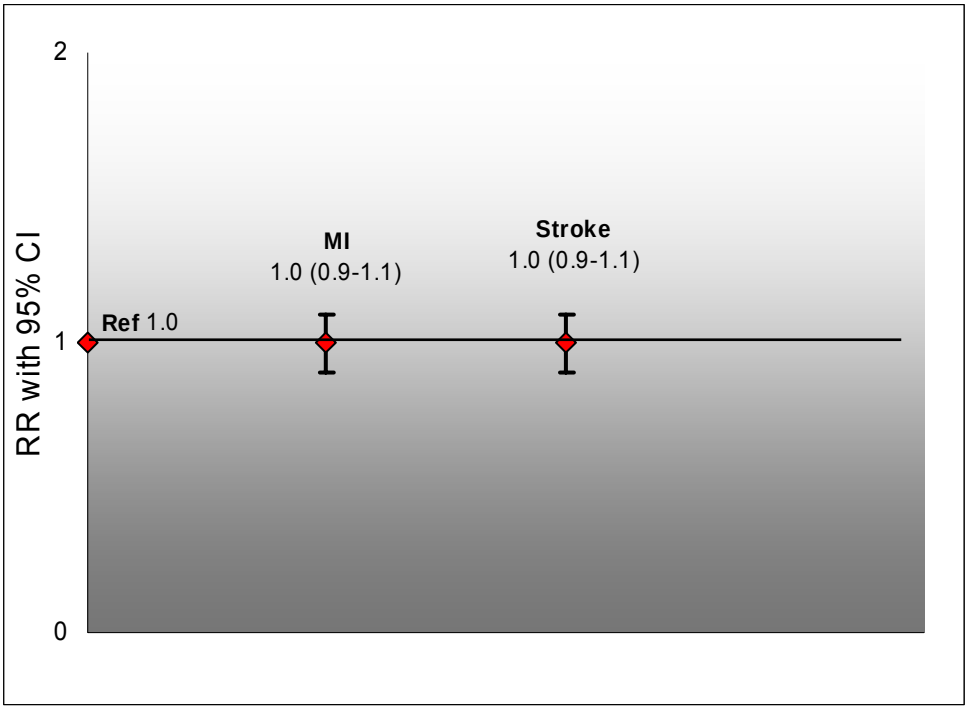
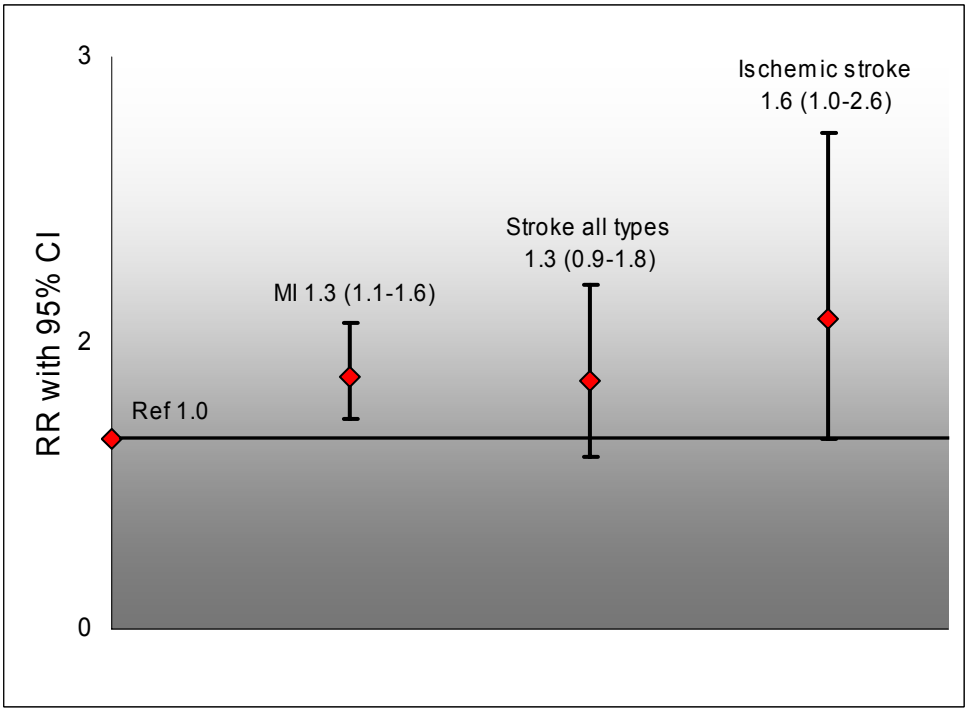


Figure 6. Adjusted relative risk* (RR) with 95% confidence interval (95% CI) for fatal myocardial infarction (MI), ischemic stroke and all types of stroke among ever snuff users.



* RR, relative risk derived from Cox proportional hazards regression model; CI, confidence interval; adjusted for age (age at follow-up was used as time scale), body mass index (weight[kg]/height[m]^2, categorized into <20, 20-24.9, 25-29.9, and ≥30) and region of residence (northern, middle and southern Sweden)

Kaplan-Meier curves of mortality among those who experienced a non-fatal myocardial infarction and ischemic stroke during follow-up showed that snuff users had a higher probability of dying (figures 7 and 8).

Figure 7. Mortality among men suffering from non-fatal myocardial infarction in relation to snuff use.

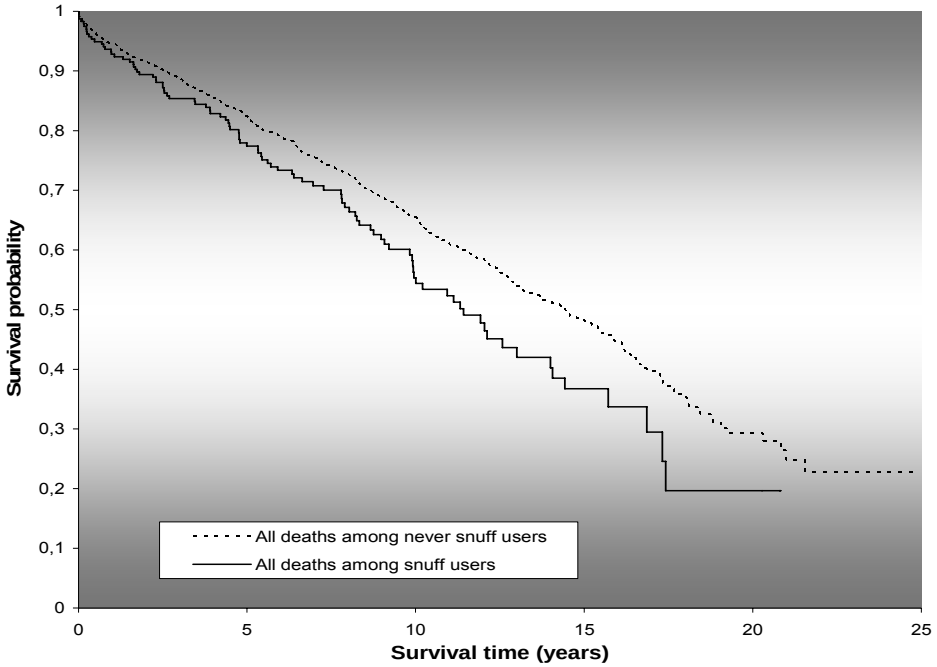
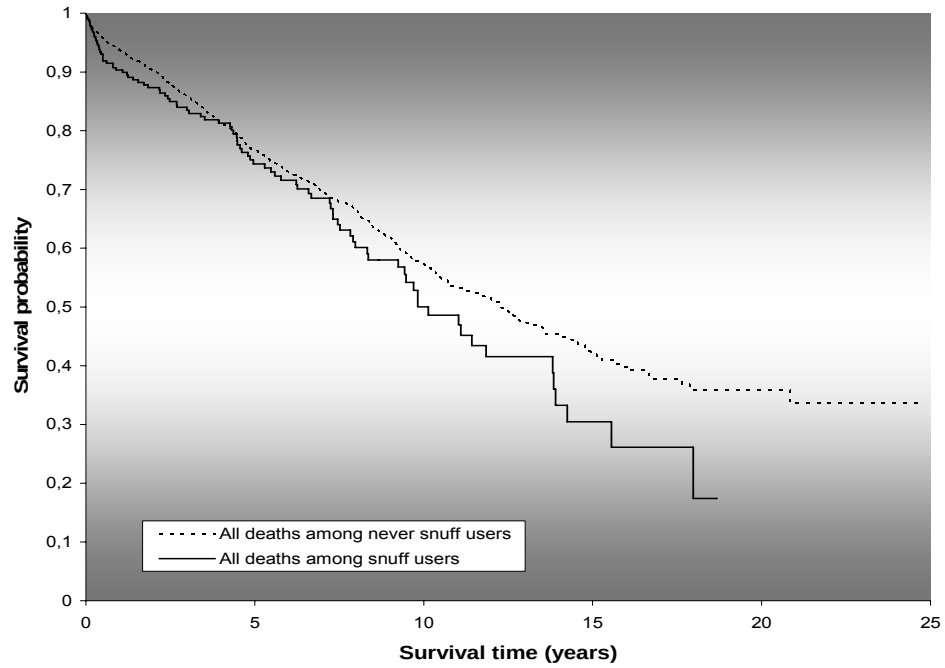


Figure 8 Mortality among men suffering from non-fatal ischemic stroke in relation to snuff use.



Paper IV: Snuff use and hypertension

More than 5 900 men had high blood pressure (systolic >=160 mmHg or diastolic>= 100 mmHg) at baseline. Among the 120 926 never smoking men included in the analyses, approximately 4 400 cases of hypertension were identified through the Inpatient Register. Among those with normal blood pressure at baseline, 751 cases with high blood pressure or hypertension were observed during follow-up.

The prevalence of high blood pressure at baseline was higher among snuff users compared to never snuff users (Table 10). Following stratification for age, slightly higher odds ratios for high blood pressure were observed among ever snuff users in the older age groups than in the younger age groups.
During follow-up an increased risk of hypertension and high blood pressure was present among snuff users, both for all subjects and for those with normal blood pressure at baseline (table 10). The effect of snuff on the risk of high blood pressure also increased with time (p=0.02).

Table 10. Prevalence and relative risk of high blood pressure (systolic blood pressure > 160 mmHg or diastolic blood pressure >100 mmHg) and hypertension according to snuff use among Swedish male construction workers

	Snuff use						
	Never	**Ever**		**Former**		**Current**	
	N	N	RR (95 % CI)	N	RR (95 % CI)	N	RR (95 % CI)
Baseline cohort (n=120 930)							
High blood pressure† at baseline	4809	1106	1.23[1] (1.15-1.33)	93	1.08[1] (0.84-1.31)	1013	1.25[1] (1.16-1.35)
Hypertension* during follow-up	3793	667	1.17[2] (0.91-1.50)	61	0.77[2] (0.34-1.74)	606	1.25[2] (0.96-1.61)
Healthy baseline with repeated measurements (n=42 005)							
High blood pressure† during follow-up	334	127	1.39[2] (1.08-1.79)	12	1.63[2] (0.87-3.08)	115	1.37[2] (1.05-1.78)
Hypertension* during follow-up	396	92	1.36[2] (1.07-1.72)	8	0.85[2] (0.40-1.79)	84	1.43[2] (1.12-1.83)

[1]OR, odds ratio derived from logistic regression model; CI, confidence interval;adjusted for age at entry, body mass index (weight[kg]/height[m]^2, categorized into <20, 20-24.9, 25-29.9, and ≥ 30) and region of residence (northern, middle ad southern Sweden)
[2] RR, Relative risk derived from Cox proportional hazard regression model; CI, confidence interval; adjusted for age (age at follow-up was used as time scale), body mass index (weight[kg]/height[m]^2, categorized into <20, 20-24.9, 25-29.9, and ≥ 30) and region of residence (northern, middle and southern Sweden).
*Cases identified in the Inpatient Register
†Cases identified at health check-up for those with more than one health check-up

DISCUSSION

Methodological considerations

Study design

Two types of epidemiological study design were used in the present thesis, case-control and cohort design. In paper I we used exposure data collected retrospectively from questionnaires in a population based case-control study. In a case-control study, patients who recently were diagnosed with the diseases under study (cases) are compared with individuals without the disease (controls) [127]. In our study cases came from a well defined population and their controls were identified and sampled from the same population. To increase efficiency the controls were matched on age and hospital catchment area [122]. The exposure distribution in the control group is supposed to reflect the distribution in the population from where the cases are generated. It is therefore important that the controls are sampled independently of exposure status. In the present study the controls were collected longitudinally throughout the study period (density sampling), in this way the exposure distribution in the population is representative for the time when the case was identified. Density sampling also ensures that odds ratios in our case-control study are a proper estimation of the relative risk [128].

A cohort study is defined by a group of individuals who are followed over time regarding disease incidence [127]. In a prospective cohort study, the exposure information is gathered prior to the disease event. In paper II-IV, we used exposure data gathered from construction workers prior to disease occurrence. A cohort member must be at risk (alive and free of the disease under study) when the follow-up starts [127]. In our studies we excluded those with disease (myocardial infarction, stroke or hypertension) prior to onset by using national Swedish population based registers. The cohort in our studies consisted of more than 300 000 men and both the diseases under study and the exposure are relatively common which makes our studies suitable for a cohort design [122], [129].

Bias

Information bias

Systematic errors may be introduced when the information on exposure or outcome is obtained, leading to information bias [127]. A person could thus be placed in an incorrect category regarding exposure or outcome. This bias may be either differential or non-differential. Differential misclassification is more problematic and could lead to either an overestimation or an underestimation of the effect. Non-differential misclassification of exposure dilutes the effect by bias towards a null-effect [122, 127]. Selection bias may be

introduced when there are systematic errors in the procedures used to select study persons from the study population or if there are any factors influencing the participation [122].

Misclassification of exposure

Paper I: Exposure information was measured by a self-reported questionnaire, and this may have introduced some misclassification. This type of misclassification, is almost always present in epidemiological studies to some extent and often it is non-differential [127], ie. independent of diseases status. However, it is possible that the exposure data provided by the cases could be influenced by disease status. Newly diagnosed cases might have a stronger will to recall exposure prior to the event than their controls. Previous studies of the SHEEP material showed no indication of recall bias [117, 130]. The exposure information from the fatal cases was gathered from the next of kin, which increases the imprecision of the exposure information, although validation studies show that information on tobacco use may have a rather high quality using information from next of kin [131].

Paper II-IV: In this prospective study, exposure information was gathered prior to disease occurrence which makes disease-related misclassification of exposure unlikely. However, by only using exposure data from the first health check-up we cannot rule out the possibility that some individuals started to smoke after enrolment. Snuff users could also have changed their habits during follow-up. The data on snuff exposure have not been validated in the present study but a previous study shows that the inconsistency over time was 2.6% regarding tobacco smoking [120]. Some studies have shown that snuff users are more prone to start smoking than non snuff users [45, 132]-[133]. Among those who reported never smoking at the first visit, 4% among never snuff users started to smoke whereas 7 % among the snuff users started to smoke. If this is the case in our study the bias would tend lead to an overestimation of the results because of confounding from smoking.

Selection bias and misclassification of disease

Paper I: The study subjects were collected independently of exposure history. The quality of diagnosis and the combination of sources used to find cases minimized the number of unidentified cases, and the risk of disease misclassification was reduced. The random sampling of controls through a complete register of the total population also decreased the risk of selection bias. The non-participation was not systematically different across age groups and geographical areas [117]. Previous studies have shown that tobacco use is more common among non-responders [101, 134]. However, considering the high response rate in our study (81% among the cases and 75% among the controls) the differences have to be quite extensive to influence the validity.

Paper II-IV: The concern of selection bias is often not as big in cohort studies as it is in case-control studies. However, in occupational studies a special type of selection bias could be introduced; the “healthy workers effect”. This bias occurs when workers are compared to the general population, because the latter also consists of individuals unable

to work due to illness. As an example, a previous study of the construction workers cohort showed a lower incidence of oesophagus cancer than the in general population [135].

The mean number of health check-ups was the same for snuff users and non-snuff users and snuff users did not appear more often in the different national health registers. Another way to prevent selection bias in paper II-IV was to only use exposure information from the first health check-up, this way we avoided the risk that health status (e.g. early symptoms of stroke) and exposure status (e.g. snuff use) might correlate with the likelihood of appearance in the later check-ups. By resetting the date of start of follow-up to the date when the Inpatient Register was complete we ensured an almost complete follow-up which makes the influence of selection bias less likely.

In paper II-IV the Inpatient Register, the Causes of Death Register and the Myocardial Infarction Register were used to identify cases of myocardial infarction, stroke and hypertension. Misclassification of disease might occur in studies where national health registers are used as a source for identification of cases and the quality of the registers is therefore of great importance. The Myocardial Infarction Register is based on combined information from the Inpatient and Causes of Death Registers. A validation study of this register showed that the sensitivity was 94.6% in 1987 and 95.4 % in 1995, respectively, and the specificity was about 97% in both years [22, 136]. An earlier study showed a lower efficiency when combining data from the Inpatient and Causes of death registers before 1987 regarding identification of myocardial infarction [137]. Previous data suggest that combining information from the Inpatient Register Causes of Death Register is an efficient way to identify cases of stroke,[138] although it may lead to inclusion of non-definite events, i.e., false positives [139]. By using only first events of myocardial infarction and stroke we decreased this risk. It was also reported that longitudinal studies of stroke subtype could be difficult [139]. However, our results showed that the distribution of stroke subtypes is in line with national data [26]. The differential effects of snuff on risks of hemorrhagic and ischemic stroke also reduced such a concern. The Inpatient Register is not an optimal source for identifying cases of hypertension. One report indicates that only 17% of all patients with hypertension can be identified in the Inpatient Register [140]. This low sensitivity might be a problem in paper IV. Although, as for all diseases studied in paper II-IV, there is no reason to believe that this misclassification is differential. Assuming that the misclassification of disease was the same in both exposure groups and both snuff users and no-users have the same probability to be found in the register, this would bias the observed associations toward null. Also the magnitude of this effect may be unimportant if mainly the sensitivity is affected, leading to underdiagnosis [127].

In paper IV blood pressure measurements at the health check-ups were used to define the occurrence of high blood pressure. Considering the direct effect from snuff on blood pressure this might have an effect on measurements. A review article indicates that the maximal elevation in blood pressure after snuff intake ranges from 4-15 mmHg for systolic blood pressure and 6-11 mmHg for diastolic blood pressure [91]. Several measures have been taken to avoid this bias. First, subjects were not allowed to use

tobacco during the health check-up and the blood pressure was measured after 5 minutes of rest in supine position, second, we used a high cut-off for the definition of high blood pressure (systolic blood pressure => 160 mmHg or diastolic blood pressure => 100mmHg). In a normotensive person, it is unlikely that the increase in blood pressure from the direct effect of snuff would rise above those values.

Confounding

Confounding could be explained as a mixing of effects. Lack of relevant information on confounders is an important issue when discussing causality in epidemiological studies. Confounders are factors that are associated with the exposure and in themselves risk factors for the disease as opposed to intermediate steps in the pathway from exposure to disease. As soon as potential confounders are unevenly distributed in the exposed and non-exposed groups, the relative risk may be affected [127]. The control of confounding depends on the quality of the information available and the influence of the factors on the risk estimates. Smoking is highly correlated with snuff use and is also an independent risk factor for cardiovascular diseases. Adjustment or restrictions to never smokers were performed in all analyses to avoid confounding from smoking on the results.

Paper I: Age and hospital catchment area were adjusted for in all analyses on the basis of the matching criteria. Further adjustment for diabetes, hyperlipideamia, hypertension, overweight, physical inactivity, and job strain had little impact on the risk estimates. Furthermore, some of these factors might be intermediates in the causal pathway which is a reason to exclude them in the analyses. Although we adjusted for smoking in all analyses there might be a residual effect of misclassification of smoking.

Paper II-IV: Factors associated with the risk of cardiovascular diseases such as age, BMI and region of residence [117], [141] were all unevenly distributed between snuff users and non snuff users and therefore adjusted for in the analyses. Unfortunately, we lacked information on a number of other potential confounders such as alcohol intake, physical activity and diet. It is not evident exactly how these potential confounders might influence the risk estimates. Several studies have shown an association between alcohol consumption and the use of snuff. This association appears to be particularly pronounced among adolescents and young adults [93, 142-144], [79] Moderate consumption of alcohol has been linked to a lower risk of coronary heart disease [145-148] but is also considered to be a risk factor for stroke, although some results showed a decreased risk of ischemic stroke from alcohol [29]. Snuff users appear to be more physically active compared to non-tobacco users or users of other forms of tobacco [93], [143], [149] Furthermore, one study conducted among mill workers showed a non-significant increase of the intake of fatty foods among smokeless tobacco users [149]. In a population based study, the heterogeneity regarding risk factors such as alcohol, physical activity and education might influence unadjusted results. However, this study is based on a cohort of construction workers and life style variables may not vary as much as in the general population. It is also noteworthy that these potential confounders are associated with both non-fatal and fatal cardiovascular disease. Consequently, it is unlikely that confounding

could fully explain the observed associations between snuff use and the risk of fatal myocardial infarction and ischemic stroke since no effect was observed for non-fatal cases. We chose not to adjust for blood pressure in the final analyses of paper II and III since blood pressure could be regarded as an intermediate factor. The results in paper IV confirm this hypothesis.

Chance

Observed associations may be due to chance. Statistical tests of significance or confidence intervals to risk estimates are helpful for determining whether a given result is a chance finding. Null results could also be due to chance, through small sample size or lack of power. However, considerations on whether the association was consistent with the a priori hypothesis, its biological credibility, its strength, the presence of dose-response relationships, consistency of subset analyses and the temporality of exposure and outcome, should also be taken into account when discussing the role of chance.

Paper I: Because of the limited amount of exposed cases in paper I it was not possible to calculate any dose-response relationships. Furthermore, all subset analyses were based on small numbers of cases, which makes random variability a possible explanation. This is also shown through wide confidence intervals.

Paper II-IV: One of the strengths of paper II-IV is the sample size and the relatively large number of exposed cases. Subset analyses regarding dose-response relationships were conducted in paper II and no clear effect was observed although the increased risk for fatal myocardial infarction was consistent in almost all groups. This was also true for subset analyses stratified in age groups both in paper II and IV, although, the precision decreased due to smaller sample size.

External validity

The possibility to generalize the findings to other populations than the one under study depends on what you know about the characteristics of the study population and of the effect of exposure in different settings. One possible explanation for the range of results could be differences between an occupational cohort and the general population in Stockholm and Västerbotten County. National data show that snuff use is most common among men with lower education but that the differences have diminished since the increase in snuff use has been more remarkable among men with higher education [3]. This could indicate that the risk from snuff use differs somewhat in the study populations since the background risk for cardiovascular disease varies. Neither can we rule out the "healthy worker effect" in the cohort study, which may mean that the general population would be more vulnerable to the effect from snuff. Because of the low prevalence of exposure among women all studies in the thesis were based on men only but there is no reason to believe that the effect from snuff use should differ between men and women. Another concern regarding the generalization of results in study II-IV is the fact that

exposure derives from the 1970s. Changes in the composition of snuff since then could make extrapolation to the type of snuff used today difficult. One of our main hypotheses is that the nicotine in snuff could have a harmful effect on the cardiovascular system. Even if the composition of snuff has changed regarding the content of nicotine, uptake of nicotine may be adjusted to maintain the nicotine levels constant, partly by making snuff more basic [112] but also through increased use.

Interpretation of findings

Paper I and II: Snuff use and the risk of myocardial infarction

The results in paper I and II indicate that there is no overall increased risk of myocardial infarction among users of Swedish moist snuff. These results remained also after additional adjustments for potential confounders (in paper I). However, both in paper I and II, an increased risk of fatal myocardial infarction were observed among never smoking snuff users. In paper I the relative risk for fatal cases was based on small numbers and should be interpreted carefully. The present results are in accordance with previous studies [90, 100, 101, 106-108, 150]. Three case-control studies from northern Sweden showed no overall risk of myocardial infarction among snuff users [100, 101, 103]. One of them observed an increased risk for fatal cases, although not statistically significant and with few exposed cases. However, the third study could not confirm this [103]. Two Swedish cohort studies showed an increased risk of mortality from cardiovascular diseases among snuff users [106, 150]. A third cohort study from Sweden showed no increased risk of IHD among snuff users but suggested a small increase in risk of fatal IHD[107]. The result for fatal outcome was based on few cases, leading to wide confidence intervals. Three American studies have been conducted on smokeless tobacco and cardiovascular mortality, two (CPS-I and CPS-II) observed increased risks [90] while the third did not [108].

The prevalence of current snuff users was higher in paper II compared to paper I, 30 % and 10 % respectively. This is due to different study populations, paper I is based on the general population in Stockholm and Västernorrland whereas paper II is restricted to construction workers where the tobacco consumption is higher than in the general population (approximately 50 % were ever smokers). However, the age distribution and geographical differences among snuff users were similar in the studies. There were fewer consumers in the older age groups and snuff use was more common in northern Sweden. These patterns are similar to the results from earlier studies [42, 100, 101, 151, 152].

In paper I an association between snuff use and smoking was observed and smokers who also used snuff tended to smoke less. This indicates that the nicotine intake is relatively constant among tobacco users regardless of whether they smoke, use snuff or mix the consumption, which is in line with previous studies [41, 42, 134, 153]. Several studies have shown that nicotine has a direct effect on the cardiovascular system by increasing the heart rate, cardiac stroke volume, coronary blood flow and vasoconstriction [55, 56, 91]. However, the difference in risks for non-fatal myocardial infarction between smokers and snuff users (paper I) suggests that it is not only the nicotine in smoking tobacco that

increases the risk but other components, such as carbon monoxide, oxidant gases, and polycyclic aromatic hydrocarbons [59]. Neither does long-term use of snuff seem to have a negative impact on blood lipids, fibrinolysis, carotid or femoral atherosclerosis and other biochemical factors associated with CVD and MI [78, 80, 85]. Oral moist snuff contains substances such as fatty acids, flavonoids and nitrate that could have a protective effect for myocardial infarction [154, 155]. This might be an explanation for the null results among snuff users in relation to non-fatal myocardial infarction.

Animal studies show that nicotine exposure can induce cardiac arrhythmias and increase the vulnerability for ventricular fibrillation following myocardial infarction [68, 69, 156, 157]. This could contribute towards explaining the observed excess risk of fatal myocardial infarction and excess mortality from cardiovascular diseases among non-fatal myocardial infarction among snuff users, suggesting that high nicotine exposure can increase the severity of myocardial infarction among snuff users leading to increased risks for a fatal outcome. The direct effect on blood pressure might be another underlying mechanism influencing the severity of the myocardial infarction. However, an earlier study explored the risk of sudden cardiac death among snuff users, and no increased risk was found, which somewhat contradicts this hypothesis. In the present cohort the snuff exposure information was from the 1970s to the early 1990s. Changes in snuff habits during the follow-up as well as changes in the composition of snuff [158], might explain the different results in the two present studies. The stronger effect of snuff use among the older age groups (paper II) might also be explained by usage of an older type of snuff.

A decreased risk for non-fatal myocardial infarction among the former snuff users has also been observed in one previous study [103] These results re difficult to interpret. One explanation could be that the results are influenced by negative confounding, e.g. former snuff users adapted to an overall healthier life style.

Paper III: Snuff use and the risk of stroke

Our finding of no overall excess risk of stroke among snuff users is in line with a previous nested case-control study conducted in northern Sweden and a nationwide cohort study[102, 107]. An earlier Swedish cohort study as well as a study based on two US cohorts (CPS-I and CPS-II) found excess risks of death from cerebrovascular diseases among smokeless tobacco users,[105], [90] while another cohort study from the US could not confirm this [108]. However, no separate analyses for subgroups of stroke were performed in any of the studies and only one assessed non-fatal and fatal events separately [107]. In our study, the effect of snuff was strongest for fatal ischemic stroke, whereas no increased risk of hemorrhagic stroke among snuff users was observed This is in concordance with findings from a Swedish study on snuff use and subarachnoid hemorrhage [104].

The difference in etiology and risk factors between hemorrhagic and ischemic stroke could be an explanation for the results in the present study. Smoking is a well known risk factor for stroke, however this effect seems more consistent for ischemic stroke than for hemorrhagic stroke [159, 160], [27, 28]. The rapid decline in risk after smoking cessation

also suggests that there could be an acute effect from tobacco. It is unclear if this is due to the effect from nicotine per se and no evident biological mechanism underlies the excess risk for ischemic stroke among snuff users. Approximately 20% of all strokes are accounted for by cardioembolic strokes and one strong risk factor for this type of stroke is atrial fibrillation [25, 31], [161], [27.]. It has been shown in animal studies that nicotine can induce cardiac arrhythmias [68, 162]. Cardiac embolisation may also contribute to explaining the observed differences of risk between ischemic and hemorrhagic stroke. Further, in vitro studies suggest that exposure to nicotine opens the blood brain barrier, which could increase the severity of the stroke [163, 164]. The excess risk of fatal unspecified stroke is probably due to the high proportion if unidentified ischemic stroke in this subgroup.

Paper IV: Snuff use and the risk of high blood pressure and hypertension

We observed a higher prevalence of high blood pressure at baseline among snuff users compared to never users. The risk of high blood pressure or hypertension during follow-up was also increased for snuff users with no history of hypertension. Two previous Swedish studies and one American study have shown an adverse effect by long-term use of smokeless tobacco on blood pressure [95, 96, 98] while other studies have failed to find such an association [79-83, 93, 97, 99]. The differences in age distribution of study populations and adjustment for confounders as well as potential selection bias could explain the heterogeneous findings. All previous studies on snuff use and hypertension were cross-sectional studies, which limits the possibility to evaluate causality. Our study is the first study using a prospective design to assess the long-term effect of snuff use on blood pressure and hypertension. We were able to restrict the cohort to a normotensive study population for follow-up, both by blood pressure measurements at health check-ups, and inpatient care for hypertension.

The acute hypertensive effect from smokeless tobacco is well documented both in human and animal studies [56, 65-67, 92-94]. Presumably this effect is due to nicotine exposure which activates the sympathetic nervous system [59, 60]. This hypertensive effect could last up to 90 minutes after intake [91] and our results regarding high blood pressure at the health check-up could partly be explained by this short term effect. However, no tobacco use was allowed during the check-up and we also used a high cut-off for the definition of high blood pressure (systolic blood pressure $\geq$ 160 mmHg or diastolic blood pressure $\geq$100 mmHg). Studies have shown that the nicotine exposure is equivalent to or higher in snuff users than in smokers [52, 55, 56] and the nicotine exposure through snuff use could also be constant during the day since there are no restrictions on snuff use whereas there are for smoking.

CONCLUSIONS

The use of Swedish moist snuff does not seem to increase the overall risk of myocardial infarction or stroke. However, it appears to be associated with an increased risk of fatal myocardial infarction and fatal ischemic stroke. Furthermore, our findings indicate that the use of Swedish moist snuff leads to an increased risk of elevated blood pressure and hypertension. In conclusion, our data provides evidence that the use of Swedish moist snuff has adverse effects on the cardiovascular system of public health significance.

Sammanfattning på svenska

I Sverige har snusbruket ökat markant de senaste decennierna och idag står snus för hälften av all tobakskonsumtion. Över 20 % av männen i åldrarna 18-79 år är dagligsnusare. Tobaksrökning är en känd riskfaktor för hjärt-kärlsjukdomar medan snusets roll för hjärt-kärlsjukdomar är mindre väl undersökt. Snusare får i sig lika stora mängder nikotin som rökare utan att få i sig många av de skadliga ämnen som bildas vid cigarrettrökning. Syftet med föreliggande forskningsarbete var att studera om långvarigt snusande ökar risken för hjärt-kärlsjukdomar, framförallt hjärtinfarkt, stroke och högt blodtryck.

Avhandlingsarbetet baseras på två stora epidemiologiska material. Den första är en fall-kontrollstudie. Studiepopulationen består av svenska män i åldrarna 45-70 år som var bosatta i Stockholms eller Västernorrlands län 1992-1994. Totalt diagnostiserades 1 437 män med en förstagångs-hjärtinfarkt (fall) och dessa matchades med män utan infarkt (kontroller) i samma ålder och samma sjukhus-upptagningsområde. Dessa två grupper jämfördes med avseende på bland annat snuskonsumtion. Det andra materialet utgörs av en nationell prospektiv kohortstudie. Samtliga anställda inom byggindustrin i Sverige blev inbjudna till hälsokontroller mellan åren 1978 och 1993. Vid dessa hälsokontroller samlades information in om bland annat tobaksvanor (rökning och snusning) och blodtryck. I vår kohortstudie exkluderades alla män som rökt, då rökning är starkt associerat med både snusning och hjärt-kärlsjukdomar. Över 100 000 snusare och icke-snusare följdes sedan upp fram till 2003/04 genom nationella hälsoregister med avseende på insjuknande och dödlighet i hjärtinfarkt, stroke och hypertension.

I det första arbetet, som baserades på fall-kontrollstudien, kunde vi inte finna några skillnader i risk för hjärtinfarkt mellan snusare och icke-snusare bland dem som aldrig rökt. För fatala hjärtinfarkter observerades en riskökning, denna riskökning var dock baserad på få exponerade fall vilket gör det svårt att dra några slutsatser. Bland kontrollerna fann vi statistiskt signifikanta associationer mellan snus och andra riskfaktorer för hjärtinfarkt, så som högt blodtryck, rökning och övervikt. Det andra arbetet baserades på kohortstudien och återigen fann vi ingen ökad risk hos snusare att insjukna i hjärtinfarkt. Däremot hade snusarna en ca 30 % ökad risk att dö i hjärtinfarkt jämfört med dem som aldrig snusat. Riskökningen var ännu högre hos dem som snusade mer än 50 gram om dagen. Dessutom hade snusare som drabbats av en icke fatal hjärtinfarkt högre dödlighet, både generellt och särskilt i hjärt-kärlsjukdomar, än de som drabbats av hjärtinfarkt men aldrig snusat. Det tredje arbetet i avhandlingen handlade om snus och risk att drabbas av stroke. Stroke delades in i undergrupper; hjärnblödning, hjärninfarkt och ospecificerad stroke. En ökad risk observerades endast för fatal stroke (alla typer av stroke sammantagna) och fatal hjärninfarkt. Hos snusare som dabbats av icke fatal hjärninfarkt sågs en högre mortalitet än hos dem som drabbats men inte snusat. I det sista arbetet fann vi att det var vanligare med högt blodtryck hos snusare än hos icke snusare. Individer med normalt blodtryck vid första hälsokontrollen följdes upp med avseende på blodtryck och hypertension. Snusare hade en ökad risk för att få högt blodtryck och hypertension jämfört med icke-snusare.

Sammanfattningsvis verkar det inte föreligga någon ökad risk att drabbas av hjärtinfarkt eller stroke hos snusare jämfört med icke-snusare. Däremot talar våra data för att det finns en ökad risk för att dö i hjärtinfarkt eller stroke, framförallt hjärninfarkt, hos snusare. Snus förefaller också öka risken för högt blodtryck vilket är en känd riskfaktor för hjärt-kärlsjukdomar.

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