Long-term Use of Smokeless Tobacco

Cardiovascular Mortality and Risk Factors

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Abstract

Little is known about the risks of cardiovascular disease associated with the use of smokeless tobacco, which produces blood nicotine levels similar to those caused by cigarette smoking. There were 900 000 smokeless tobacco users in Sweden in 1996.

Epidemiological studies of 136 036 construction workers (6 297 smokeless tobacco users, 28 501 smokers and 32 546 never-users of tobacco), surveyed through 1971-74, regarding the general health profile, blood pressure, sick leaves and disability pensions were conducted together with a 12-year follow-up study of all cause mortality and cardiovascular mortality.

Hypertension (blood pressure >160/90) was most common in smokeless tobacco users, particularly after the age of 45 (RR 1.8; 95% c.i. 1.5-2.1). Compared to never-users, respiratory, circulatory, musculoskeletal and mental disorders were slightly more common in smokeless tobacco users, but significantly more common in smokers. During follow-up, smokeless tobacco users, who were middle-aged at the start of follow-up, had a doubled relative risk of dying of cardiovascular disease (RR 2.1; 95% c.i. 1.5-2.9) and smokers had a triple risk (RR 3.2; 95% c.i. 2.6-3.9) compared with never-users. The risk of dying of cancer was similar in smokeless tobacco users and never-users, whereas smokers showed more than a doubled risk (RR 2.5; 95% c.i. 2.2-3.0).

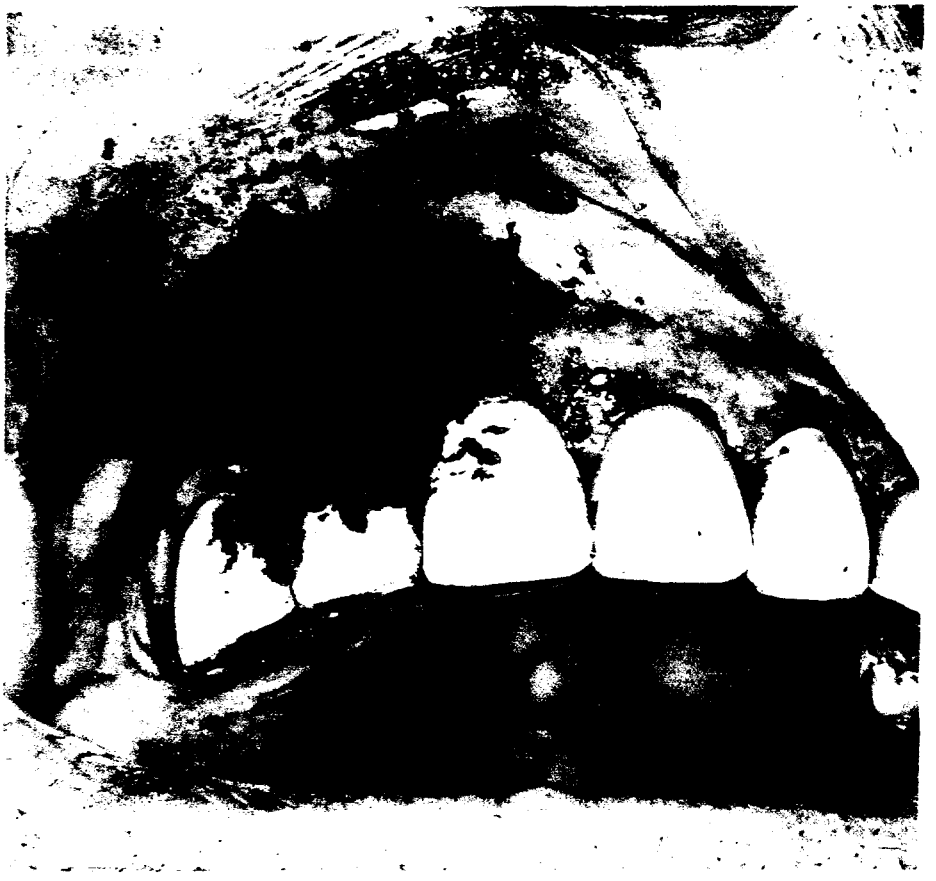
Clinical studies of 151 healthy middle-aged firemen (50 smokeless tobacco users, 33 smokers and 68 non-users) were made to evaluate the influence of long-term smokeless tobacco use on physical performance, cardiovascular metabolic risk factors, ultrasonographic signs of atherosclerosis and diurnal blood pressure variations.

Both smokeless tobacco users and smokers had significantly elevated heart rates during the daytime ($p<0.05$) compared with non-users. Daytime diastolic blood pressures were also significantly elevated in both smokeless tobacco users and smokers ≥45 years of age.

The metabolic cardiovascular risk (based on serum lipids, lipoproteins, fibrinogen, PAI-1, insulin and glucose), calculated as the "atherogenic index", was significantly elevated ($p<0.001$) only in smokers and the 10-year future risk of cardiovascular events (Framingham CHD risk index) was 13.2% in smokers ($p<0.001$) and 4.6% in smokeless tobacco users ($p=0.3$) compared with 3.4% in never-users. Smokeless tobacco users did not exhibit any significant signs of accelerated atherosclerosis at ultrasonographic examination of the carotid artery, as did smokers. Smokeless tobacco users did not reveal any significant reduction in maximal physical capacity, whereas the performances of smokers were significantly poorer ($p<0.001$) compared with non-users.

It is concluded that the use of smokeless tobacco involves as high exposure to nicotine as smoking, which causes the release of sympathoadrenergic stimuli. This seems to signify an elevated risk of cardiovascular stress involving higher heart rate and blood pressure levels, which might influence the risk of fatal cardiovascular events. However, it does not seem to involve the same high risk of accelerated atherosclerosis as smoking.

Key words: Smokeless tobacco, smoking, nicotine, cardiovascular diseases, hypertension, physical fitness, exercise test, atherosclerosis, ultrasonography, risk factors, ambulatory blood pressure.



The traditional application method for moist snuff in Sweden.
Photo: Jan Bergström

List of papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I Bolinder G, Ahlborg B, Lindell J.
Use of smokeless tobacco: blood pressure elevation and other health hazards found in a large-scale population survey.
J Intern Med 1992;232:327-334.

II Bolinder G, Alfredsson L, Englund A, de Faire U.
Smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers.
Am J Publ Health 1994;84:399-404.

III Bolinder G, Norén A, Wahren J, de Faire U.
Long term use of smokeless tobacco and physical performance in middle-aged men.
Eur J Clin Invest 1997;27:427-433.

IV Bolinder G, de Faire U, Alfredsson, L.
Effects of long-term smokeless tobacco use on metabolic cardiovascular risk factors and hemostatic function.
Submitted.

V Bolinder G, Norén A, de Faire U, Wahren J.
Smokeless tobacco use and atherosclerosis-an ultrasonographic investigation of carotid intima media thickness in healthy middle-aged men.
Atherosclerosis 1997;132:95-103.

VI Bolinder G, de Faire U.
Ambulatory 24-hour blood pressure monitoring in healthy, middle-aged smokeless tobacco users, smokers and non-tobacco users.
Submitted.

Contents

Introduction

The use of smokeless tobacco is an ancient custom in Sweden, practiced since the 18th century. The predominant merchandise is moist snuff, consumed by 99% of the Swedish habitual users. During the first half of this century, after some decades of decreasing usage, a significant rise in consumption has taken place between 1970 and 1996. There are about 900 000 users in Sweden at present, constituting almost 20% of all males. The habit is still quite uncommon in women, but it increases yearly. 5 639 tons of smokeless tobacco (including 7 tons of chewing tobacco) were sold in 1996.

The discussions of the long-term health effects of smokeless tobacco use, i.e. when used for decades, have been focused mostly on whether it might lead to the development of oral leucoplakias, or whether it can cause oral cancer, based on the fact that carcinogenic chemicals are present in tobacco. In Sweden, where the use of oral snuff is widespread, the incidence of oral cancer is lower than in many other industrial countries where the use of snuff is uncommon. Extensive reviews of the present scientific knowledge regarding the health effects of smokeless tobacco have been compiled both in Sweden and in the USA. No final statement has been made to exempt the Swedish moist snuff from being carcinogenic, but the risk of developing malignancies due to the use of snuff evidently seems to be quite low, compared to the substantial risk of both oral and other cancers from smoking tobacco.

Other important health consequences of the use of smokeless tobacco are associated with its content of nicotine. In spite of a large body of scientific research on possible long-term effects of nicotine, most studies have been conducted on smokers, involving the simultaneous exposure to large amounts of other potentially harmful substances. Nicotine is a central stimulating drug with high abuse liability. It also has a lot of complicated and contradictory effects on neurological function, vascular tone, cardiac control and autonomic homeostasis. Based on the pharmacological actions of nicotine and on findings of an increased cardiovascular risk in smokers, it has been suggested that the long-term influence of nicotine might comprise an increased risk of cardiovascular disease, such as myocardial infarction, coronary artery disease, stroke, hypertension or atherosclerosis.

The present study is focused on the possible harmful effects on the cardiovascular system, which might be attributable to the long-term exposure to nicotine in habitual use of smokeless tobacco. The elimination of combustion products by the use of smokeless tobacco makes it possible to study health consequences that might be more unambiguously associated with the exposure to nicotine.

Background

Tobacco

The history of tobacco

In 1493 Columbus and his crewmen brought the tobacco plant to Europe from the West Indies, where the natives smoked tobacco in pipes for ceremonial and medicinal purposes, and also inhaled tobacco powder through the nostrils [44, 192].

At first the plant was used for medicinal purposes, as it was thought to relieve or cure a great variety of symptoms of ill health and also to prevent the plague. In 1559 Jean Nicot, the French ambassador at the Portuguese court, presented snuff to Catherine de Medici, the Queen Mother of France, to treat the asthma and migraine of her son, the young François II. The name Nicot was preserved when Carl von Linné named the plant "Nicotiana Tabacum" in his system of plant classification in 1735 [44].

The use of tobacco spread quickly throughout Europe and the rest of the world during the 17th century. Snuff became an expensive pleasure and during the 17th and 18th centuries, the use of smokeless tobacco, both in the form of nasal snuff and as chewing tobacco, was widespread, especially in the upper social classes, where it became an integral part of the fashionable life [60].

However, as early as the 16th century the use of tobacco was attacked by the church, the state and by science [44]. In 1604 King James I raised the tax on tobacco by 4 000 per cent and stated in his "Counterblast to Tobacco" that it is a "custom loathsome to the eye, hateful to the nose, harmful to the brain and dangerous to the lungs". Tobacco was also thought to cause infertility, apoplexy (stroke) and cancer and to reduce the fighting qualities of soldiers (an interesting point, considering the indispensable cigarette of the 20th century World War soldier). In many countries, like Russia, Turkey, and China there were periods with severe punishment and even the threat of death for its use or traffic in it.

Despite the various actions of governments, religious bodies, scientists and physicians, tobacco usage in all its forms continued to increase and flourish throughout the world. Undoubtedly, one of the main reasons is the highly addictive properties of nicotine, but also its modest stimulating central nervous effects, compared to most other addictive and much coveted drugs. Nowadays the worldwide use of tobacco is maintained with the tacit approval of governments because of the need for tax revenues and by the intensive marketing efforts of the tobacco industry, and the resigned silence of most physicians [200].

The use of smokeless tobacco

Swedish moist snuff has been manufactured since the early 18th century and reached its maximum production in 1919 [106]. In the US a decline in smokeless tobacco use occurred during the first decades of this century, mainly due to the prohibition of spitting in order to prevent the dissemination of tuberculosis [44,60,223]. At the same time, cigarette smoking increased in popularity. The use of smokeless tobacco remained widespread, however, in many parts of the world, both in developed countries like the US and in Sweden (the country with the highest prevalence of smokeless tobacco use per capita in the world at the present time) and in developing countries in Central and South-East Asia [214].

In 1992 the European Union (EU) prohibited the sale of moist snuff in all countries of the Union, except in Sweden, where the use of snuff was regarded as "traditional" [68] As the prohibition has not yet been implemented by law in most countries, moist snuff is still available as well as other smokeless tobacco products not embraced

by the restrictions (dry snuff, chewing tobacco).

While cigarette smoking has declined both in Sweden and in the US during the past three decades, the consumption of smokeless tobacco has risen significantly [48,171,214]. Its use was previously most common among elderly people, but with marketing efforts directed towards young people, the highest prevalence is now found among teenagers and young adult males [214, 230]. About 20 percent of all males in Sweden use "moist snuff" regularly [4,152,199] implying 900 000 persons, of which >500 000 use only smokeless tobacco and approximately 335 000 use both cigarettes and smokeless tobacco. Eight percent of the users are women. In the US, there are about 12 million smokeless tobacco users, but the habit is irregularly distributed [214]. It has strong support among young male athletes, especially in sports like baseball (US) [47] and ice-hockey (Sweden) [33]. An increasing number of young women in Sweden are now adopting the habit of using smokeless tobacco.

The habitual use of tobacco is usually established before or around the age of 20 in most developed countries, regarding both cigarette smoking and the use of smokeless tobacco [215]. Very few individuals have started to use tobacco after the age of 25 [59]. Unfortunately, the age of onset seems to be decreasing in all countries. In Sweden, the change in habit from smoking cigarettes to using smokeless tobacco seems much more common than the opposite [152]. Thus, at ages exceeding 40, most habitual tobacco users have been exposed to the constituents of tobacco for more than two decades.

This presentation will mainly deal with the modern industrially manufactured smokeless tobacco products used in the US and Sweden, and not with the vast supply of different tobacco mixtures used in developing countries (betel quid, ash, lime, nass, khaini, mishri, zarda, kiwam etc.) described elsewhere [113].

Categories of products

Smokeless tobacco is mainly used as chewing tobacco or moist snuff. In the US, chewing tobacco is marketed in the loose-leaf, plug or twist versions. Nowadays, the use of dry snuff is very rare. Moist snuff is finely cut or ground dark tobacco leaves, mixed with water and flavouring [214]. The "pinch" is held in place between the lip and the gum without chewing (see photo, page 3). Moist snuff is the predominant product in Scandinavia, used by ≥99 per cent of the smokeless tobacco users [199] and by approximately 50 per cent of the US smokeless tobacco users [214]. Most smokeless tobacco products are made alkaline with different kinds of salt to facilitate nicotine absorption through the oral mucosa, see Table I. Licorice flavouring is common in the US, but is used only in a minor part of Scandinavian products [199].

Table I. Composition of Swedish moist snuff (not fermented) [168,169].

Major contents	% of the 2500 identified chemical components
Tobacco	40-45
Water	45-60
Sodium carbonate	1.2-2.5
Sodium chloride	1.5-2.5
Moisturizer	1.5-3.5
Flavouring	<1
Nicotine	0.5-1.3
TSNA[1]	4-5 ppm
PAH[2]	>5 ppm

[1]Tobacco specific nitrose arrines
[2]Polycyclic

Health effects of smokeless tobacco, other than circulatory

Local mucosal effects in the mouth

"Snuff dipper's lesion" is nowadays the most common term for the clinically observable changes in soft tissue morphology as a result of long-term smokeless tobacco use [9,10,104,122]. The lesion is characterised by a local thickening and hyperkeratosis of the epithelium [15], which is usually reversible when smokeless tobacco use is interrupted. Gingival recession and discoloration of the teeth are usual findings and are generally not reversible to the same extent as the epithelial lesions on discontinuing tobacco use. The degree of damage is related to an increased pH, increased nicotine content and period of

exposure (years and amount of tobacco used) [148]. The transformation of lesions into premalignant leucoplacias or clinical squamous cell carcinoma seems to be rare.

Smokeless tobacco and cancer

Scientific observations concerning the health effects of smokeless tobacco were first noted in 1761 by John Hill, a London physician observing that nasal cancer could develop as a consequence of using snuff [101,170]. In Sweden, the use of snuff use was regarded as a risk factor for cancer of the mouth, nose and oesophagus in the 1930s [5].

During the last 10 to 20 years a number of experimental and epidemiological studies have been made to evaluate the role of smokeless tobacco use in the development of oral cancer and other forms of cancer. Expert reports based on all available scientific literature on the matter have been published both in the US, by the Advisory Committee to the Surgeon General, and in Europe, by, among others, the World Health Organization, without reaching any conclusive statement of the evidence for the carcinogenicity of smokeless tobacco use in humans [4,51,59, 113,186,214,230]. Still, in the 1986 Report from the US Surgeon General, it was concluded that

> "the oral use of smokeless tobacco represents a significant health risk. It is not a safe substitute for smoking cigarettes. It can cause cancer and a number of noncancerous oral conditions and can lead to nicotine addiction and dependence".

Oral cancer incidence

The incidence of oral cancer varies greatly from 3-5 per cent of all cancers in many industrialized countries to 25 per cent of all malignancies in Asian countries, such as India [214]. In Sweden, where the habit of using moist snuff has been widely spread for more than a century and where cancer statistics are highly reliable, the incidence of oral cancer is low. If all oral cancers are included, the yearly incidence is 8.6 cases/100 000 individuals, compared with 11 cases/100 000 in the US and about 15/100 000 in many other industrialized countries where the use of oral smokeless tobacco is much more infrequent [113,230].

It appears to be beyond doubt, however, that the use of chewing tobacco, together with different mixtures of flavouring, alkaline substances and a variety of natural products, when used in populations with poor oral hygiene and a low nutritional status, is causally related to the development of oral cancer. One of the most cited investigations in the Western world, is a case control study by Winn et al in 1981 [236] of women in the tobacco cultivating areas of North Carolina, USA, which did reveal a relative risk for white snuff users of 4.8 (for black women 1.5) to develop oral cancer compared with non-users, and a positive dose-response relationship was found as well. On the other hand, most epidemiological investigations regarding the use of smokeless tobacco in industialized countries have failed to demonstrate a significantly increased cancer incidence [4,159]. Methodological problems connected with most studies regarding the classification of tobacco use, confounding by simultaneous or earlier smoking, alcohol consumption, differences in dietary habits, and the duration and extent of tobacco consumption all hinder an unequivocal interpretation. However, regarding the role of exposure to chemicals in the development of oral cancer, smoking and alcohol consumption are the dominant risk factors in the Western world.

Nitrosamines and other constituents related to cancer

The content of nitrosamines in tobacco (Table I) is presumed to account for the possible raised risk of cancer in smokeless tobacco users. Tobacco-specific nitrosamines in smokeless tobacco (N-nitrosornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butone) have been shown to be potent carcinogens in animal tests [113]. The biological relevance of carcinogenicity is based on findings of mutations, micronuclei, sister chromatid exchange and cell formation due to exposure to extracts of smokeless tobacco [113,214].

Other possible ingredients of smokeless tobacco that might increase the risk of developing cancer are small concentrations of polycyclic aromatic hydrocarbons, polonium-210 and naphthalenes [214]. The simultaneous occurrence of human papilloma virus (HPV), herpes simplex vi-

rus or Candida albicans infections might also contribute to an increased risk of oral cancer [73, 138].

It has also been suggested, however, that antimutagenic and anticancerogenetic substances are present in smokeless tobacco, giving rise to difficulties in evaluating the results of experimental studies of a single exposure to tobacco carcinogens in animal models [107]. Whether tobacco contains these substances to a degree compatible with a substantial reduction of the carcinogenecity of nitrosamines, has not yet been elucidated.

Other cancers

A limited number of investigations concerning cancer at other sites than the oral cavity (upper digestive tract, pancreas, bladder) have been performed [113,190,214], but the findings are inconclusive. Relative risk estimates seldom exceed 2.0, a common limit for good evidence of causality in carefully controlled studies in epidemiological research.

Summary-smokeless tobacco and cancer

To sum up, all smokeless tobacco products contain potentially cancerogenic nitrosamines, although the contents differ greatly between products. A substantial reduction of the nitrosamine content has also been accomplished by several manufacturers in recent years. Experimental and epidemiological studies and case reports mostly describe a consistent pattern of an increasing risk of cancer due to the use of smokeless tobacco, with a dose-response pattern with an increasing risk with longer durations and higher levels of tobacco consumption. However, compared with the extremely high risk of developing cancer from tobacco smoking (according to the WHO, 33 per cent of all cancers in the industrialized world are caused by smoking), it seems as if the risks associated with the use of smokeless tobacco are of relatively minor importance. On the other hand, compared with the awareness of precautions against other possible cancer risks in society, such as the contents of food, the working environment, domestic chemicals, UV radiation and air pollution, smokeless tobacco use might be more harmful to health than any of these risk factors. One must consider that the use of smokeless tobacco is usually initiated at very a young age and continued for decades.

Gastrointestinal effects

There is little knowledge of the local gastrointestinal mucosal effects of long-term smokeless tobacco use. Intravenously infused nicotine was shown to decrease pancreatic bicarbonate secretion in animals [127,128], supporting a connection between the increased incidence of peptic ulcers in smokers [125] and exposure to nicotine [17,129]. In the light of the similar exposure to nicotine in smokers and smokeless tobacco users, one might expect to find similar effects in both types of tobacco user. Regarding inflammatory bowel disease, smoking has been shown to increase the risk of Crohn's disease, but to decrease the risk of ulcerative colitis [40, 43], as well as of aphthous stomatitis [82]. However, the few studies published on smokeless tobacco or transdermal nicotine use have not revealed the same findings as in smokers [160, 201], which might be explained by more alkaline fluid being swallowed by smokeless tobacco users, or by differences in personality or alcohol consumption. However, our increasing knowledge of peptic ulcer disease, the causal connection with infections of helicobacter pylorii bacteria and the role of tobacco in immune defence mechanisms demand further investigation.

Pregnancy and offspring

No studies on pregnant smokeless tobacco users have been made in the industrialized world, as the habit has been more common among men and elderly people. In India, higher stillbirth rates, lower birth weights, changes in sex ratio and changes in placental morphology have been found among tobacco-chewing women [2,130, 131]. With the growing popularity of the habit among young girls, the question of possible health risks for mother and child becomes highly relevant. Smoking is a major risk factor for low birth weight, reduced fertility, spontaneous abortion and complications during pregnancy [62, 97,102,174]. Nicotine readily crosses the placental barrier, leading to substantial blood nicotine levels in the foetus, including its developing central nervous system. The use of smoke-

less tobacco or other nicotine-containing products during pregnancy may be a less harmful alternative to smoking, but it still exposes the foetus to a highly addictive drug, with potent effects on uteroplacental vascular regulation, which might negatively influence pregnancy outcome. Recent data also indicate that exposure to nicotine might be causally related to the sudden infant death syndrome (SIDS) through adverse effects on breathing regulation during sleep [94,145]. It must therefore be the last alternative when smoking cessation seems unattainable during pregnancy [24]. The consequences for breast feeding might be similar to those of smoking, i.e. impaired breast-milk production, and a shorter lactation period, as vasoconstrictive effects of nicotine might cause inadequate breast feeding. Nicotine also concentrates in the breast milk to be ingested by the infant. It also affects the odour of the milk.

Smokeless tobacco and body weight

Smokers exhibit lower body weights than nonusers of tobacco [74,89,115,140,221], (on an average, 2.7-4.5 kg [21]), and the difference becomes more obvious with increasing age (Paper I). Smoking cessation is associated with a significant weight gain of about 3 to 4 kg [234]. Nicotine is presumed to account for an increased metabolic rate [54,108], partly due to the energy-demanding destruction and release of triglycerides [45], together with increased glucose oxidation, as well as increased release of noradrenaline, serotonin and dopamine leading to reduced appetite. Weight studies of smokeless tobacco users are sparse, but despite an exposure to nicotine similar to that in smokers, no reduction of body weight or body mass index has been observed [36,66]. This finding was confirmed also in the present cohort study (Paper I). Presumably, nicotine does not explain all metabolic alterations, and there are perhaps behavioural differences superimposed on the metabolic effects of nicotine in subjects with different tobacco habits [116].

An important question is whether discontinuing the use of smokeless tobacco leads to a weight gain or not. This has not been sufficiently investigated, but one study indicates weight gain also in smokeless tobacco users following cessation [7]. There is also the question of whether nicotine delivered as smokeless tobacco or nicotine replacement therapies might inhibit smoking-cessation-related weight gain. Nicotine gum has been found to suppress weight gain in a linear fashion with increasing nicotine doses [58], whereas no such effect was found by others [204]. Data from the present study (Paper IV) indicate that subjects switching from smoking to smokeless tobacco use, do not experience the same increase in body weight as those who quit smoking without any alternative nicotine supply.

Non-nicotine-related adverse metabolic effects

The licorice content of many US brands of smokeless tobacco is suggested to contribute to blood pressure elevation because of its content of glycyrrhizinic acid, which has potent mineralocorticoid hormone activity [228]. Swedish snuff does only contain licorice in a few products. On the other hand, snuff also contains substantial amounts of sodium (see Table I), which might exert additional effects on blood pressure elevation [22,96].

Nicotine

Nicotine in smoked and smokeless tobacco

The only known reason to make use of tobacco is the nicotine content. Whenever nicotine has been removed from cigarettes or smokeless tobacco, the product has never found any market [215]. About 4 000 compounds are generated by the burning of tobacco. The gaseous phase of tobacco smoke contains, among a large number of other chemical compounds, carbon monoxide, carbon dioxide, nitrogen oxides, ammonia, volatile nitrosamines and hydrogen cyanide. The particulate phase of tobacco smoke contains nicotine, water and "tar", i.e. mainly polycyclic aromatic hydrocarbons [81]. Health hazards associated with smoking are thought to be caused mainly by the contents of nicotine, carbon monoxide and "tar". However, the causal connection between nicotine and human disease is yet to be elucidated, as studies on long-term exposure to nicotine alone have not been possible, until the development of modern nicotine delivery sys-

tems like the gum, patches and nasal spray [29,215]. As far fewer people use these nicotine products for a substantial amount of time, compared with the use of tobacco, it still remains difficult to obtain basic epidemiological data on the consequences of long-term exposure to nicotine. Therefore, the different way of nicotine administration, when using smokeless tobacco, presents the possibility of studying any diversities or similarities in health effects with the same exposure to nicotine as in smokers [29,86,178], but without exposure to the multitude of other potentially harmful substances in tobacco smoke.

The daily average use of smokeless tobacco in Sweden is 19 g of moist snuff/day [186,199]. This amount contains about 150 mg of nicotine (0.8 per cent), approximately half of which is absorbed, i.e. 50-75 mg. This can be compared to smoking cigarettes with a medium nicotine content. The average consumption in Sweden at present is 15 cigarettes/day, containing approximately 1 mg nicotine/cigarette, >90 per cent of which is absorbed. Thus the daily intake of nicotine is much higher in habitual smokeless tobacco users than in smokers (50-70 mg vs. 15 mg), but still peak levels of nicotine are similar in both groups due to differences in the absorption pattern (see below).

Pharmacology of nicotine

Nicotine is a natural liquid alkaloid (Figure 1). It is a colourless, volatile base (pKa=8.5) which turns brown and acquires the smell of tobacco on exposure to air. The pharmacological actions of nicotine are often complex and unpredictable as it has a variety of neurological and chemosensitive effects. It exerts its effects at three major physiological sites; the neuromuscular junction; the autonomic ganglia and the central cholinergic synapse [85]. It acts both as a stimulant and a depressant, and the ultimate response represents the summation of its different and opposing effects. In the peripheral nervous system, its initial action is stimulant with a subsequent more persistent depression of all autonomic ganglia [81,114]. While the cardiovascular effects of nicotine are mostly due to stimulation of sympathetic ganglia and the adrenal medulla, the gastrointestinal effects are due largely to parasympathetic stimulation, giving rise to an increased tone and motor activity of the bowel. In inexperienced users nausea and vomiting may occur due to a massive stimulation of the autonomic nerve system, but rapid neuroadaptation attenuates this effect with repeated supply of nicotine [81].

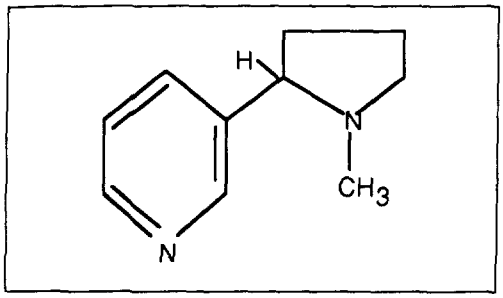


Figure 1. The molecular structure of nicotine.

Effects of nicotine on metabolism

Through its primary effects on the central and peripheral nervous systems (Figure 2), affecting the release of neurotransmitters like adrenaline, noradrenaline, dopamine and acethylcholine, nicotine induces the release of a multitude of hormones, such as antidiuretic hormone (ADH), cortisol, ACTH, growth hormone (GH) and endorphins. Mobilisation of free fatty acids (FFA), by an increase in adipose tissue lipolysis, occurs in response to the sympathoadrenergic stress effects [215]. The hemostatic system is also affected by nicotine, through an increase in platelet adhesiveness, thought to be caused by reduced formation of prostacyclin [25,163].

Nicotine is very poisonous, with a fatal dose of approximately 1 mg/kg body weight. Intoxication by nicotine-containing insecticides or, in children, by ingesting tobacco, can be lethal due to central paralysis of respiration [81].

Nicotine absorption

Nicotine can be absorbed from the respiratory tract, through mucous membranes and also through the skin [19]. It has a half-life of about two hours, and its main metabolites are cotinine and nicotine-1'-N-oxide [81,215]. Cotinine, with a half-life of 18-20 hours, is used as a quantitative indicator of nicotine intake [78,93].

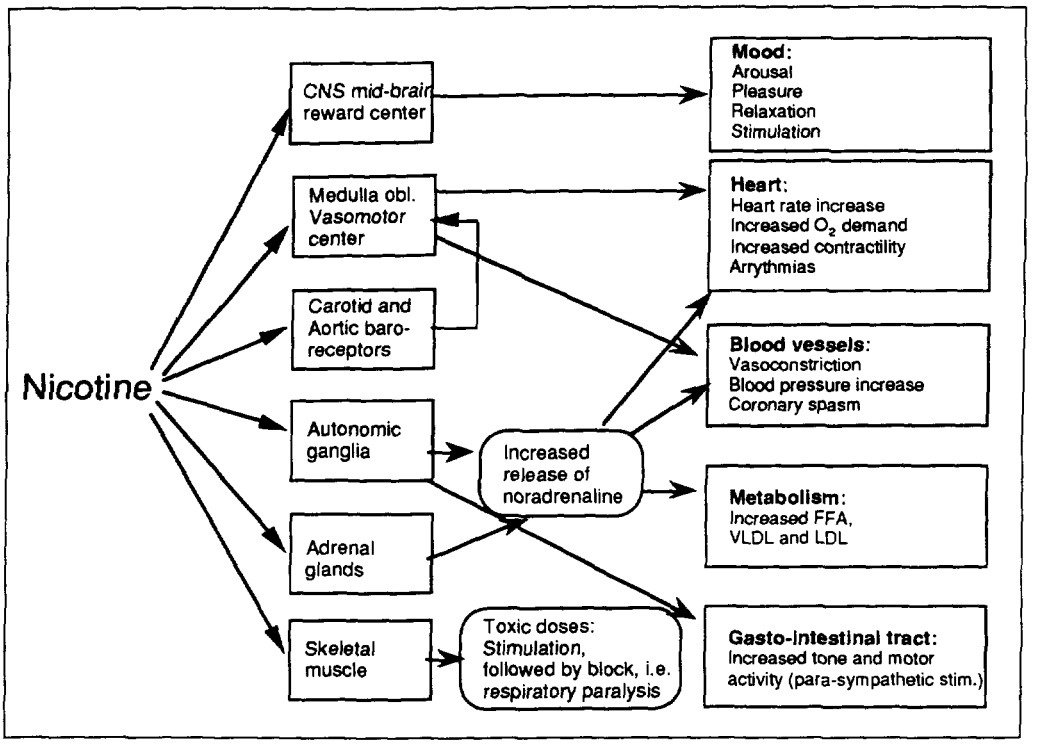


Figure 2. Major pharmacological actions of nicotine.

The absorption of nicotine through the buccal mucosa is less rapid than the almost instantaneous absorption on inhaling tobacco smoke into the lungs [20,28]. Still, there is a rapid increase in blood nicotine level during the first 10 minutes after oral exposure [109]. The absorption is facilitated by an increased pH, and most smokeless tobacco products have a pH between 7.5 and 8.5. The average blood nicotine levels are similar in habitual smokers and smokeless tobacco users [20,29,86,178,181]. Smokeless tobacco users seem, however, to absorb a larger total amount of nicotine through the gastrointestinal mucosa by swallowing, followed by a first-pass metabolism of nicotine to pharmacologically inactive metabolites in the liver [27,109]. This results in equal levels of blood nicotine, but significantly higher levels of cotinine in smokeless tobacco users than in smokers.

Effects of nicotine on the CNS – nicotine dependence

Nicotine is the substance in tobacco that causes addiction, i.e. the compulsive craving for tobacco, deprived of voluntary control, irrespective of its administration in the form of smoked or smokeless tobacco [215]. In the CNS, nicotinic receptors seem to be present on both noradrenergic, dopaminergic and serotonergic nerve terminals and, on stimulation with nicotine, significant effects of increased vigilance, arousal and, to some extent, locomotor control are achieved [85]. The evolutionary primitive mesolimbic dopamine system in the midbrain, which is deeply involved in reward mechanisms, as well as motivational behaviour, seems to be the focus for self-administration of various drugs of abuse, including nicotine. The pharmacological and behavioural processes that determine nicotine

addiction are similar to those that determine addiction to such drugs as heroin and cocaine [215]. The pharmacological reward and reinforcing effects of nicotine, including euphoriant and anxiety-reducing qualities, overshadow all intellectual awareness of the dangers of tobacco use [67].

Withdrawal and abstinence

If the nicotine supply is discontinued, about 80 per cent of habitual users experience withdrawal symptoms, implying dysphoric and depressed mood, insomnia, irritability, frustration, anger, anxiety, difficulty in concentrating, restlessness, decreased heart rate and increased appetite, to various degrees [21,88], see Table II. Therefore, most regular tobacco users try to attain blood levels of nicotine sufficiently high (usually about 20-50 μg/L) [26,109,178] to avoid the discomfort of abstinence. Smokeless tobacco users tend to keep their blood levels constant by changing the quid regularly during the day. The average usage of smokeless tobacco in Sweden is 13 hours per day [11], and a number of subjects also use it during sleep. This continuous venous supply leads to a tonic nicotine concentration pattern, differing from smokers who obtain nicotine in more of a wave-motion pattern with high arterial peak concentrations of nicotine alternating with lower concentrations.

Most symptoms of withdrawal reach maximal intensity within 48 hours after cessation and diminish gradually over a period of two to three weeks, whereas the force of habit might lead to a desire to use tobacco for months and years after cessation [21].

Table II. Common nicotine withdrawal symptoms.

Restlessness
Irritability
Aggressiveness
Fatigue
Decreased ability to concentrate
Increased appetite
Sleeplessness
Craving for nicotine
EEG-changes
Decreased heart rate
Decreased blood pressure
Weight gain

Nicotine and the "doping" question

The pharmacological effects of nicotine involves properties of reinforcement, increased concentration and raised awareness. The classification of doping agents includes substances that may enhance performance and/or be injurious to health [33], i.e. entail effects that either prolong endurance, reduce exhaustion, increase physical performance or "stimulate". The complicated pharmacology of nicotine with both stimulant and depressant actions has contributed to an unclear picture of nicotine as a doping agent in sports [197]. Up to now, the effects of nicotine on muscular strength, speed or endurance have not been unequivocally established. However, the central effects with increased catecholamine release, similar to those of other psychostimulants such as amphetamines, with increased attention and euphoriant actions, with positive effects on mood and motivation, as well as the potential of nicotine to alleviate the deleterious effects of stress on performance [46,85,134,217], constitute basis enough not to exclude nicotine from further discussions of doping properties. A strong reason for the International Olympic Committee not to classify nicotine as a doping agent is of course the large number of tobacco users and the huge problem of supervision, with enormous economic consequences.

In the light of the reinforcing effects of nicotine, it is interesting to note that doping control laboratories detect a substantial percentage of nicotine-positive urine samples. In 2 600 Swedish routine competition and unannounced out-of-competition urine tests, 30% of the male and 15% of the female samples were found to contain nicotine. In sports like weightlifting, boxing, bandy, baseball and ice-hockey there were 40-50% positive tests. In 1 200 international athletics tests, 24% of the males were positive for nicotine, and 10% of the females [33]. It therefore remains an intellectual challenge, as well as an ethico-medical issue, to discuss the appropriateness of accepting the use of a drug in sports, that creates a chemical addiction in most users and leads to obvious withdrawal symptoms on discontinuation. It is an exciting thought to visual-

ise the Swedish national hockey team fighting for an Olympic gold medal during nicotine withdrawal.

Nicotine, smokeless tobacco and circulatory effects

Acute hemodynamic effects of nicotine

Nicotine can increase the heart rate by exciting sympathetic or paralysing parasympathetic cardiac ganglia, and it can decrease the heart rate by inverse actions [81]. Nicotine also causes a discharge of adrenaline from the adrenal medulla, which accelerates heart rate and raises blood pressure [19,85]. The predominant acute cardiovascular effects of nicotine [53] result in an increase in heart rate, 10-20 beats/minute, systolic blood pressure, 5-10 mmHg [29,229], cardiac output, stroke volume and coronary blood flow, as well as cutaneous vasoconstriction and increased muscle blood flow [6,29,136,196]. The hemodynamic effects appear to be more pronounced immediately after cigarette smoking than after smokeless tobacco use, but, on the other hand, the increase in blood pressure and heart rate seems to persist for a longer period after exposure to smokeless tobacco [29]. Vibrationinduced white fingers, so called traumatic vasospastic disease, has been shown to be significantly more common in both smokeless tobacco users and smokers, as a sign of an acute influence of nicotine [61]. During physical performance, nicotine has been found to raise heart rate and blood pressure at submaximal work levels [79,103,132,188,195,218].

Long-term exposure to nicotine and cardiovascular effects

Smoking and cardiovascular disease

Smoking is a major risk factor for coronary and peripheral vascular disease [112,176,211,225, 232] and a number of potential pathophysiological mechanisms have been proposed to explain the epidemiological links between cigarette smoking and obstructive coronary artery disease. There is a strong correlation between smoking and early signs of atherosclerosis as determined by carotid ultrasonography investigations [52,92, 110,135,182]. Smoking causes a variety of effects on lipid metabolism [150,216], coagulation [32,119,143], and hemodynamic function [6,34, 196] and potentiates endothelial dysfunction [99,100,162,166,167]. Smoking seems to be responsible for causing an excessive inflammatory-fibroproliferative response in the vascular wall endothelium and smooth muscle layer, with an adverse effect on the release of growth factors, and cytokines and on vasoregulatory mechanisms [176]. Smoking also involves dyslipidemia, with raised LDL, total cholesterol, and triglyceride levels [41,150] unfavourable fat distribution [140,235], hyperglycemia and insulin resistance [14,57,63,69,149], as well as an altered hemostasis [35], especially disturbances in the fibrinolytic system [32,65,95,119,233], all of which contribute to the development of both diabetes and cardiovascular disease [169,191].

Nicotine, smokeless tobacco and cardiovascular disease

Whether continuous exposure to nicotine for decades, as in for example, the use of smokeless tobacco, involves increased cardiovascular risks similar to those connected with smoking, is essentially a question of the causality of nicotine in the progress of smoking-related diseases, such as severe atherosclerosis, peripheral arterial disease, myocardial infarction and cerebrovascular disease [23,133]. This topic has not been sufficiently investigated [42,214], but in some studies, nicotine has been suggested to contribute to adverse cardiovascular and metabolic effects when delivered by transdermal patches, by chewing gum or as smokeless tobacco [27,64,137,155, 172,194,198,202], whereas other studies show no harmful effects of such use of nicotine [7,66, 111,153]. Animal studies of nicotine administration in experimental atherosclerosis are also inconsistent and inconclusive concerning the causal role of nicotine [42,187].

Metabolic effects connected with the accelerated atherosclerosis and increased risk of myocardial infarction in smokers, entailing dyslipidaemia, with raised LDL, total cholesterol, and triglyceride levels, unfavourable fat distribution, hyperglycaemia and insulin resistance [35,41,165] and disturbances in the fibrinolysis system [65, 95,119,233] have been investigated also in smokeless tobacco users [7,14,64,189,202]. No significant differences compared with non-users of tobacco has been found in most studies,

even though some tendencies towards slightly raised risk levels have been observed for some variables. The overall impression is that atherosclerosis appears to be less causally related to nicotine than to other components of tobacco smoke.

Nicotine and hypertension

In contrast to the blood pressure elevating effect of acute exposure to nicotine, smokers generally exhibit a lower prevalence of hypertension than non-users in most epidemiological studies [31,76,80,83,91,157]. An inverse relationship between blood cotinine levels and blood pressure has also been demonstrated [30]. There are, however, reports indicating an increased incidence of hypertension in smokeless tobacco users [1,79,90,132,183,229]. Other reports, mainly investigating young subjects, have not been able to confirm this finding [66,185].

The principal pharmacological action of nicotine, apart from its psychoactive mood-regulating effects, is activation of the sympathetic nervous system, involving increases in heart rate, blood pressure, myocardial contractility and peripheral vascular resistance. In recordings of heart rate acceleration, it seems as if a continuous supply of nicotine by habitual smoking or smokeless tobacco use results in sympathetic nervous activation nearly 24 hours a day. Sympathetic overactivity is an early integral part of the pathophysiology in a large proportion of patients with hypertension [118]. Increased heart rate has also been correlated to an increase in cardiovascular mortality [120].

Different hypotheses concerning the reasons for the paradoxical lower blood pressure found in smokers than in non-smokers have been presented:

1. The lower body mass index in smokers. But this cannot fully explain the difference, as it persists also after control for body mass index [83,184].
2. Reduced myocardial contractility, as smokers have a higher incidence of cardiovascular disease. Still lower blood pressures are found also in cohorts of healthy smokers long before clinical signs of coronary heart disease may occur.
3. There might be a reduced sensitivity of the baroreceptor reflex mechanism, a view supported by animal studies [18,145].
4. Findings of increased blood pressure variability in smokers [193]. There might be an adaptive or rebound effect when smoking subjects are abstinent, which is often the condition when clinical studies are made. This is supported by recent ambulatory blood pressure monitoring, showing no difference or slightly increased blood pressures in smokers compared to non-smokers during the daytime [13,123,139, 161,193,219], whereas one study found lower blood pressures throughout the day [144].
5. There might be a blunted postural response in autonomic cardiac regulation, which might explain why the lower average blood pressure in smokers is found mainly when it is measured with the subject seated or at rest [98].

Nicotine and physical performance

Nicotine acts on the neuromuscular junction, where it releases acethylcholine thereby inducing a small depolarisation. In laboratory experiments nicotine causes a muscle contraction, followed by paralysis [85]. Intoxications of nicotine also cause fatal respiratory paralysis. Whether the nicotine levels of habitual users entail any influence on physical performance, on muscular strength, speed or endurance have not been unequivocally established, as mentioned earlier [197]. A few studies of physical performance in smokeless tobacco users have not revealed any reduction of working capacity or oxygen uptake in healthy subjects [16]. Cigarette smoking has been associated with poor physical fitness and smokers show reduced cardiovascular endurance and lower oxygen uptake in comparison with non-smokers [16,49,50,146]. The acute effects of smokeless tobacco during exercise have been studied in habitual users, mostly in the age around 20 years [16,79,132,188,203,218]. The findings indicate an elevated heart rate at rest, during exercise at submaximal work loads, and during recovery after exercise, but not at maximal exercise.

Aims of the study

Main objective

The main objective of the present project was to investigate the relationship between long-term use, i.e. for several decades, of smokeless tobacco and cardiovascular disease and to elucidate the role of nicotine, in the light of the well-documented cardiovascular risks associated with cigarette smoking.

Specific topics

Do long-term users of smokeless tobacco, compared to non-users or smokers:

I. Exhibit any difference regarding ill-health, as determined by medical check-ups, sick leave and disability pensions?

II. Show any difference in cardiovascular mortality?

III. Exhibit any difference in physical performance?

IV. Exhibit metabolic alterations compatible with an increased cardiovascular risk?

V. Show early signs of atherosclerosis, as determined by carotid artery ultrasonography?

VI. Show any noticeable alterations of diurnal blood pressure and heart rate?

Methods

Papers I and II

Subjects

In 1974 there were 183 865 union-registered workers in the Swedish construction industry (construction workers, electricians, painters and sheet-metal workers). From 1969 to 1992, the Swedish Construction Industry's Organization for Working Environment Safety and Health offered regular voluntary health check-ups to all employees, every two to every three years. The present studies are based on the 135 036 subjects examined during 1971-74. About 25% of the workers did not report for the health examination, and there is no record of whether the employees were not reached by the notice to attend or were not willing to come.

In the first investigation, the study group was restricted to only blue-collar workers, leaving 97 586 subjects for the major analysis. The second study included also white-collar workers, with a restriction to men only (<0.5% women), Figure 3.

Procedures

Body stature

A standardised programme was followed for the medical examination. The body mass index (BMI) was calculated as body weight in kg/(height in m)^2 [124]. Body mass indices were divided into ≤20.0; 20.1-25.0; 25.1-30.0 and >30.0 [72]. For the blood pressure evaluations of Paper I, a normal body mass index was defined as BMI 22-26.

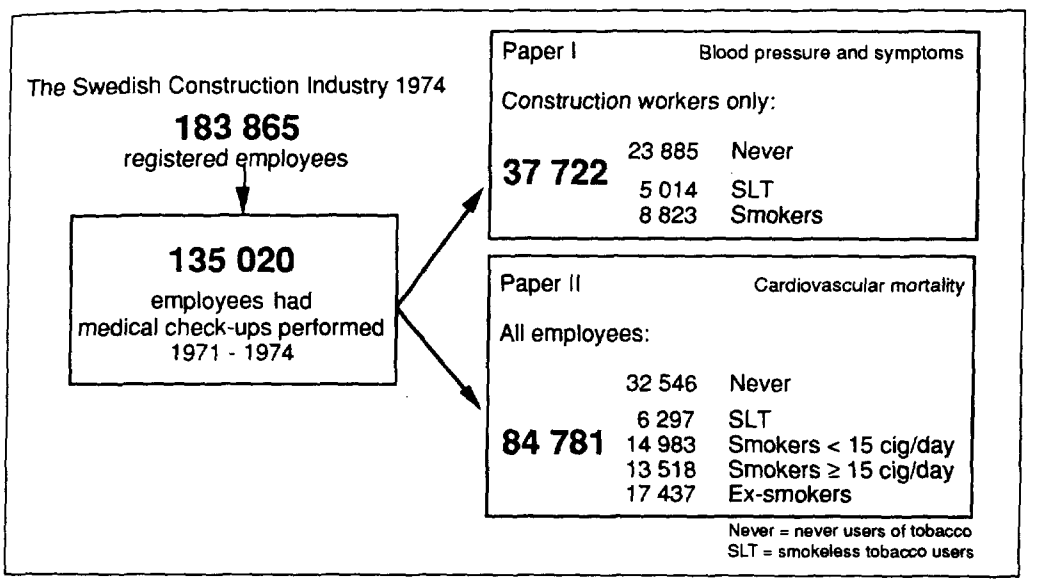


Figure 3. Study population, Papers I and II.

Blood pressure and heart rate

Blood pressure was measured after 5 minutes of rest in a supine position, using a standard mercury manometer on the upper arm; the systolic level was recorded when phase 1 (Korotkoff) sounds were heard and the diastolic level at phase 5 (disappearance of sounds). Blood pressure was recorded to the nearest 2 mm Hg. Heart rate was recorded as beats/minute, simultaneously with the blood pressure measurement. In the analysis, blood pressure was divided into four categories: systolic blood pressure ≤140, 141-159, 160-179 and ≥180 mmHg and diastolic blood pressure <85, 85-94, 95-104 and ≥105 mmHg. Blood pressure and heart rate data were missing for 0.2% of the subjects.

Questionnaire

A questionnaire containing questions about type of occupation, tobacco use (type, amount and duration for smoked tobacco and duration for smokeless tobacco) and about the past and present history of symptoms and disorders involving various organ systems was completed together with a nurse (the questionnaire has been published elsewhere [36]). The last intake of tobacco was not recorded, but no subject was allowed to smoke in the waiting room or to use tobacco during the examination.

Tobacco habits

The classification of tobacco habits is shown in Table III and was aimed at isolating subjects with a single type of exposure to tobacco for the analysis.

Sick-leave, disability pension and mortality data

Information about sick-leave frequency and disability pension diagnoses was obtained from the Swedish National Social Insurance Board.

The members of the study population identified between 1971 and 1974 and who were alive on 1 January 1974 were followed regarding cause-specific mortality during the period 1974 through 1985 with the aid of the National Cause of Death Register [156] with certification of the underlying cause of death according to the International Classification of Diseases, 8th revision (ICD-8). The underlying cause of death is defined as the illness that started the chain of events that directly led to death. The diagnoses specifically studied were:

ischæmic heart disease, ICD-8: 410-414;
cerebrovascular disorders, ICD-8: 430-438;
all cardiovascular diagnoses, ICD-8: 390-458;
all malignant neoplasms, ICD-8: 140-209.

Designation	Definition
Non-users	Never used any tobacco
Smokeless tobacco users	Smokeless tobacco users, without any present or former use of smoked tobacco
Smokers <15 cig/day	Cigarette smoking less than 15 cigarettes per day, no other present or former tobacco use
Smokers ≥15 cig/day	Cigarette smoking more than 15 cigarettes per day, no other present or former tobacco use
Ex-smokers <5 y	Former cigarette smoking, no other former or present tobacco use, stopped smoking 1 - 5 years ago
Ex-smokers >5 y	Former cigarette smoking, no other former or present tobacco use, stopped smoking >5 years ago
Others	Mixed tobacco use, pipe smokers, cigar smokers

Table III. Classification of tobacco habits, Papers I and II.

The validity of the National Cause of Death Register has been evaluated [56,222].

Quality of exposure data

The validity of the registered exposure data from the health check-ups has been studied by other investigators [154]. For 89 per cent of the subjects examined more than once (2-3 years apart), tobacco consumption data were in perfect concordance, whereas 2.6 per cent were found to have declared ex-smoker or current smoker status in the first examination and never-smoker status the second time.

Etiological fraction-attributable risk

A formula to calculate the proportion of cases that would disappear if the exposure to a certain predisposing or causal factor should be removed, is useful when applying relative risk estimates on a public health level. It is calculated as follows (where EF is the etiological fraction expressed as a percentage, and f is the proportion, x/100, of the identified cases being exposed):

$$EF=(RR-1)/RR * f$$

As an example, if the relative risk of developing oral cancer is 4.1 for smokers and 95% of the cases are smokers, the formula gives

$$(4.1-1)/4.1 * 0.95=0.72$$

i.e. 72% of oral cancers would disappear if there were no smokers. This formula was used to calculate cardiovascular mortality attributable to the exposure to smokeless tobacco, based on findings from Paper II.

Statistics

For subjects with different tobacco consumption habits, relative risks and prevalence odds ratios, together with 95% confidence intervals (C.I.), were calculated for symptoms, sick leave and disability pensions in comparison with the non-users. Account was taken of potential confounding regarding age (Paper I). Relative risks of death due to specific causes, together with 95% confidence intervals, were estimated. To adjust for potential confounding factors such as age (five-year brackets), area of domicile, blood pressure, blood pressure medication, previous cardiac symptoms, diabetes, and body mass index, the Mantel-Haenszel procedure was used [177] and 95 percent confidence intervals were estimated according to Greenland et al. [84]. The analyses of the relationship between different tobacco habits and mortality were performed both for the entire cohort and for workers entering the study at an age of 35-54 and 55-65 years (Paper II).

Papers III-VI

Subjects

In 1993 there were 269 firemen, 35-60 years of age, in the Stockholm City Fire Brigade. In connection with the annual compulsory fitness test, they were offered an extended health examination including measurements of biochemical cardiovascular risk factors, a maximal exercise test, 24-hour ambulatory blood pressure monitoring and an ultrasound examination of the carotid artery intima-media wall thickness. 203 subjects (75%) were willing to participate, and 151 of these were called in for investigation within the time limits of the study. Non-participating subjects (both non-responders and those who were willing to come) were equally distributed amongst the 9 different fire departments.

Procedures

Clinical procedures

Body stature, blood pressure and heart rate. Body height and weight were measured and the body mass index was determined (BMI=kg/m^2). Waist circumference was measured at the level half way between the lower rib margin and the iliac crest, with the patient standing. Hip circumference was measured at the most prominent point between hips and buttocks. The waist/hip ratio was calculated. The sagittal abdominal diameter was measured with the guidance of a water level, with the patient lying flat on a firm bed, at both the umbilical and iliac crest level. Blood pressure was determined by standard sphygmomanometry to the nearest 2 mmHg after 5 minutes of rest in a supine position, as the mean of two separate measurements. Heart rate was recorded at the same time.

Questionnaire. Tobacco consumption habits, physical activities during working hours and lei-

sure time, family histories of cardiovascular disease and parental death before the age of 60 were recorded by means of a questionnaire, together with a specially trained nurse. Physical activity during work was divided into active, i.e. fireman duties and compulsory physical training during working hours, or sedentary, i.e. no physically demanding duties. Leisure-time exercise was divided into two exercise levels; low=≤ once a week, medium/high=2-4 times a week. Alcohol and coffee consumption habits were recorded as self-reported as none, low, medium or high consumption. Symptoms and family history of angina pectoris, hypertension or myocardial infarction were recorded as yes/no answers.

Tobacco habits. Tobacco consumption habits were categorized according to the subgroups shown in Table IV, where duration of the tobacco consumption habit is also presented. For intergroup comparisons between different tobacco habit groups, the selection of subjects was slightly different depending on the analysis made. For papers IV and V, where studies of atherosclerosis and metabolic risk factors were done, no ex-users of tobacco were included in the reference group (never-users) to avoid any influence of earlier exposure to tobacco when evaluating the results. However, in the analysis of physical performance and 24-hour blood pressure monitoring, ex-users were included in the reference group (non-users). The division of subjects with regard to tobacco consumption habits for the analyses in Papers III-VI are shown in Figure 4.

Non-participants. Seven subjects were unable to perform the maximal exercise test because of an unsuitable schedule, and these subjects did not undergo the ultrasound examination either, as it was performed before the exercise test. Sixteen subjects were omitted in the 24-hour blood pressure monitoring because of inadequate technical quality, medication or night work (9 non-users, 3 smokeless tobacco users and 4 smokers).

Exercise test. The exercise investigation was performed as a graded maximal exercise test on a MedGraphics™ computerised test bicycle (Medical Graphics Corporation, St Paul, MN, USA). The initial work load was 50 W, increased by 20W every minute until volitional exhaustion. Heart rate, ECG and respiratory rate were recorded continuously. O_2 uptake and CO_2 production were measured continuously and respiratory

Table IV. Classification of tobacco habits-Papers III-VI.

	Non-users n (68)	Smokeless tobacco users n (50)	Smokers n (33)	Years of tobacco use median (25th, 75th percentiles)
Never-users of tobacco	42	-	-	0
Ex-users for ≥5 years[1]	15	-	-	13 (10-20)
Ex-users for ≤5 years[2]	11	-	-	24 (20-29)
Smokeless tobacco users[3]	-	29	-	25 (19-27)
Ex-smokers, now smokeless tobacco[4]	-	21	-	24 (17-31)
Smokers[5]	-	-	26	28 (20-30)
Smoking+smokeless tobacco use[6]	-	-	5	30 (20-31)
Ex-smokeless, now smoking[7]	-	-	2	32 (30-35)

1= Stopped smoking or using smokeless tobacco more than five years prior to examination.
2= Stopped smoking or using smokeless tobacco less than five years prior to examination.
3= Daily smokeless tobacco use for more than 6 months.
4= Stopped smoking more than 6 months ago, daily smokeless tobacco users for more than six months.
5= Daily smoking for more than six months.
6= Daily smoking plus daily or occasional smokeless tobacco use.
7= Stopped using smokeless tobacco more than six months ago, daily smokers for more than six months.
n = Numbers in different tobacco habit groups. Total numbers in brackets.

gases were sampled via a mouthpiece, using the pulmonary gas exchange system CPX/MAX from MedGraphics™. Systolic blood pressure was recorded every three minutes. Heart rate and systolic blood pressure were also measured at the 190 W work load level.

The ECG recordings were all evaluated by the same investigator, without knowledge of the subject's tobacco status. A horizontal ST-segment depression ≥1 mm during exercise was regarded as a sign of myocardial ischæmia. ST segment changes <1 mm were recorded, but not classified as pathological. Arrhythmias before, during and after work were noted.

Carotid ultrasonography. The examination was performed with an ultrasound scanner (Acuson 128 Mountain View, CA) equipped with a linear 5 and 7-MHz probe. In the majority of cases we used the 7-MHz probe, but in a few cases the 5-MHz probe was used due to deeply positioned vessels, making it difficult to properly identify the vessel wall. The patient was placed in the supine position with his head turned to the left. The ultrasound probe was placed over the right carotid artery and a complete examination of the vessel was made, including the morphology and flow conditions, using 2D-mode and Doppler (colour and spectral).

Simultaneous ECG recordings were made and at the point of best visibility of the wall structures, the image was frozen on the R-wave (end diastole) over the bulb area visualising the distal part of the common carotid artery and the proximal part of the bulb. Altogether, 6 images were frozen (3 of the distal common carotid artery and 3 of the proximal bulb) and recorded on videotape.

Measurements of intima-media thickness and lumen diameter. The frozen images from the videotapes were analysed in a computerized analysing system consisting of a PC-controlled framegrabber (Imaging Technology FG-100) with an extra monitor and a digitiser (Summagraphics MM-1201). The intima-media thickness was defined as the distance between the leading edge of the intima-lumen interface and the leading edge of the media-adventitia interface of the far wall [226,231]. The lumen diameter was defined as the distance between the leading edges of the intima-lumen interface of the near wall and the

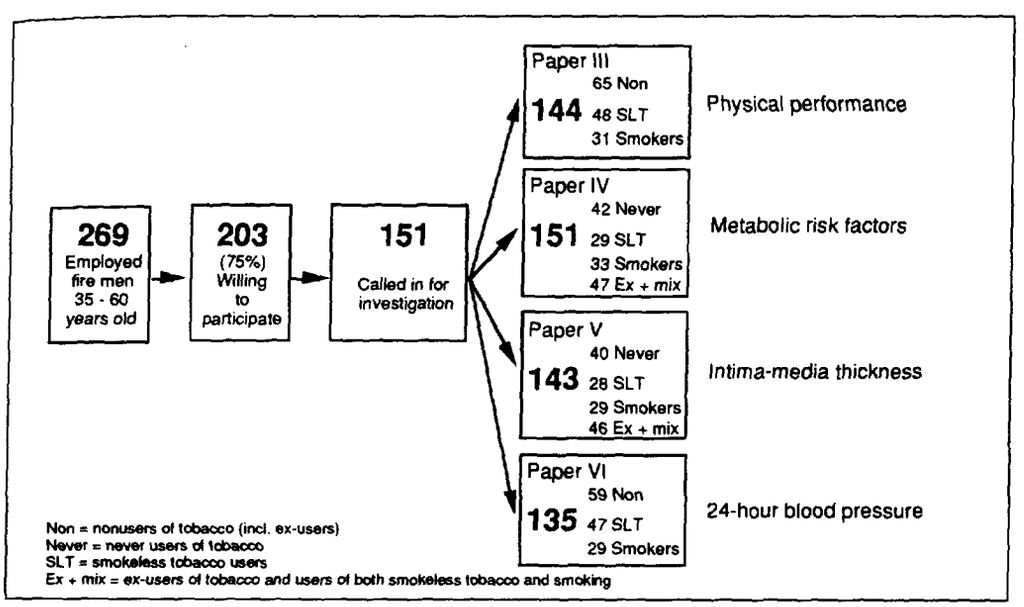


Figure 4. Study population, Papers III-VI.

lumen-intima interface of the far wall. The lumen diameter was measured in the distal part of the common carotid artery. The intima-media thickness was measured along a 10-mm-long section of the distal part of the common carotid artery and in the proximal part of the bulb. The minimal, maximal and mean values for intima-media thickness and lumen diameter from each of the 3 frozen images from the 2 measured sections were calculated. Plaque formations were registered regardless of the location in the vessel and were defined as a 100% increase in I/M-thickness compared to adjacent normal-sized intima-media thickness. Both the sonographic recordings and the analysis of measurements were done by the same examiner in a blinded fashion without access to information on the subjects' tobacco consumption habits.

Ambulatory 24-hour blood pressure recording. Ambulatory blood pressure was recorded using the Suntech Accutracker® II (Suntech Medical Instruments Inc. NC, USA). The method of measurement is auscultatory through a microphone placed over the brachial artery, using simultaneous ECG recordings for R-wave gating. Systolic and diastolic blood pressures were determined from phase I and V Korotkoff sounds. Blood pressure was recorded every 15 minutes during the daytime (06.00-24.00) and every 30 minute during the night (00.00-06.00), resulting in approximately 84 recordings per individual. Artefacts were defined as SBP>250 mmHg, DBP >SBP, DBP<30 mmHg or DBP>150 mmHg. Data were analysed as means of SBP, DBP and HR over 24 hours, daytime and nighttime, and the averages of consecutive 3-hour periods. Blood pressure variability was defined as the standard deviation of the mean value of the systolic or diastolic blood pressure during the period of time referred to (24 hours, daytime and nighttime or 3-hour periods) for each individual.

Casual blood pressure measurements were determined in the morning at 8.00-8.30 the day after the ambulatory monitoring was completed, after 5 minutes rest in a supine position, as the mean of two separate measurements. Heart rate (HR) was registered by palpation.

Diary during ambulatory 24-hour blood pressure recording. The 24-hour ambulatory recordings were all carried out during a weekday free from periods of normal fireman duties or shift work, with daily activities recorded as periods of sleeping hours, unusual physical effort, smoking/smokeless tobacco use, alcohol intake, meals, and driving. The diary entries were chiefly used to record sleeping hours, and to identify exposure to unusual physical effort, like hard training or sport-related activities. Tobacco users were instructed to consume tobacco ad libitum according to their usual habits. Tobacco consumption data were analysed only to confirm tobacco use during the recording period, as blood cotinine measurements before the ambulatory monitoring were used to estimate the habitual daily nicotine intake.

Laboratory procedures

Blood test. Venous blood samples were drawn from an antecubital vein, without the use of a tourniquet, at 7.30-8.00 a.m. after overnight fasting and >8 hours' abstention from tobacco.

Nicotine and cotinine. The levels of nicotine and cotinine (the primary metabolite of nicotine) in blood plasma were determined by capillary gas chromatography. Cotinine levels were used to estimate the intake of nicotine [78]. Cotinine, with a half-life of about 18 hours, is a good quantitative indicator of habitual nicotine intake [180]. Cotinine values below 10 µg/L were considered to confirm non-user status.

Lipids and lipoproteins. S-cholesterol, HDL-cholesterol and triglycerides were measured following separation of serum after clotting and centrifugation at 3 000 rpm. Samples were stored at -70°C. S-cholesterol and triglycerides were measured using routine Vitros (Ektachem) "dry chemistry" technology. HDL-cholesterol was measured after precipitation with Mg^{2+} and dextran sulphate [224]. S-LDL cholesterol was calculated according to Friedewald [75]. Lp(a) was measured using a kinetic nephelometric immunoassay technique (Beckman reagent, USA). Lipoprotein AI and lipoprotein B were determined by turbidity immunoassay methods.

Glucose and insulin. Blood glucose was measured by an enzymatic glucose oxidase method and S-insulin was measured using a radioimmunoassay technique (RIA 100, Pharmacia, Sweden). Insulin-like growth factor-I was extracted by separation with acid-ethanol and determined by a radioimmunoassay technique.

Measurements of blood coagulation and fibrinolysis. PAI-1 activity was determined by adding a certain amount of tissue-type plasminogen activator (t-PA) to diluted plasma and measuring residual t-PA activity in arbitrary units. One unit corresponds to the amount that inhibited one international unit of t-PA (calibrated with reference preparation 83/517 for t-PA, National Institute for Biological Standards and Control, London, UK). Fibrinogen was analysed by a polymerisation test [220].

Blood cell count. Hemoglobin, leucocytes and platelets were measured using Coulter technology. All laboratory results were monitored longitudinally by the internal quality control system and by means of external quality assessment schemes (Labquality, Helsinki, Finland).

Calculations

Insulin resistance index. The computer-solved homeostasis model analysis (HOMA) calculated by Matthews, as

$$(\text{fasting insulin}/22.5\ e^{-\ln \text{fasting glucose}})$$

is an estimate of insulin resistance that correlates well ($r=0.88$, $p<0.0001$) with estimates obtained using the euglycaemic clamp [141].

Atherogenic index. The calculation of

$$\frac{(\text{total cholesterol} * \text{Apo B})}{(\text{HDL cholesterol} * \text{Apo A1})}$$

aims at a better estimate of the individual's propensity for atherosclerosis than separate lipoprotein components, according to Høstmark [112]

Framingham CHD risk index. The risk for future cardiovascular events was estimated using the formula described by Anderson et al [8], including age, total cholesterol, HDL cholesterol, systolic blood pressure, diabetes, left ventricular hypertrophy, smoking and the time for prediction (10 years was used) based on findings from the Framingham study.

Statistics

Means and standard deviations were computed for the whole study population and for the different tobacco habit groups separately, for each of the outcome measures and when appropriate, medians and 25th and 75th percentiles. Geometric means were calculated for skewed variables. Analysis of variance (ANOVA) was used to determine any differences between the tobacco habit groups, and Fisher's PLSD test (protected least significant difference) was used as a post hoc test of significance. For skewed variables, non-parametric tests were used for comparisons between the groups (Mann-Whitney when comparing two groups, Kruskall-Wallis when comparing three groups).

Covariates that might influence cardiovascular morbidity, such as age, body mass index, waist/hip ratio, physical training level and alcohol consumption, were entered in a multivariate regression model to adjust for possible confounding, and Student's t-test was used for post hoc tests of significance for differences between adjusted values. Univariate linear regression or Spearman's rank correlation coefficient (for skewed data) was used to analyse the nature of relationships between single measurements associated with an increased cardiovascular risk.

Prevalence odds ratios and 95 percent confidence intervals were used for dichotomised self-reported data for each tobacco habit group with non-users (Papers III and VI) or never-users (Papers IV and V) as the reference group.

Ethical considerations

The handling of the data registers of construction workers was approved by the Swedish Data Inspection Board and by the boards of the National Trade Unions of Construction workers, Electricians, Sheet metal workers and Painters. The study protocol of the clinical studies was approved by the Ethics Committee of the Karolinska Hospital, and the Safety Representative Committee of the Stockholm Fire Brigade.

Results

Paper I

Health screening

General health profile of the construction worker cohort

Data on the health examinations of 37 722 individuals were analysed. Both smokers and smokeless tobacco users had significantly elevated odds ratios for almost all symptoms. However, smokeless tobacco users were consistently at lower risk than smokers. Figure 5 shows the age-adjusted prevalence of symptoms, expressed as odds ratios with the never-users as the reference group. For respiratory symptoms, such as cough in the morning (not shown in the figure), smokers had an eight times higher risk than never-users (OR 7.9, 95% c.i. 7.2-8.5), but also smokeless tobacco users showed significantly more frequent respiratory symptoms (OR 2.1, 95% c.i. 1.8-2.4).

Gastrointestinal symptoms, such as reflux and peptic ulcer, did not occur more often in smokeless tobacco users than in never-users, despite the high exposure to nicotine, whereas smokers reported peptic ulcer symptoms three times as often as never-users.

Traumatic vasospastic disease, owing to the exposure to vibrations from hand-tools, was significantly more common among both smokeless tobacco users and smokers.

Smokeless tobacco users had slightly higher body mass index measurements than never-users, and in both these groups the BMI values increased with age. On the other hand, smokers showed no significant increase in body mas index with age, and they had significantly lower values in all age groups compared with never-users and smokeless tobacco users.

Sick leave and disability pension

Frequent sick leave (≥4 times/year) or long-term sick leave (≥30 days/year) was significantly more frequent and almost twice as usual in smokers (OR 1.7, 95% c.i.1.6-1.8), but not in smokeless tobacco users.

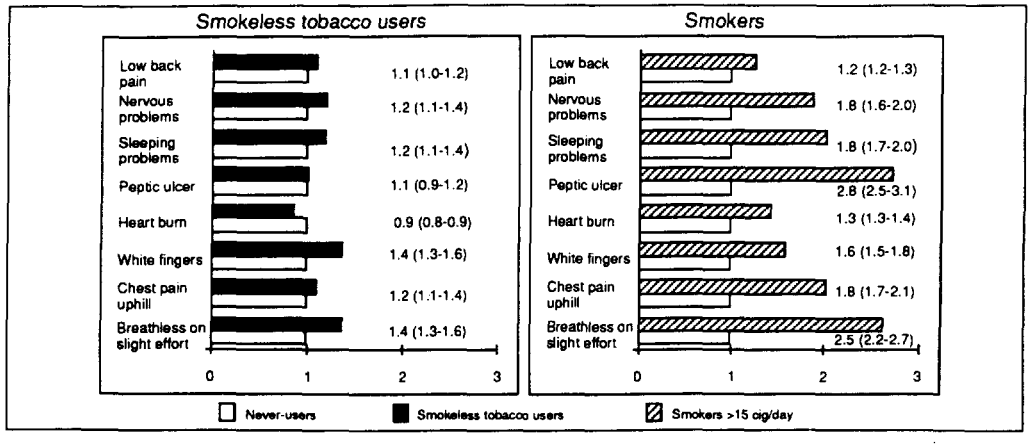


Figure 5. Prevalence of self-reported symptoms (adjusted for age) expressed as odds ratios with 95% confidence intervals, for smokeless tobacco users and smokers, compared with never-users (Never-users OR 1.0).

During the years 1971-74, a total of 11 959 disability pensions were granted in the Swedish construction industry, 35% of which also being identified in the health check-up registers. 1 370 were found in the analysed tobacco habit groups and the most frequent diagnosis as musculoskeletal disorders (48%), followed by cardiovascular disease (23%). Both smokeless tobacco users and smokers exhibited an excess incidence of disability pensions, most marked in the middle-aged group of 46- 55 year-olds (OR 2.5, 95% c.i. 1.7-3.5; OR 2.3, 95% c.i. 1.7-3.1, respectively), compared with never-users. Hypertension, a rare diagnosis as a cause of disability pensioning (75 cases in the examined groups), occurred three times as often in smokeless tobacco users (OR 3.0, 95% c.i. 1.9-4.9), whereas smokers showed no excess risk compared with never-users.

Blood pressure and heart rate measurements

Blood pressure values were dichotomised into systolic blood pressure >160 mmHg or lower and diastolic blood pressure >90 mmHg or lower. As shown in Figure 6, where data on subjects within the range of normal body weight (BMI 22-26) are presented, hypertension became significantly evident during the fifth decade of life. Smokeless tobacco users were at higher risk of hypertension than never-users, whereas smokers were at lower risk in all age groups. The same pattern was seen for subjects with overweight (BMI>26) and underweight (BMI<22).

At ages under 45, only smokers showed a significantly higher prevalence of heart rate, >80 beats/minute, compared with never-users; but at older ages, both smokers and smokeless tobacco users had a similar excess risk for elevated heart rate (OR 1.4, 95% c.i.1.3-1.6).

Paper II

Cardiovascular mortality

During the follow-up period 1974-85, there were a total of 8 293 deaths in the whole study cohort and 57 per cent were found in the analysed tobacco groups. Cardiovascular disease was the most common cause of death among the construction workers. Ischæmic heart disease caused 38 per cent of the deaths, implying a crude cumulative mortality of 2.3 per cent during the 12-year follow-up period.

The all-cause mortality was analysed in the different tobacco habit and age groups and are presented in Figure 7. Smokers exhibited the highest death rates in all age groups. Smokeless tobacco users also showed higher death rates than never-users, but less pronounced rates than smokers. After the age of 70 (data not shown), the overall mortality rate in smokers increased much more rapidly than among smokeless tobacco users, even though smokeless tobacco users were at higher risk than never-users in all age groups.

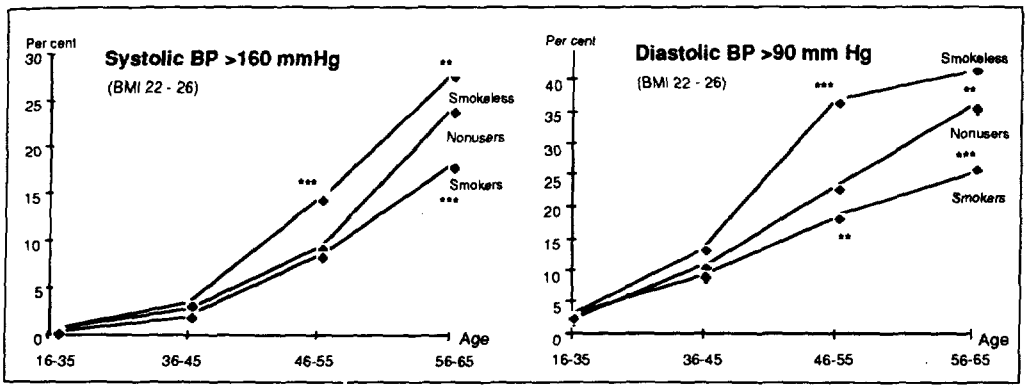


Figure 6. Prevalence of systolic blood pressure >160 mmHg and diastolic blood pressure >90 mmHg in different age and tobacco habit groups in subjects with a normal body mass index (BMI 22-26).

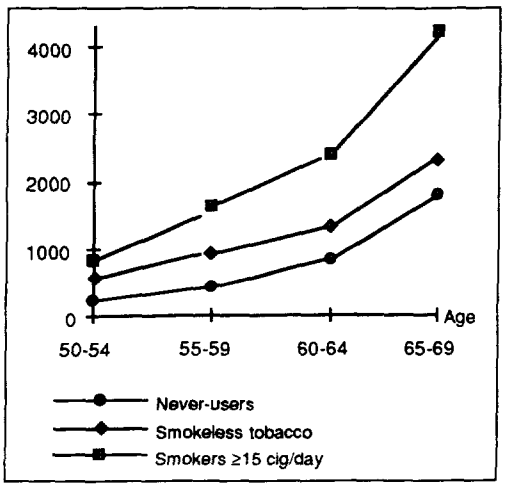


Figure 7. The all-cause mortality/100 000 individuals in the Swedish construction industry during a 12-year follow-up period (1974-85). Based on subjects registered at health check-ups 1971-74 and in the Swedish National Cause of Death Register (952 deaths among the 21 241 subjects comprising the illustrated tobacco habit groups).

The excess risk of dying of any cardiovascular disease was most pronounced for smokers (OR 1.9; 95% c.i. 1.7-2.2), with a dose-response relationship. In ex-smokers, the excess risk diminished with the time since smoking was stopped. Smokeless tobacco use was also found to be associated with an excess risk of dying of any cardiovascular disease (OR, 95% c.i. 1.4; 1.2-1.6), whereas regarding death from cancer, no excess risk was observed (OR 1.1, 95% c.i. 0.9-1.4). Although the present study was not aimed at analysing different cancer diagnoses in detail, it was obvious that smoking had a dose-response relation to the overall cancer risk and that the excess risk diminished gradually with the time since smoking was stopped. For smokers of more than 15 cigarettes per day the overall excess risk of dying of cancer was 2.5 (95% c.i. 2.2-3.0).

As construction workers over the age of 55 constitute a selection of physically very fit subjects according to the so-called "healthy worker effect", an analysis of the specific causes of death in workers who were 35-54 on entering the study was performed. Table V shows the relative risks observed in this group. For smokeless tobacco users, the relative risk of dying from any cardiovascular disease was 2.1 (95% c.i. 1.5-2.9), compared to the never-users, and for smokers of more than 15 cigarettes per day, the relative risk was 3.2 (95% c.i. 2.6-3.9). Death from stroke was less common than death from ischæmic heart disease, but with regard to tobacco habits, the same risk pattern as for ischæmic heart disease was observed (Figure 8). The relative risk of stroke among the younger smokeless tobacco users was close to 2 compared to the never-users, but the number of cases was small, and therefore the confidence interval was wide.

Lung cancer was studied specifically in order to evaluate whether hidden smokers could be found among the declared smokeless tobacco users. Three deaths from lung cancer were found in the whole smokeless tobacco user group and, compared to the never-users, the relative risk was 0.9 (95% c.i. 0.2-3.0).

Table V. Specific causes of death for 12 years of follow-up in workers who were 35-54 years old on entering the study.

	Nonusers		Smokeless tobacco users		Smokers 1-14 cig/day		Smokers ≥15 cig/day		Ex-smokers since 1-5 years		Ex-smokers since >5 years	
n at risk	13784		1672		5225		5785		2882		5005	
Diagnosis	No	RR	No	RR 95% c.i.	No	RR 95% c.i.	No	RR 95% c.i.	No	RR 95% c.i.	No	RR 95% c.i.
IHD	123	1.0	35	2.0 (1.4-2.9)	128	2.6 (2.1-3.4)	162	3.3 (2.6-4.2)	37	1.4 (1.0-2.1)	67	1.2 (0.9-1.6)
Stroke	16	1.0	4	1.9 (0.6-5.7)	17	2.7 (1.4-5.4)	19	3.0 (1.5-5.7)	4	1.2 (0.4-3.7)	5	0.7 (0.2-1.9)
All cardiovasc	154	1.0	44	2.1 (1.5-2.9)	164	2.7 (2.2-3.4)	199	3.2 (2.6-3.9)	46	1.4 (1.0-2.0)	83	1.1 (0.9-1.5)
All cancer	128	1.0	22	1.2 (0.8-1.9)	62	1.2 (0.9-1.7)	116	2.2 (1.8-2.9)	42	1.6 (1.1-2.2)	62	1.1 (0.8-1.5)
Lung-cancer	5	1.0	1	1.2 (0.2-9.1)	16	8.1 (3.2-20.4)	43	21.4 (8.5-54.1)	7	6.7 (2.3-19.7)	3	1.2 (0.3-4.5)
All deaths	410	1.0	105	1.9 (1.6-2.4)	317	2.0 (1.7-2.3)	437	2.6 (2.3-3.0)	114	1.3 (1.1-1.6)	189	1.0 (0.9-1.2)

Relative risks (RR) adjusted for age and for region of origin, for tobacco users compared to nonusers.
No is the number of deaths in the group.
IHD = ischemic heart disease.

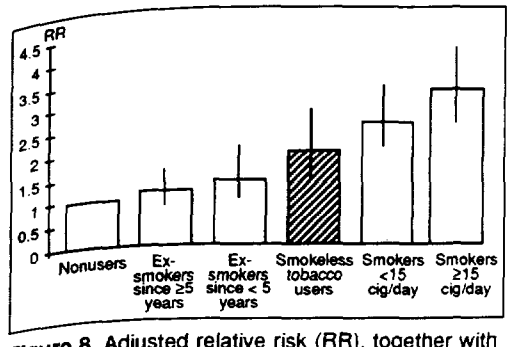


Figure 8. Adjusted relative risk (RR), together with 95% confidence interval, of dying of ischæmic heart disease among subjects in different tobacco habit groups as compared to non-users (only subjects 35-54 years of age when entering the study included).

Papers III-IV

Characteristics of the study population

There were no significant differences between non-users and smokeless tobacco users regarding age, body mass index, waist-hip circumference ratio, physical training level, consumption of coffee and alcohol, or family history of cardiovascular disease, as shown in Tables VI and VII. Smokers, however, were slightly, but significantly, older than the two other groups and also showed a tendency to central obesity. They also consumed more coffee and alcohol, had more sedentary occupational duties, and showed a higher prevalence of parental cardiovascular disease and premature death. The average daily tobacco consumption of cigarettes and smokeless tobacco was similar to the average consumption of the Swedish population, and almost all tobacco users, except those who had quit smoking more than five years ago, had used tobacco for more than 20 years (Table IV).

Paper III

Physical performance

Regular users of smokeless tobacco, with exposure to tobacco for more than 20 years, showed similar maximal oxygen uptakes (mean 3.48 L min^{-1}, SD 0.49, n=48) to those in non-users (mean 3.52 L min^{-1}, SD 0.51, n=65). However, a significantly lower maximal oxygen uptake was found for smokers (mean 2.96 L min^{-1}, SD 0.49, n=31) than for non-users ($p<0.001$), see Figure 9. In smokeless tobacco users, higher blood pressure and heart rate values were observed at rest and submaximal exercise after exposure to tobacco shortly before the exercise test, but not at maximal exercise.

Table VI. Life style characteristics and family history data of the study population.

	Non-users n=68		Smokeless tobacco users n=50		Smokers n=33	
	per cent	OR	per cent	OR, c.i.	per cent	OR, c.i.
Occupation, sedentary	10.3	1.0	4.0	0.4 (0.1-1.8)	39.4	5.7(2.0-16.2)
Physical training, low	13.2	1.0	10.0	0.7 (0.2-2.3)	51.5	7.0(2.6-18.5)
Alcohol intake, medium/high	70.6	1.0	76.0	1.3 (0.6-3.0)	94.0	6.5(1.4-29.5)
Coffee intake high	18.6	1.0	21.2	1.2 (0.5-3.0)	31.0	2.0 (1.7-5.4)
Family history of MI	25.0	1.0	20.0	0.8 (0.3-1.8)	42.4	2.2 (0.9-5.3)
Family history of HT	33.9	1.0	25.5	0.7 (0.3-1.6)	37.9	1.2 (0.5-3.0)
Parent died ≤ 60years of age	19.1	1.0	18.0	0.9 (0.4-2.4)	39.4	2.8 (1.1-6.9)

OR= odds ratio, comparisons made with non-users as reference group.
C.i.= 95 per cent confidence interval.
n = *number in group.*
Occupation, sedentary = no physically demanding duties.
Physical training = self-reported physical training during spare time dichotomised into low or medium/high.
Alcohol and coffee intake dichotomised according to self-reported data: low or no intake = low; medium or high intake = high.
MI = myocardial infarction.
HT = hypertension, self-reported known myocardial infarction or hypertension in either of the parents.

Table VII. Basic characteristics of the study population (means ± standard deviations), with comparisons of tobacco users with non-users and tobacco consumption data with medians and, within brackets, 25th and 75th percentiles.

	Non-users n=68	Smokeless tobacco users n=50	Smokers n=33
Age (years)	44±7	45±6	48±6*
Height (cm)	181±7	180±6	180±5
Weight (kg)	84.2±8.1	82.6±8.8	81.9±7.6
BMI (kg/m^2)	26±2	26±2	25±2
Waist/Hip ratio (cm/cm)	0.89±0.05	0.89±0.05	0.92±0.06**
Tobacco (g/day or cig/day)	0	21 (14-36)[2]	15 (10-21)[3]
Blood nicotine (μg/L)[1]	0 (0-0.3)	3.2 (1.6-4.8)	3.2 (1.7-8.2)
Blood cotinine (μg/L)[1]	4.0 (0.7-5.8)	333 (232-421)[4]	213 (163-359)

n = total number in each group.
BMI = body mass index.
Comparisons made with non-users, significance level of analysis of variance (ANOVA):
* = $p<0.05$, ** = $p<0.01$.
n = number in group.
1 = after overnight abstension.
2 = grams of smokeless tobacco/day,
3 = cigarettes smoked per day.
4 = $p<0.001$ when comparing smokeless tobacco users with smokers.

In spite of the findings of higher heart rates and blood pressures at submaximal exercise levels in smokeless tobacco users, there were no indications of a significant influence on maximal exercise capacity in these healthy, physically well-trained subjects. However, long-term smokeless tobacco users did not perform better than non-users and, in all age groups, they exhibited, if anything, slightly lower maximal oxygen uptakes.

Paper IV

Metabolic risk factors

Table VIII shows the results of the blood tests, with all values adjusted for differences in age, body mass index, waist-hip ratio, physical training level and alcohol consumption. Significantly higher values of parameters compatible with an increased cardiovascular risk, such as serum lipids, fibrinogen and insulin, were found only in smokers.

The calculations of indexes related to an increased coronary risk profile indicated that the atherogenic index (AI) and insulin resistance index (IR) were significantly elevated for smokers ($p<0.001$) and slightly, but not significantly, elevated for smokeless tobacco users (AI $p=0.14$ and IR $p=0.12$). The predicted risk of cardiovas-

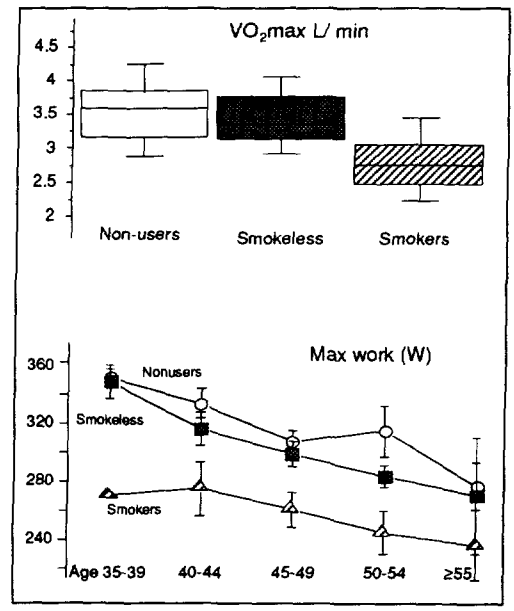


Figure 9. a) Box plot showing maximal oxygen uptake in different tobacco habit groups. **b)** Maximal work load in different tobacco habit and age groups.

Table VIII. Laboratory analysis of metabolic risk factors for cardiovascular disease in the different tobacco habit groups.

	Never-users of tobacco (n=42)	Smokeless tobacco users (n=29)	Smokers (n=33)	Significance (p-value[1])
Serum cholesterol (mmol/L)	5.2±0.9	5.3±1.0	5.8±1.1	0.005
HDL cholesterol (mmol/L)	1.4±0.3	1.2±0.3	1.0±0.3	<0.001
LDL cholesterol (mmol/L)	3.4±0.8	3.6±0.9	3.9±1.0	0.02
Serum triglycerides (mmol/L)	1.0±0.5	1.2±0.5	2.5±2.2	<0.001
Apo-A-I (g/L)	1.52±0.22	1.39±0.22	1.35±0.19	0.003
Apo-B (g/L)	1.24±0.28	1.37±0.38	1.61±0.45	<0.001
Apo-B/Apo-A-I	0.83±0.23	0.97±0.33	1.23±0.38	<0.001
Lp (a) (g/L)	0.18±0.23	0.22±0.23	0.31±0.45	0.1
B-Glucose (mmol/L)	4.6±0.5	4.5±0.5	5.0±0.7	0.002
S-Insulin (mU/L)	6.5±2.6	7.8±3.8	8.8±4.5	0.008
S-IGF1 (µg/L)	176±43	192±40	168±44	0.69
Fibrinogen (g/L)	2.61±0.59	2.75±0.48	3.16±0.67	<0.001
PAI-1 (IU/ml)	11.9±15.2	11.2±10.7	19.5±20.6	0.02
Trombocytes (10^9/L)	235±36	228±41	249±53	0.17
Leucocytes (10^9/L)	5.2±1.1	5.5±1.1	7.7±1.7	<0.001
Hemoglobin (g/L)	142±9	145±10	148±8	0.01

Means and standard deviations, adjusted for differences in age, body mass index, waist-hip ratio, physical training level and alcohol consumption.
n = number in each group.
[1]Comparisons between smokers and never-users after adjustments using Student t-test for normally distributed variables; for skewed variables, Kruskal-Wallis non-parametric test. Significance level, $p<0.05$. No significant differences were found on comparing smokeless tobacco users with never-users.
HDL=high-density lipoprotein.
LDL=low-density lipoprotein.
Apo-=apolipoprotein.

cular events (Framingham CHD risk index) was also significantly increased in smokers ($p<0.001$) compared to both smokeless tobacco users and never-users (mean values 13.2% vs 4.6% and 3.4% respectively), as shown in Figure 10.

Paper V

Carotid artery intima-media wall thickness

In the clinical ultrasonographic evaluation of the possible influence of smokeless tobacco use on atherosclerosis, as determined by the intima-media wall thickness of the carotid artery and bulb, no significant signs of increased wall thickness were observed in smokeless tobacco users, compared with never-users, in spite of more than 20 years of smokeless tobacco use. Smokers, however, exhibited significantly increased intima-media wall thickness compared to never-users (see Table IX). Smokers showed 5-20% greater maximal intima-media wall thickness than never-users, as an early sign of progressive atherosclerosis in asymptomatic subjects. The calculated mean increase in intima-media wall thickness was 0.02 mm/year in smokers, compared with 0.005 mm/year in never-users.

The formation of plaques was observed only in the tobacco user groups. More than a third of the smokers were found to exhibit carotid plaque formation, whereas this was an unusual finding among smokeless tobacco users (only two subjects) and not found at all among never-users.

In a univariate regression analysis the intima-media wall thickness was significantly correlated with total cholesterol, triglycerides, LDL-cholesterol, and the ApoB/ApoA ratio. In a multivariate analysis taking account of biochemical

risk factors, age, body mass index, blood pressure and tobacco use, only age was significantly correlated with intima-media wall thickness. For smokers, there was also a dose-response relationship regarding the amount of tobacco consumed and the occurrence of plaque. The effects of the interaction of increased serum cholesterol levels and intima-media wall thickness are illustrated in Figure 11, as well as in a box plot of the individual mean values of the carotid bulb measurements. In subjects with a family history of cardiovascular disease or diabetes, the intima-media wall measurements were found to be significantly increased (mean difference 0.06-0.12 mm) compared to subjects without this family history.

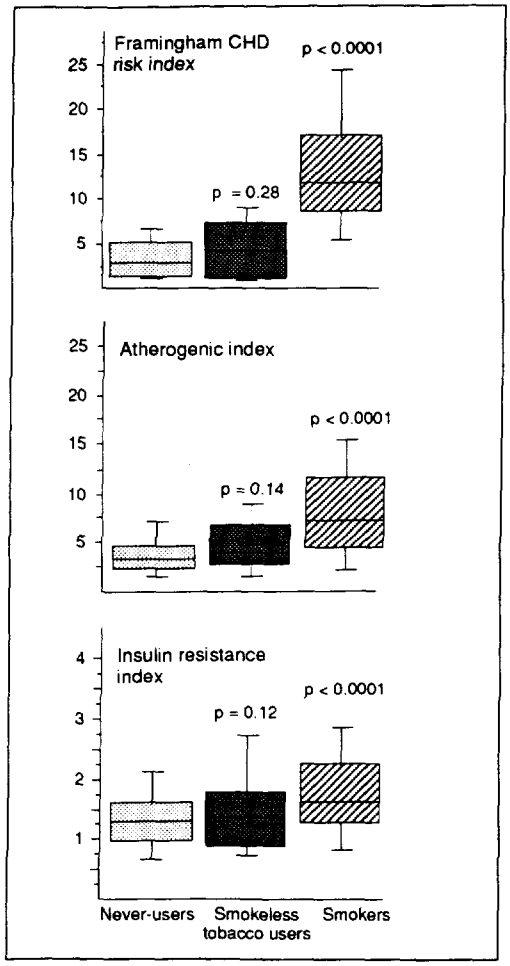


Figure 10. Box plots showing the 10th, 25th, 50th, 75th and 90th percentiles of three indexes related to cardiovascular risk, based on previously used and published formulas, using metabolic and clinical measurements. ANOVA and Fisher's tests for comparisons of different tobacco habit groups with never-users; p<0.05 was regarded as significant. (Framingham index, see [8] atherogenic index, see [112] insulin resistance index, see [141]).

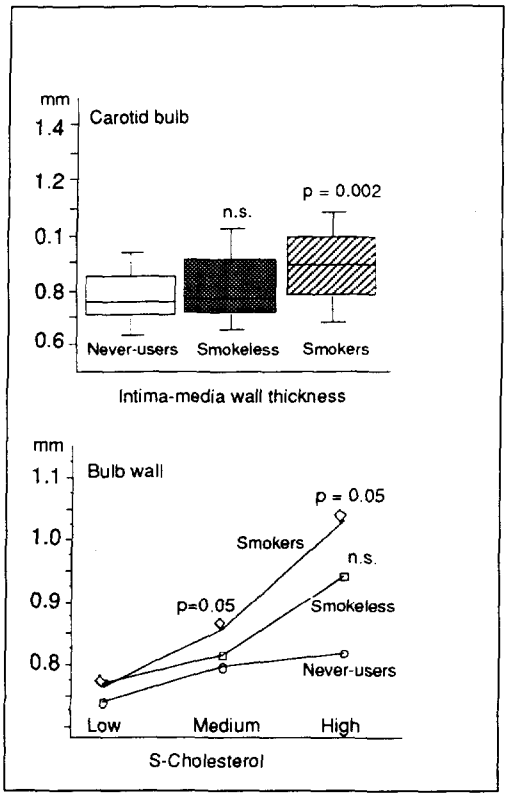


Figure 11. a). Box plot showing the 10th, 25th, 50th, 75th and 90th percentiles of the individual mean values of the carotid bulb wall thickness in the different tobacco habit groups. ANOVA and Fisher's tests were used for comparisons with never-users. For smokeless tobacco users, p=0.48; for smokers, p=0.002.

b) Interaction line plot for carotid bulb intima-media thickness in different tobacco habit groups, with different serum cholesterol levels (low=3.20-4.70, medium=4.71-6.80, high=6.81-7.90 mmol/L). p <0.05 for differences in smokers compared to never-users, both at medium and high cholesterol levels. The differences found for smokeless tobacco users were not significant.

Table IX. Ultrasonographic evaluation of right carotid artery.

	Never-users of tobacco (n=40)	Smokeless tobacco users (n=28)	Smokers (n=29)	Significance (p-value[1])
Wall thickness (mm)				
Common carotid (mean)	0.68±0.11	0.67±0.11	0.74±0.13	0.03
Common carotid (max)	0.79±0.15	0.81±0.13	0.83±0.15	0.08
Carotid bulb (mean)	0.78±0.12	0.80±0.13	0.87±0.19	0.002
Carotid bulb (max)	0.95±0.15	1.01±0.18	1.14±0.34	<0.001
Lumen diameter (mm)				
Lumen (mean)	5.79±0.67	5.83±0.61	5.73±0.47	0.81
Lumen (min)	5.63±0.65	5.63±0.60	5.55±0.46	0.78
Plaque[2] (per cent)	0	7.1	37.9	<0.001

n = number in each group.
Mean=mean values of three measurments.
Min=smallest measurement.
Max=largest measurement.
Lumen diameter measured in the proximal part of the common carotid artery.
[1]*Comparisons between smokers and never-users with analysis of variance, significance level p<0.05.*
No significant differences were found on comparing smokeless tobacco users with never-users.
[2]100% increase in IM thickness compared to adjacent normal-sized wall thickness.

Paper VI

24-hour blood pressure monitoring

During daytime, ambulatory heart rates were significantly ($p<0.05$) elevated in both smokeless tobacco users and smokers compared with non-users (69±14 and 74±13 respectively vs. 63±12 beats/minute) as presented in Table X and Figure 12. Blood pressure measurements showed no significant differences in younger subjects with different tobacco habits, whereas in subjects ≥45 years old, ambulatory daytime diastolic blood pressures were significantly elevated, on average 5 mmHg, in both smokeless tobacco users and smokers ($p<0.001$) compared with

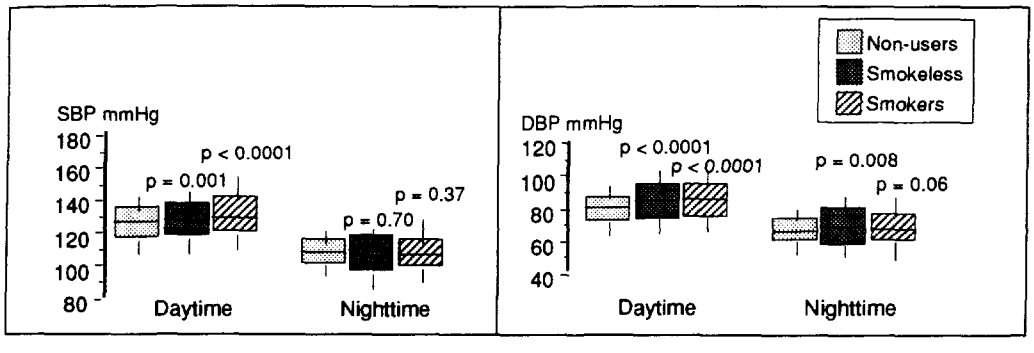


Figure 12. Box plot showing the 10th, 25th, 50th, 75th and 90th percentiles of blood pressure measurements during daytime and nighttime in subjects ≥45 years old in the three tobacco habit groups. ANOVA comparisons are made with non-users as the reference group. Fisher's PLSD test was used to determine significance ($p<0.05$=significant).

Table X. Blood pressure values at clinical examination and through 24hour ambulatory monitoring in different tobacco habit groups.

	Non-users (*n*=59)	Smokeless tobacco users (n=47)	(p-value[1])	Smokers (n=29)	(p-value[1])
Blood pressure					
SBP Casual[2]	124±12	123±13	ns	119±18	ns
DBP Casual[2]	78±7	78±10	ns	78±11	ns
Mean SBP, 24-h	123±7	127±9	<0.05	128±12	<0.05
Mean DBP, 24-h	77±9	79±9	ns	81±11	ns
Mean SBP, daytime	126±8	131±10	<0.05	131±12	<0.05
Mean DBP, daytime	79±9	81±10	ns	83±11	<0.05
Mean SBP, nighttime	108±8	106±10	ns	110±12	ns
Mean DBP, nighttime	66±9	67±10	ns	68±12	ns
Heart rate (beats/min)					
Casual[2]	57±9	60±7	ns	58±9	ns
Mean, 24-h	62±12	65±14	<0.05	69±14	<0.05
Mean, daytime	63±12	69±14	<0.05	74±13	<0.05
Mean, nighttime	54±9	56±12	<0.05	58±11	<0.05

All values are means and standard deviations adjusted for differences in age, body mass index, waist-hip ratio, physical training level and alcohol consumption.
n=number in each group.
[1]Comparisons between tobacco users and never-users, after adjustments, using Student's t-test.
Significance level p<0.05
ns = not significant.
[2]measured at 8.30 a.m., after 5 minutes of supine rest.
SBP= systolic blood pressure
DBP= diastolic blood pressure.
Daytime=06.00-24.00.
Nighttime=00.00-06.00.

Table XI. Ambulatory blood pressure monitoring in subjects ≥45 years old. Mean values during daytime working hours (09.00 - 18.00), comparing tobacco users with non-users of tobacco.

	Non-users (*n*=34)	Smokeless tobacco users (*n*=23)	(p-value[1])	Smokers (n=18)	(p-value[1])
Hours					
09.00-12.00					
SBP	128±14	131±15	0.03	133±16	<0.001
DBP	81±13	87±15	<0.001	87±14	<0.001
12.00-15.00					
SBP	124±15	134±18	0.08	134±18	<0.001
DBP	79±13	84±17	<0.001	86±13	<0.001
15.00-18.00					
SBP	126±14	128±14	0.34	135±19	<0.001
DBP	81±13	85±14	<0.001	87±13	<0.001

All values are means and standard deviations.
n= number in group.
ANOVA comparisons are made with non-users as the reference group
[1]= Fishers PLSD test for significance (p<0.05= significant).
SBP= systolic blood pressure
DBP= diastolic blood pressure.

non-users, see Table XI and Figure 13. Nighttime measurements showed only minor differences between the tobacco habit groups. In smokers, the clinical measurements of heart rate and systolic blood pressure, after 5 minutes of supine rest, were found to be significantly lower compared with the ambulatory mean values, see Table X. There was a strong negative correlation between physical fitness, as determined by maximal oxygen uptake, and heart rate in all tobacco habit groups.

A strong positive correlation was found between cotinine (major nicotine metabolite) and blood pressure in smokeless tobacco users (systolic blood pressure, r=0.48. p<0.001; diastolic blood pressure, r=0.41, p=0.005), whereas an inverse relationship was found in smokers (systolic blood pressure, r =-0.12, p=0.47; diastolic blood pressure, r =-0.03, p=0.84), indicating additional and more complex influences on vascular tone in smokers than that of nicotine in smokeless tobacco users.

It was also found that subjects with a family history of hypertension showed significantly higher ambulatory blood pressure measurements than subjects without such a family history.

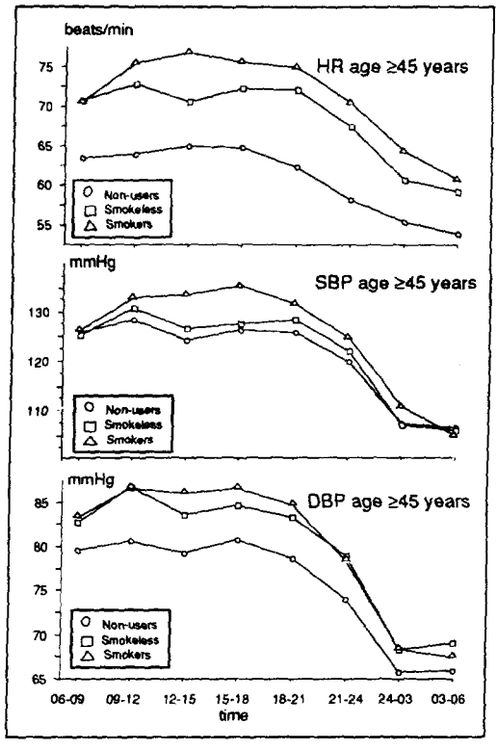


Figure 13. Mean values of heart rate (HR), systolic (SBP) and dia-stolic (DBP) blood pressure in subjects ≥45 years old (non-users, n=34; smokeless tobacco users, n=23; smokers, n=18) during three-hour periods.

General Discussion

Methodological considerations

The computerised data registers of the health check-ups on Swedish construction workers from 1971 to 1992 contain a large base of information on more than 130 000 men, many of whom have been examined more than once, and are suitable for a variety of epidemiological investigations. It is also the largest register known in the world with information on smokeless tobacco use, which of course makes follow-up studies of morbidity and mortality highly interesting, despite the methodological objections that can be raised against the reliability of tobacco habit classification and other self-reported data. At any rate, owing to the considerable size of the register, and the fact that misclassifications most certainly are non-differential, i.e. not dependent on whether the individual will suffer from disease or not [164], the register still comprises one of the best sources of information on the long-term effects of smokeless tobacco use. However, regarding validity, the exposure data tested by Nyrén et al [154] did show a high degree of concordance for tobacco consumption statements.

The extensive questionnaire used for the periodic health check-ups during 1971-74 contained 236 different questions regarding the working environment, present and past medical history and symptoms, as well as tobacco habits [36]. The analysis was restricted to the answers to only 13 questions, selected to represent a comprehensive collection of information about the general health status with regard to the respiratory, circulatory, gastrointestinal, musculoskeletal and mental organs. When all questionnaire responses were analysed, the same pattern was seen as for the published data regarding tobacco habit groups. Smokers were at a relative risk exceeding 1.0 for all but seven questions, one of which concerned cardiovascular symptoms: "Have you ever suffered from hypertension?" (RR 0.8), which is in conformity with the clinical findings of lower blood pressure measurements in smokers.

The analysis of blood pressure measurements used for the assessment in Paper I was limited to dichotomised values, i.e. quantitative measures of the prevalence of subjects with blood pressure values exceeding established levels of clinical hypertension. Furthermore, the blood pressure level was assessed by only one measurement, not the mean of two or three measurements, which should have increased the reliability. A qualitative analysis of the hypertensive subjects in the different tobacco habit groups should have contributed to a more detailed evaluation, for example, regarding the prevalence of borderline hypertension and established hypertension. Hopefully, the register will be available for extended future analyses, even though it has now been abandoned by the construction industry due to organizational reasons. The absence of information on alcohol consumption is also a problem when interpreting the results, as alcohol use is correlated with the prevalence of hypertension, coronary heart disease and also with tobacco use [12,76,77,147].

Healthy worker effect

Standardised mortality ratios (SMR) are often used to compare the mortality ratio of a defined group of subjects, with the mortality ratio of the general population (observed cases/expected cases). As population-based data comprise both healthy and unhealthy subjects and data on, for example, an industrial working population contains a selection of active workers healthy enough to be employable, allowance must be made for differences in age, work status, causes

of death etc. when comparing standardised mortality ratios [142].

In the studies on construction workers, it is important to consider that the high physical demands in these professions imply that, in the older age groups, only very healthy individuals will be employable. The findings of more pronounced excess risks of cardiovascular mortality in the younger tobacco users in the construction industry (Papers I and II), compared with tobacco users in older age groups, is probably due to this healthy worker effect.

The same positive cardiovascular selection is valid for the firemen group, examined in Papers III-VI. Also middle-aged smoking firemen were superior in physical performance than 18-year old Swedish conscripts [227], which is in line with the findings of other investigators [39,151].

Thus, the calculated risks of cardiovascular morbidity and mortality might underestimate the strength of the relationship between smokeless tobacco use and cardiovascular morbidity.

Ætiological fraction-attributable risk

In studies of different risk factors and their possible influence on mortality and morbidity, one must consider the consequences of the reported risk estimates on a national public health level, and not only on the personal risk level.

Estimates of the *ætiological fraction* of a specific exposure (see Methods, Papers I and II for calculation), i.e. the percentage of the identified cases of the investigated disease that would be removed if the exposure did not exist, are useful when applying scientific results on a public health level. Even though findings of relative risks and exposure data should be interpreted with much caution, being fully aware of all the pitfalls of population-based information, the attributable risk estimate does at least give some indication of how large a number of individuals in a defined population might be at risk. High relative risk estimates for a disease, in which the causal exposure is extremely unusual, do not call for the same kind of public health actions as a high relative risk together with high exposure (smoking being the best example). A moderate risk elevation for a very common exposure, such as smokeless tobacco, might still lead to ill-health in hundreds or thousands of individuals which could have been avoided.

At present, 50% of all deaths in Sweden, in both men and women, are attributable to cardiovascular diseases. If 20% of the male population is exposed to smokeless tobacco, and this exposure would involve a relative risk of 1.4 of premature cardiovascular death compared to non-users (Paper II), the attributable deaths due to smokeless tobacco consumption would be 5.7%, i.e. about 1 300 excess cases. From a public health perspective, this issue cannot be disregarded, considering the increasing number of smokeless tobacco users. In a comparison with oral cancer, which up to now has been the main health-related consequence associated with the use of smokeless tobacco, where the risk estimates range between 0.8 and 4.5 in different studies made in the US and Europe [87], a similar estimate of the public health consequence can be calculated. With the same relative risk estimate for oral cancer of 1.4 attributable to smokeless tobacco use, this would involve about 30 excess cases yearly according to the actual oral cancer incidence in Sweden. Thus, minor elevated risk estimates are of much greater importance when considering cardiovascular diseases in the population.

Risk factors

Risk factors are statistical associations. Risk factor is the term used to describe an association of a characteristic finding in healthy persons that might be related to the subsequent development of disease in the population at risk [42,177], but it is usually not enough to cause the disease. Specific risk factors can account for 40-50% of all morbidity and mortality from cardiovascular disease. At least 300 different potential risk factors for cardiovascular disease have been reported [42], and many of them interact synergistically. The general aims of epidemiological research are not only to map out the relationship between different inherited or acquired qualities in subjects from different populations and with different types of ill-health, but more importantly, to sug-

gest actions and evaluate the effects of modification or elimination of the risk factor. Most preventive work in medicine is based on a successful combination of epidemiological investigations and interventional actions. The final goal is of course to reduce individual suffering, but, necessarily, at a reasonable cost to society [175].

Tobacco and risk

The question of tobacco use as a risk factor is complicated for many reasons. Few other chemical exposures have been so thoroughly investigated as smoking and ill-health. More than 100 000 scientific articles have analysed the influence of smoking on cancer, lung disease, cardiovascular disease, pregnancy outcome, ageing, hormonal effects etc. [205-216]. There is an overwhelming amount of evidence for designating smoking as the single most important preventable threat to health and cause of premature death in the industrialised world [216]. Still, the scientific community was slow to accept this statement. Not until the 1960s was smoking regarded as the chief contributor to an excess number of deaths from lung cancer and myocardial infarction [205]. There are, however, still a lot of areas, relating to the mechanisms responsible for the actions of tobacco on disease to be elucidated, one of which is the role of nicotine [214,215].

There is a problem in interpreting tobacco use and health risks. Tobacco use is very common in most industrialised societies, and death from cardiovascular disease is also the most common cause of death. All diseases linked to an increased risk when using tobacco can also be contracted without using tobacco, and all users of tobacco do not contract tobacco-related disease. When assessing how different lifestyle factors might influence longevity, people usually give priority to short-term pleasure, than to the long-term probability of disease and death. Tobacco as a risk factor has the advantage of being completely abolishable and the disadvantage of containing a highly addictive drug, and thus being less easily influenced by rational considerations. Therefore regulations on a national and community level seem necessary to achieve changes in behaviour to make possible sensible decisions without exorbitant demands on fact-based knowledge on the part of the individual consumer.

Risk modification regarding smoking has been tried by developing cigarette filters and low-tar and low-nicotine cigarettes, but the net health impact, especially regarding cardiovascular disease, of these product changes does not seem impressive [26,121,158].

The US Surgeon General statement in 1988 that nicotine is the drug in tobacco that causes addiction and that nicotine does not seem to be the major substance in tobacco smoke causing adverse health effects has influenced the rapid development of nicotine delivery systems by the pharmaceutical industry [71,117,179] and also the development of new supportive strategies for smoking cessation [105,204]. Also, the use of smokeless tobacco has been regarded as a preferable alternative to smoking, with reference to the large number of premature deaths that could be avoided if all smokers switched to smokeless tobacco [70,173,181].

Smokeless tobacco-cardiovascular effects

Exposure to nicotine does not seem to contribute to an increased atherosclerotic process in the same way as smoking. However, there might be a more pronounced tendency to develop hypertension compared to non-use and smoking. The higher heart rates and blood pressures noted during the daytime in smokers and smokeless tobacco users were probably due to the effects of nicotine. Data from the Framingham study indicated heart rate to be linearly related to cardiovascular, coronary and all-cause mortality [120]. The beneficial effects of beta-blocker treatment for the prevention of reinfarction have been suggested to be related to the pharmacological reduction of heart rate [126].

The hypothesis of a blunted postural response in autonomic cardiac regulation which might explain why the lower average blood pressure in smokers is found mainly when it is measured with the subject seated or at rest [98] is supported by the results of the present study, where smok-

ers exhibited much more important differences between clinical measurements after 5 minutes of rest and the mean values of 24-hour monitoring, compared to smokeless tobacco users.

Whether chronic exposure to nicotine might negatively affect coronary blood flow and myocardial function and excitability is still largely unknown. The present cohort study of cardiovascular mortality (Paper II) exhibited a significant relative risk of 2.0 (95% c.i. 1.4-2.9), compared with never-users, of dying of ischæmic heart disease for smokeless tobacco users aged 35-54 years when entering the study and during 12 years of follow-up, whereas a case control study of fatal and non-fatal myocardial infarctions in Northern Sweden, where smokeless tobacco use is common, did not exhibit any excess risk in smokeless tobacco users aged 35-54 years, compared with non-users, and only a low, and not significant excess risk in 55-64-year-old subjects [111]. However, the different results could partly be due to differences in the analysis of data, with regard to comparisons made with non-users (also including ex-users) instead of never-users. Another observation that might support the hypothesis of increased cardiovascular risk with the use of smokeless tobacco, is the analysis of age at myocardial infarction. In the Northern Sweden study 25% of myocardial infarctions in never-users, 37% in smokeless tobacco users and 48% in smokers occurred before the age of 55. The corresponding figures for the study in Paper II (with a study population probably influenced by the healthy worker effect) was 17% in never-users, 20% in smokeless tobacco users and 29% in smokers.

Studies of physical performance in smokeless tobacco users have not revealed any reduction of working capacity or oxygen uptake in healthy subjects [16], which is regularly found in smokers [16,49,55,146]. Further studies are needed on the health consequences of an added stress caused by combining nicotine exposure with, for example, aerobic exercise, especially for those already affected with cardiovascular disease. Most of the clinical consequences of chronic smoking do not appear until after the age of 65, and even if smokeless tobacco use might have less negative health effects than smoking, potential long-term adverse effects cannot yet be dismissed.

Smokeless tobacco and health hazards – other than circulatory

In the present observational study of Swedish construction workers (Paper I), users of smokeless tobacco did not exhibit any increased prevalence of gastrointestinal symptoms compared with non-users, whereas smokers, as shown in other studies [125], showed an almost threefold prevalence of peptic ulcer. In the light of the similar exposure to nicotine in smokers and smokeless tobacco users, these findings might be explained by more alkaline fluid being swallowed by smokeless tobacco users, but also by possible differences in personality or alcohol consumption. More attention needs to be paid to the effects of smokeless tobacco on gastro-intestinal function.

In Paper II, the overall cancer mortality was not found to be elevated in smokeless tobacco users compared with never-users, but no detailed analysis has been made of different sites and types of cancer. The findings are, however, in accord with a recently published report from the Swedish National Board of Health and Welfare on the health effects of smokeless tobacco in which two (not yet published) Swedish studies are cited [3].

The overall profile of ill-health, as determined by organ specific symptoms, sick-leave data and disability pensions (Paper I), was found to be significantly worse in smokeless tobacco users than in never-users of tobacco. Still, smokers exhibited the greatest health risks for all comparisons made, except regarding hypertension. The causal role of smokeless tobacco on different kinds of ill-health must be questioned in the same way as regarding smoking. Far from all manifestations of ill-health in smokers are causally related to tobacco smoke. In many subjects, the use of tobacco often occurs together with other behaviors related to ill-health, such as alcohol consumption, less physical activity, dietary deficiencies and readiness to take risks, all of

which interfere with the feasibility of drawing conclusions from epidemiological findings. Statistical adjustments simply may not be sufficient to control for such differences.

An alternative to smoking?

Many physicians in Sweden regard smokeless tobacco as an innocent stimulant and do neither ask or document whether their patients use it. Patients with hypertension, diabetes, myocardial infarction, gastroesophageal reflux, peptic ulcer, venous insufficiency or pregnant women repeatedly see their physicians and receive treatment, but are never asked whether they might have this habit or not. Still, nearly one out of every three men in the younger age groups use it, as well as an increasing number of women.

Is the use of smokeless tobacco preferable compared to the much more dangerous smoking? It is probably not wise to convey the message in such a simplistic way. In epidemiological science, the basic approach is to compare exposed subjects to unexposed subjects. On almost all occasions when smokeless tobacco users have been studied in comparison with non-users of tobacco, they have exhibited significant signs of or tendencies to increased ill-health [4,113,214, 230]. Since the use of smokeless tobacco is a completely different way to administer nicotine, it certainly warrants comparisons with smoking. It is a consistent finding that smoking involves far more health hazards than the use of smokeless tobacco.

However, a physician or scientist should not be prepared to suggest any kind of addictive drug to be a good choice for anyone concerned with his or her nicotine use. Subjects who are not able to quit smoking must of course be helped to use less dangerous products, but the message that smokeless tobacco is less harmful must be delivered very carefully, so as not to be interpreted as an affirmation of nicotine use as a part of healthy behaviour [200].

Perspectives

Smokeless tobacco – important fields of research

Based on our present knowledge of the pharmacological actions of nicotine, the following areas of research demand further elucidation:

Circulatory

- The propensity of smokeless tobacco users to develop angina pectoris.
- Prevalence of hypertension in smokeless tobacco users in the general population.
- The influence of smokeless tobacco on cardiac arrhythmias.
- The influence of smokeless tobacco on the course of sudden death.
- The predisposition to vasospastic disorders and microcirculatory disturbances in smokeless tobacco users.
- Influence of smokeless tobacco on peripheral vascular disease.
- Effects of smokeless tobacco on microangiopathy and nephropathy in diabetes.

Metabolic

- Influence of smokeless tobacco on lipoprotein metabolism in dyslipidaemic patients.
- Effects of smokeless tobacco on the metabolic syndrome and insulin resistance.
- Effects of long-term smokeless tobacco use on body weight, basal metabolism and eating behaviour.

Gastrointestinal effects

- Effects of smokeless tobacco on saliva secretion and buffer capacity.
- Effects of smokeless tobacco on the secretion and composition of gastric juice.
- Smokeless tobacco in the course of heartburn and peptic ulcers.
- Effects of smokeless tobacco on intestinal motility.

Pregnancy and fœtal outcome

- Smokeless tobacco and pregnancy outcome, birth weight, fœtal morbidity and mortality.
- Smokeless tobacco use and fœtal nicotine addiction.
- Smokeless tobacco and semen quality.

Nervous system

- Smokeless tobacco and erectile function.
- Smokeless tobacco and neurodegenerative disorders.

Summary and Conclusion

The risk of adverse health effects is evidently less serious in smokeless tobacco users than in smokers, as illustrated by the mortality ratios in the Swedish construction industry in Figure 7. However,

- smokeless tobacco users exhibited higher cardiovascular mortality ratios than non-users in all age groups,
- smokeless tobacco users exhibited increased heart rates and blood pressures compared with non-users, especially after the age of 45,
- smokeless tobacco users had more symptoms of traumatic vasospastic disease,
- smokeless tobacco users were more frequently granted disability pensions for hypertension and other cardiovascular diseases,

indicating that the habit might have a causal influence on cardiovascular disease. Still the influence of smokeless tobacco use on atherosclerosis seems to be of little, although not negligible, importance.

All tobacco products contain carcinogenic substances and substantial quantities of nicotine. Apart from its psychoactive properties, nicotine has abundant vasoregulatory effects, through the mediation of cholinergic as well as adrenergic stimuli. Most studies of cardiovascular effects imply that the continuous circulatory stress caused by nicotine is associated with an increase in cardiovascular events, compared with non-users of tobacco. Nicotine also influences the release of hormones from the endocrine system, the regulation of gastrointestinal activity and affects the foetus in pregnant women.

For the individual, it might be difficult to evaluate the risks associated with the exposure to smokeless tobacco based upon epidemiological end points like cancer incidence or cardiovascular morbidity when all data impart the knowledge that smoking involves much more important health risks. One must still keep in mind that the use of smokeless tobacco involves exposure to one of the most addictive substances known. The advantages of experienced pleasure and delight on occasional use, often seem to be overshadowed by a continuous struggle to avoid abstinence symptoms in long-term habitual users. Cessation of smokeless tobacco use, is in many subjects, even more difficult than cessation of smoking.

Closing words by Dr John Hill, 1761

John Hill, MD (1716-1775), a most cultivated scientist and humanist in London during the 18th century Enlightenment. He bacame "Inspector General of Great Britain", Member of the Imperial Academy, Member of the Swedish Noble Order of Wasa for his scientific achievments. He published 76 works, both scientific and literary. He was a systematic botanist and was the first in England to adopt the Linneaen system of plant classification.

"Let it not appear strange, that snuff, which can affect all this mischief, is not found in every instance to do it. In many persons it is the cause of disorders, which they perhaps do not attribute to it, and of which their physician himself may seek some other cause: but if the number was small of those who suffer, in comparison of those who take snuff, what wise person would yet engage in it? If only five in a hundred ruined their constitutions by it, who shall be able to say, when he enters on the custom, whether he shall be one of the ninety-five who escape, or of the five that perish.

If the instances here recited, alarm and caution those, who, by the same custom, run themselves into like danger, the purpose of this publication is answered: they will see the importance of controlling their inclination in this point: and they may have the comfort to be assured, that those mischiefs, which have arisen, or may arise from this cause, tho' no medicine can relieve them, will in a great degree, if not entirely, cease, on leaving off the practice which occasioned them" [101].

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