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# HEALTH EFFECTS OF SNUS USE

PROSPECTIVE STUDIES OF CARDIOVASCULAR  
DISEASE, WEIGHT GAIN, AND OBESITY

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## ABSTRACT

Use of snus is most prevalent in Nordic countries, and especially in Sweden, where 18% of men and 3% of women are daily users. Snus is also used to a minor extent in the United States where an increasing interest is seen for the product. The high levels of nicotine in snus could affect risk of cardiovascular disease (CVD) and may lead to metabolic disturbances, but the extent of these potential effects is not completely understood. The aims of this thesis were to assess the associations between use of snus and CVD and excess body weight. The study-specific aims were to assess the impact of snus use on risk of ischemic heart disease (IHD) and stroke (Study I), acute myocardial infarction (AMI) (Study III), and stroke and its subtypes (Study IV). Further, the specific aim of Study II was to assess the association between snus use and weight gain and obesity.

Study I was based on a subset of the Swedish Twin Registry and Study II on the Stockholm Public Health Cohort. In Studies III and IV, data from the Swedish Collaboration on Health Effects of Snus Use were analysed. This collaboration was set up to increase the understanding of health effects of snus use and comprises the study populations from Studies I and II, and six other Swedish cohorts. Current snus use was considered the exposure and never users of tobacco or non-current snus users acted as the reference category. In studies of the risk of CVD, participants were followed in the Inpatient Register and the Cause of Death Register for incident events. In Study II, of the associations between snus use and weight gain and obesity, information on tobacco use as well as height and weight was collected via self-administrated questionnaires on two occasions five years apart. A weight gain of more than 5% during follow-up was considered an event, as was reaching a body mass index (BMI)  $\geq 30$ . Study-specific and pooled hazard ratios (HR) with 95% confidence intervals (CI) of incident events of CVD and risk of death following a CVD were calculated using Cox proportional hazards regression models with attained age or age at diagnosis as the time scale. Logistic regression was used to estimate odds ratios (OR) and 95% CI of case-fatality (within 28 days) after a CVD, as well as the association between snus use and weight gain and incident obesity.

No increased risk of CVD was observed among snus users compared to non-users when followed for the maximum time of follow-up. Case-fatality after an AMI or a stroke, regardless of subtype, was increased among snus users, as was risk of death during total time of follow-up. The adjusted ORs of 28-day case-fatality following an AMI or stroke were 1.28 (95% CI 0.99–1.68) and 1.42 (95% CI 0.99–2.04), respectively. Use of snus was also associated with weight gain (OR 1.31, 95% CI 1.04–1.65) and incident obesity (OR 1.93, 95% CI 1.13–3.30) in adjusted models.

In conclusion, snus use appears to be associated with both weight gain and obesity, indicating a possible metabolic effect of nicotine. Although snus use was not associated with incident CVD, use was associated with case-fatality and risk of death among those who suffered an AMI or a stroke. Confounding could not be ruled out as a potential explanation for the relationships between snus use and either weight gain/obesity or CVD prognosis.

## LIST OF PUBLICATIONS

- I. Hansson J, Pedersen NL, Galanti MR, Andersson T, Ahlbom A, Hallqvist J, et al. Use of snus and risk for cardiovascular disease: results from the Swedish Twin Registry. *Journal of Internal Medicine*. 2009; **265**(6): 717–24.
- II. Hansson J, Galanti MR, Magnusson C, Hergens MP. Weight gain and incident obesity among male snus users. *BMC Public Health*. 2011; **11**: 371.
- III. Hansson J, Galanti MR, Hergens MP, Fredlund P, Ahlbom A, Alfredsson L, et al. Use of snus and acute myocardial infarction: pooled analysis of eight prospective observational studies. *Eur J Epidemiol*. 2012 Jun 22.
- IV. Hansson J, Galanti MR, Hergens MP, Fredlund P, Ahlbom A, Alfredsson L, et al. Stroke and snus use: pooled analyses of incidence and survival in the Swedish collaboration on health effects of snus use. (In manuscript).

# CONTENTS

1	INTRODUCTION.....	1
2	BACKGROUND.....	2
2.1	Snus - Swedish Moist Smokeless Tobacco.....	2
2.1.1	Use of snus in an international perspective .....	2
2.1.2	Lifestyle and other characteristics associated with snus use.....	2
2.1.3	The role of snus in smoking initiation and cessation .....	3
2.2	Nicotine absorption and effects.....	3
2.3	Cardiovascular disease .....	4
2.4	Overweight and obesity.....	4
2.5	Health effects of snus use.....	5
2.5.1	Ischemic heart disease and acute myocardial infarction .....	5
2.5.2	Stroke.....	5
2.5.3	Weight gain, overweight, and obesity .....	5
2.5.4	Other health effects .....	6
3	AIMS .....	8
4	MATERIALS AND METHODS .....	9
4.1	Participants and data collection.....	9
4.1.1	The Construction Workers Cohort.....	9
4.1.2	The Malmö Diet and Cancer Study .....	9
4.1.3	Multinational Monitoring of Trends and Determinants in Cardiovascular Disease .....	9
4.1.4	The National March Cohort.....	11
4.1.5	The Screening Across the Life-Span Twin Study.....	11
4.1.6	The Scania Public Health Cohort.....	11
4.1.7	The Stockholm Public Health Cohort.....	12
4.1.8	The Work, Lipids, and Fibrinogen Study.....	12
4.2	Definition of exposure and identification of covariates .....	12
4.2.1	Study I.....	12
4.2.2	Study II .....	12
4.2.3	Study III and Study IV .....	13
4.3	Follow-up and ascertainment of outcome.....	14
4.3.1	Cardiovascular disease .....	14
4.3.2	Weight gain and obesity.....	14
4.4	Statistical analyses .....	15
4.5	Ethical approval .....	18
5	RESULTS .....	19
5.1	Study I.....	19
5.2	Study II.....	19
5.3	Study III .....	20
5.4	Study IV .....	21
6	DISCUSSION.....	23
6.1	Main findings .....	23
6.1.1	Cardiovascular disease .....	23
6.1.2	Weight gain and obesity.....	24
6.2	Methodological considerations .....	24

6.2.1	Selection bias.....	24
6.2.2	Information bias .....	25
6.2.3	Confounding.....	26
6.2.4	Pooled analyses .....	27
6.3	Conclusions.....	28
7	SAMMANFATTNING PÅ SVENSKA .....	29
8	ACKNOWLEDGEMENTS.....	31
9	REFERENCES.....	32

## LIST OF ABBREVIATIONS

AMI	Acute Myocardial Infarction
BMI	Body Mass Index
CI	Confidence Interval
CVD	Cardiovascular Disease
CWC	Construction Workers Cohort
HR	Hazard Ratio
ICD	International Classification of Diseases
IHD	Ischemic Heart Disease
MDCS	Malmö Diet and Cancer Study
MONICA	Multinational Monitoring of Trends and Determinants in Cardiovascular Disease Study
NMC	National March Cohort
OR	Odds Ratio
RR	Relative Risk
SALT	Screening Across the Lifespan Twin Study
Scania_PHC	Scania Public Health Cohort
SEP	Socioeconomic Position
Sthlm_PHC	Stockholm Public Health Cohort
WC	Waist Circumference
WHO	World Health Organization
WHR	Waist-Hip-Ratio
WOLF	Work, Lipids, and Fibrinogen Study



# 1 INTRODUCTION

Snus has been used in Sweden since the 19<sup>th</sup> century and was the predominate form of tobacco used until the 1920s. During that time, the typical snus user was a man and the prevalence among women was low. After a decrease in use during the mid-1900s the use of snus increased again (1) as a result of intense marketing and a focus on new and younger target groups. By 2011, 11% of the Swedish population used snus daily and the habit was still more prevalent among men than women (18% vs. 3%) (2). Snus is used to some extent in other Nordic countries (3), and is currently being introduced to new markets such as the United States (4).

There is reason to believe that snus, through its high levels of nicotine, could affect the risk of cardiovascular disease (CVD) and have metabolic effects, such as influencing the accumulation of visceral fat. Studies investigating the association between snus use and body fatness (5-7), however, have reached conflicting conclusions, and most studies of risk of CVD (8-19) have been small, and only a limited number of studies have investigated the risk of fatal outcomes (9, 11, 13, 15, 18, 19). Hence the health effects of snus use are still not clearly understood.

From a public health perspective, the importance of research on the health effects of snus use grows with the increasing number of users both in Sweden and in other parts of the world. Studies of these effects can almost exclusively be performed using data on Swedish men, among whom the prevalence of snus use is, and historically has been, high. Further, Swedish data offers the opportunity for long-term follow-up in health registers with high validity. The studies presented in this thesis investigate several aspects of the relationship between snus use and CVD, and the associations between snus use and weight gain and obesity.

## **2 BACKGROUND**

### **2.1 SNUS - SWEDISH MOIST SMOKELESS TOBACCO**

Snus is a type of smokeless tobacco sometimes referred to as Swedish moist smokeless tobacco or snuff. Snus consists of dry, finely ground tobacco, aromatic substances, salt, water, and humidifying agents. Users obtain high levels of nicotine, which is the primary addictive substance in smokeless tobacco (20). A dip, a sachet, or loose ground tobacco is placed between the gum and upper lip (21) and the average user keeps each dip in place for 60–70 minutes (22). Most users change dips continuously and the total duration of snus use often reaches above 12 hours per day (22).

Snus became widespread in Sweden in the 19th century and was the predominant form of tobacco used until the 1920s (1). During the first half of the 20<sup>th</sup> century, the number of snus users decreased substantially and reached a prevalence of less than 10% among young men in the 1960s. Historically, snus was used almost exclusively by men, and the prevalence among women has always been low. The decrease in use was followed by a steady increase after an intense advertising campaign by the Swedish Tobacco Company (1). From 1969 to 1973, the percentage of adolescents using snus doubled, and the mean age among snus users decreased from 41 to 30 years (1). Over the following years, the prevalence continued to increase and the habit became more common and accepted among new groups of users such as women and people with higher education. In 2011, 18% of men and 3% of women in Sweden used snus daily, and 10% and 12%, respectively, were daily smokers (2).

#### **2.1.1 Use of snus in an international perspective**

Snus use can be considered a Swedish phenomenon and the prevalence in Sweden is considerably higher than in other countries. When joining the European Union, Sweden negotiated an exception from the existing ban on snus. Snus is used to some extent in other Nordic countries, foremost by men in Norway (11%) and Iceland (7%). Finland and Denmark, even though being members of the European Union and thereby covered by the ban, have a prevalence of 2.5% and 1%, respectively (3).

In the United States, where snus has only been available for a few years (23), 1.8% of adults were daily users in 2009 according to the Centers for Disease Control and Prevention (4).

#### **2.1.2 Lifestyle and other characteristics associated with snus use**

Attempts have been made to describe social and lifestyle characteristics among snus users and the results have differed over time periods and contexts. During the first half of the 1900s, the typical snus user was a man, often a manual worker, of advanced age and from a rural area (1). Today snus use is more common among younger people (24) and use is associated with having low education and low or intermediate income (24, 25). It is also more common among manual and skilled workers (2, 24) and the prevalence of use is still more common in rural areas (25). Lifestyle factors associated with snus use are current and former smoking (17, 25), risky alcohol consumption, and low consumption of

fruit and vegetables (24). A study from the 1990s reported that snus users on average were less physically active as compared to non-users (26), but a recent study of snus users in Stockholm found no differences in level of physical activity between users and non-users (24) and a Finnish study of military conscripts found snus users to be more active in regular sports activities (27).

### **2.1.3 The role of snus in smoking initiation and cessation**

There is a long and on-going discussion about what role snus has played regarding the low smoking prevalence in Sweden (28-38). Some believe that the low prevalence of smoking can be attributed to the use of snus (39, 40) and argue that the ban on snus in the European Union should be lifted and that access to snus would promote smoking cessation. Others claim that smoking cessation and snus initiation have occurred in different groups of the Swedish population, smoking cessation mainly among older people while younger people started using snus (30), and that the low prevalence of smoking is an effect of successful public health efforts (30, 41). Use of snus has been associated with a reduced risk of becoming a smoker (40), as well as with smoking cessation (40, 42-44). There are, however, also reports of increased probability of becoming a smoker among snus users (42, 43), although this association is weaker than the opposite. Further most Swedes who quit smoking still do so without using snus (45). A report from the European Union Scientific Committee on Emerging and Newly Identified Health Risks concluded in 2008 that there is not enough evidence to draw conclusions on the effect of snus use on smoking prevalence (21). They further stated that it cannot be foreseen what consequence lifting the ban on snus in other European countries would lead to.

## **2.2 NICOTINE ABSORPTION AND EFFECTS**

Nicotine from snus is absorbed through the oral mucosal membrane facilitated by an alkaline pH (46). In snus users, the nicotine concentration in the blood reaches its maximum level after 35 minutes (47) and the nicotine levels among habitual users are similar to those from smoking (46, 47). Although blood levels of nicotine fall rapidly after smoking, they plateau during and after snus use (46). According to Benowitz and colleagues (46), this is due to continued absorption of nicotine up to 60 minutes after the tobacco was removed, and is probably a consequence of absorption of nicotine that has been swallowed and/or a slow release of nicotine from the mucous membranes. Nicotine has an average half-life of two hours in the body and, as a result, a snus user who uses snus for more than six to eight hours each day will have nicotine in the blood stream continuously during the day and even during the night (48).

The potential health effects of snus use are considered to be due to the extensive exposure to nicotine. Nicotine activates the sympathetic nervous system resulting in an acceleration of heart beat (by about 10–20 beats per minute) and increased blood pressure (by about 5–10 mm Hg) (46). Further, nicotine has been reported to increase levels of circulating catecholamine and free fatty acids, and this could increase levels of total cholesterol and decrease levels of high-density lipoprotein as shown in studies on smokers (49). The hyperlipidemia and the endothelial injury resulting from this could promote atherosclerotic vascular disease (50).

Nicotine affects insulin resistance, which in turn is related to altered body composition and increased visceral fat (51). Further, nicotine exposure acts as an appetite suppressant (52). This might be the explanation behind the paradox that smokers on average weigh less than non-smokers (51, 53-55), but still tend to have a higher percentage of visceral fat (51) and a higher body mass index (BMI) (56) than non-smokers as shown in some studies. There might also be a dose-response relationship between the number of cigarettes per day and waist circumference (WC) (57). Further, it has been suggested that the release of cortisol from nicotine plays a role in increased visceral fat (51).

### **2.3 CARDIOVASCULAR DISEASE**

CVD includes diseases of the heart, vascular diseases of the brain, and diseases of blood vessels (58). It is often caused by atherosclerosis that results in increased risk of blockage of blood flow or thrombosis. CVD is the leading cause of disability and death in the world and is attributed to 10% of the global disease burden. Ischemic heart disease (IHD) and stroke are the most common types of CVD and account for 46% and 34% of all CVD among men (58). IHD includes acute myocardial infarction (AMI), angina pectoris, and other acute or chronic IHDs (59). Stroke can be differentiated into two types, haemorrhagic and ischemic. Ischemic stroke is caused by a blockage of an artery in the brain or leading to the brain (58). Haemorrhagic stroke is caused by aneurysms or other malformations, atherosclerosis, or damage from uncontrolled high blood pressure leading to a ruptured blood vessel and causing pressure on the surrounding tissue (58). It can be intracerebral (inside the brain) or subarachnoid (on the surface of the brain in the subarachnoid space). A stroke that is not specified as ischemic or haemorrhagic is called an unspecified stroke.

Age and genetics are important risk factors for CVD, but lifestyle also plays a central role, and smoking is one of the major preventable risk factors for CVD (60-62). Besides the delivery of nicotine, smoking increases inflammation, thrombosis, and oxidation of low-density lipoprotein cholesterol (63), all of which are associated with CVD. The INTERHEART study estimated that smokers have a nearly threefold increased probability of AMI (60) and a twofold increased probability of suffering ischemic or intracerebral haemorrhagic stroke (62). For AMI, additional modifiable risk factors include abnormal lipids, diabetes, hypertension, psychosocial stress, and abdominal obesity. In this study, protective effects were observed from moderate alcohol consumption, physical activity, and consumption of fruit and vegetables (60). Similarly, risk factors for stroke included cardiac diseases (such as atrial fibrillation), hypertension, abnormal lipids, abdominal obesity, binge drinking, diabetes, poor diets, depression, and psychosocial stress, whereas regular physical activity appeared to be protective (62).

### **2.4 OVERWEIGHT AND OBESITY**

The World Health Organisation (WHO) defines overweight as having a BMI (weight in kg/height in cm<sup>2</sup>)  $\geq 25$  and obesity as having a BMI  $\geq 30$  (64). Other commonly used measures of overweight and obesity are waist-hip-ratio (WHR) and WC. These measures correlate with BMI, but the three are not completely interchangeable (65).

The world prevalence of overweight and obesity doubled from 1980 to 2008, and, according to the WHO, 2.8 million people die each year as a result of these conditions (66) making it the sixth most important risk factor contributing to the overall burden of disease (67). In Sweden, 36% of the adult population are overweight and 13% are obese (68). Overweight and obesity are associated with increased risk of AMI (60), ischemic stroke (62, 69), diabetes (70), and certain types of cancer (71) as well as overall mortality (70, 72-76). Although genes play an important role in how individuals metabolize calories, excess body weight is commonly caused by an imbalance between calorie intake and the calories expended (77).

## **2.5 HEALTH EFFECTS OF SNUS USE**

### **2.5.1 Ischemic heart disease and acute myocardial infarction**

Studies on risk of IHD overall and AMI specifically have found no excess risk among snus users (8, 9, 11-15, 17) compared to non-users. Most studies have been limited by a small number of exposed cases and their results are, therefore, hard to interpret. Studies on fatal events have reported conflicting results (9, 11, 13, 15, 19). Three studies found no associations between snus use and fatal IHD/AMI (9, 11, 15), but two (13, 19), based on the same cohort, found a positive association. The first of these two found an increased risk of fatal IHD that appeared higher among younger participants than older (19). The second found an increased risk of fatal AMI with a more pronounced association among heavy users (13). In the latter study, the risk pattern was similar across age categories. Further, snus users had a higher probability of dying following a non-fatal myocardial infarction from any cause, and from CVD specifically, in this study (13).

### **2.5.2 Stroke**

No overall increased risk of stroke have been reported among snus users compared to non-users (10, 15, 17, 18), and the single available study on subtypes of stroke reported a null association for all types (18). Two studies have investigated the risk of fatal stroke among snus users (15, 18). One was too small to draw any conclusions (15), and the other reported a moderately increased risk among users compared to those who never used tobacco (18). This study further separated stroke into subtypes and found that the increased risk was limited to ischemic stroke.

### **2.5.3 Weight gain, overweight, and obesity**

Of the seven available studies of the association between snus and weight, only three employed a longitudinal design and they all differed in outcome measures. Intense snus use was associated with becoming obese in one study (5) and lack of snus use was associated with maintaining weight in another (7). However, no difference was reported between snus users and non-users with regards to weight gain (6). Results from cross-sectional studies are also conflicting; an association between snus use and increased BMI were reported in some studies (6, 11, 17), but no association with BMI (24, 78), WHR, or WC (78) were reported in others.

## 2.5.4 Other health effects

Snus use has been associated with an increased risk of all-cause mortality (19, 79) and discussed in relation to many different health outcomes. Below follows a short summary of the current evidence for these effects.

### 2.5.4.1 Heart failure

Only one study (80) has been conducted on the risk of heart failure among snus users, but the study included data from two cohorts. Risk of heart failure was increased among snus users from both cohorts, and the association seemed more pronounced among older users (80).

### 2.5.4.2 Metabolic syndrome

An increased risk of the metabolic syndrome among heavy snus users was reported by Norberg and colleagues (5). Among the separate components of the metabolic syndrome, snus use was associated with obesity and elevated levels of triglycerides, but not with hypertension, increased fasting plasma glucose levels or diabetes, or low HDL cholesterol (5). No association with the metabolic syndrome was found in a cross-sectional study, that was based on a limited number of cases (81).

### 2.5.4.3 Pre-diabetes and type 2 diabetes

Studies on the association between snus use and type 2 diabetes and related end points are scarce, and only two had a longitudinal design. One observed no association between snus use and fasting plasma glucose levels  $\geq 5.6$  mmol/L or diabetes (5), and the other did not have a sufficient number of exposed cases to draw any conclusions (82). Of the four cross-sectional studies, one found an association with type 2 diabetes among heavy consumers of snus in a smoking-adjusted model (83), whereas the others found no associations with diabetes (11), glucose intolerance (84), or fasting glucose levels (26).

### 2.5.4.4 Blood pressure and hypertension

Acute effects from snus use on heart rate and pulse have been reported (85, 86), although the results from studies on associations between snus use and high blood pressure are inconclusive (16, 17, 26, 84, 86-89). Of the four studies available on hypertension among snus users, two were cross-sectional (11, 90) and two were longitudinal (5, 16). Although they used different definitions of hypertension (ranging from  $\geq 130/85$  mm Hg to  $\geq 170/95$  mm Hg), all four studies found an association between snus use and hypertension.

### 2.5.4.5 Biomarkers of cardiovascular disease

Of the two studies on snus use and atherosclerosis, neither found an association (88, 91). However, snus use could affect fibrinogen levels (26). Further, there have been reports of associations with increased levels of serum triglycerides from one study (88), but another study found no such association (84).

#### 2.5.4.6 *Cancer*

Snus contains tobacco-specific nitrosamines; carcinogens formed from nicotine and related tobacco alkaloids (92). A systematic review from 2008 concluded that snus use is associated with increased risk of oesophageal cancer and pancreatic cancer, but not with lung cancer or oral cancer (93). Subsequent to this review, Roosaar and colleagues (79) found increased risk of oral and pharyngeal cancer among current users of snus. Colon and rectal cancer seem unrelated to snus use (94). Further, a study of survival among cancer patients showed a 15% increased risk of cancer-specific death among snus users as compared to non-tobacco users (95).

#### 2.5.4.7 *Inflammatory diseases*

There is no evidence of associations between snus use and inflammatory diseases such as multiple sclerosis (96, 97), rheumatoid arthritis (97), ulcerative colitis (97, 98), or Crohn's disease (97, 98), although there are only a limited number of studies available.

#### 2.5.4.8 *Oral health*

Oral mucosal lesions (lesion in the mucous membrane of the cavity of the mouth) are associated with use of snus (99-101). There have been reports of a dose-response association where lesions seem to be more severe in users of loose snus than among users of portion-bags (99), and the risk appears to increase with hours per day of snus use (100, 101). However, for most users the lesions disappear after cessation (99). In recent studies, Hugoson and colleagues found no association with dental caries (102), or with frequency of probing pocket depth ( $\geq 4$  mm), periodontal disease, or gingivitis (101). There have, however, previously been reports of increased prevalence of gingival recessions in adolescent snus users (103).

#### 2.5.4.9 *Pregnancy outcomes*

Nicotine from maternal tobacco use during pregnancy passes to the foetus via the placenta where concentrations can be up to 15% higher than maternal levels (104). Maternal snus use has been shown to increase risk of very preterm (less than 32 weeks of gestation) and moderately preterm (32–36 weeks of gestation) birth, and the increase in risks apply to both spontaneous and induced preterm births (105). However, women who stop using snus early in pregnancy reduce their risk to that of a non-user (106). Further, maternal snus use has been associated with stillbirth (107), reduced birth weight (by an average of 39 grams) (108), and with increased risk of neonatal apnea (109). The seemingly protective effect of smoking on preeclampsia has not been observed among snus users (110).

### **3 AIMS**

The overall aim of this thesis was to advance the knowledge of health effects of snus use. Specifically, the aims were to assess the associations between use of snus and CVD and excess body weight. The study-specific aims were:

- To assess the associations between use of snus and risk of CVD, specifically IHD and stroke (Study I).
- To assess the associations between use of snus and both weight gain and obesity (Study II).
- To assess the association between use of snus and risk of AMI (Study III).
- To assess the associations between use of snus and risk of stroke overall and by subtype (Study IV).

## **4 MATERIALS AND METHODS**

This thesis is based on four studies and includes data from eight cohorts. Study I is based on the Screening Across the Life-Span Twin Study (a subset of the Swedish Twin Registry), Study II on the Stockholm Public Health Cohort, and studies III and IV on the Swedish Collaboration on Health Effects of Snus Use. The collaboration was set up to increase the understanding of health effects of snus use and comprises data from eight Swedish cohorts, including the study populations in Studies I and II. All cohorts had information on tobacco use and participants could be followed for incident events of the respectively studied outcomes in national health registers. Below follows a description of all the included cohorts, which are also summarized in Table 1.

### **4.1 PARTICIPANTS AND DATA COLLECTION**

#### **4.1.1 The Construction Workers Cohort**

The Swedish Construction Industry's Organisation for Working Environment, Safety and Health offered outpatient care, mainly preventive health check-ups, to construction workers from 1969 to 1993 (111). Participants were recruited via invitation letters and advertisements at building sites. Before the health examination, all participants received an extensive questionnaire regarding work environment, medical history, and lifestyle. The questionnaire was handed in at the time of physical examination and answers were double-checked by a nurse. Approximately 75% participated (n=386 000) and constitute the Construction Workers Cohort (CWC). Studies III and IV are based on information given at the first visit from 1978 and onwards because use of snus was not assessed regularly before then (13, 111).

#### **4.1.2 The Malmö Diet and Cancer Study**

The main objective with the Malmö Diet and Cancer Study (MDCS) was to investigate the impact of diet on cancer incidence and mortality (112). A total of 68 000 individuals living in Malmö between 1991 and 1996, aged 44–74 years old, were invited to take part in the study. Another 5 000 were recruited through advertisements in local newspapers. Data were collected by self-administered questionnaires, dietary assessments, anthropometric measurements, and blood samples. The questionnaire contained questions on tobacco use, education, and other social and lifestyle factors. Snus use was reported as current or non-current, and included information on amount consumed. In all, 28 098 participants (a 40% response rate) gave full information, and 11 063 were men (113).

#### **4.1.3 Multinational Monitoring of Trends and Determinants in Cardiovascular Disease**

The WHO initiated the MONICA project (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) in the early 1980s (114). The purpose was to evaluate the extent to which changes in traditional cardiovascular risk factors could explain mortality trends. Thirty-eight populations from 26 countries participated in the MONICA project with random samples drawn from population-based registers.

**Table 1.** Description of the Included Cohorts

Study	Study population	Data collection	Period of recruitment	End of follow-up	Response rate (%)	Current exclusive snus use (%)	Detailed information available on snus use	Amount	Former use
							<i>Duration</i>		<i>Former use</i>
CWC	Employees within the construction industry, national	Questionnaire	1978–1993	2007	75	29	Yes	Yes	Yes
MDCS	Population-based, Malmö City	Questionnaire	1991–1996	2007	40	2	No	Yes	No
MONICA	Population-based, Norrbotten and Västerbotten Counties	Questionnaire	1986–2004	2007	69–81	17	Yes	Yes	Yes
NMC	Participants in a charity walk, national	Questionnaire	1997	2006	unknown <sup>a</sup>	6	No	Yes	Yes
SALT	Twins born in Sweden between 1926–1958, national	Structured telephone interview	1998–2002	2008 (2003/2005) <sup>b</sup>	74	12	Yes	Yes	Yes
Scania_PHC	Population-based, Scania County	Questionnaire	1999–2000	2007	58	14	No	No	No
Sthlm_PHC	Population-based, Stockholm County	Questionnaire	2002	2007	62	15	No	No	Yes
WOLF	Employees, Västernorrland, Jämtland, and Stockholm Counties	Questionnaire	1992–1998	2003	82	19	Yes	Yes	Yes

<sup>a</sup>The participation rate could not be computed due to the nature of the data collection

<sup>b</sup> In Study I, participants were followed through 2003 in the Cause of Death Register and through 2005 in the Inpatient Register

Potential participants received an invitation to an examination at a health care centre and a questionnaire. The first survey within the Northern Sweden MONICA was sent out in 1986 followed by surveys in 1990, 1994, 1999, 2004, and 2009 (114). The survey and examination procedures varied somewhat between years of sampling but generally included questions on lifestyle, social factors, and health. Information on current and past snus use was reported, as well as duration and intensity of use. The examination assessed, among other things, weight and height, blood pressure, levels of cholesterol, and insulin resistance (114). The participation rate varied between 69 and 81% and 10 586 persons had participated by 2009, 5 212 of whom were men (115). In the Swedish Collaboration of Health Effects of Snus Use, male participants from the Northern Sweden MONICA, recruited from 1986 through 2004, were included.

#### **4.1.4 The National March Cohort**

In 1997, the Swedish Cancer Society organized charity walks in 3 600 different locations throughout Sweden called the National March. Participants were asked to answer a questionnaire focusing mainly on their physical activity and energy intake, but also including questions on other lifestyle and social characteristics (116). The main objective was to study how lifestyle affects the risks of cancer and other diseases. Tobacco use was reported as consumption during different five to ten year periods of life and included information on intensity of use. Information was given by 40 729 participants who constitute the National March Cohort (NMC). Of these, 14 585 were men (117).

#### **4.1.5 The Screening Across the Life-Span Twin Study**

The Swedish Twin Registry was established in the 1950s to study health consequences of alcohol use and smoking (118). The register has collected data from twins on several occasions and consists of three birth cohorts; those born in 1886–1925, 1926–1958, and 1959–1990. From 1998 to 2002 an attempt was made to contact all twins born in 1958 or earlier (119). The data collection was called Screening Across the Life-Span Twin Study (SALT), consisted of structured telephone interviews, and reached a response rate of 74%. The interview included questions on medical history, social factors, and lifestyle. Information on tobacco included current and former use, total duration, intensity, and age at onset. For the purpose of this thesis (Studies I, III, and IV) the study population was restricted to the 18 335 male participants in SALT born between 1926 and 1958. Four men later asked to be removed from the register which left 18 331 men eligible for inclusion.

#### **4.1.6 The Scania Public Health Cohort**

From 1999 to 2000, a multipurpose health survey was sent out to 25 000 men and women between 18 and 80 years old living in Scania (120). The sample was drawn from a population register, and survey questions covered health, lifestyle, and social factors. Snus use was reported as current or non-current, while questions on smoking were more extensive. A total of 13 604 persons answered (58% response rate) and were included in the Scania Public Health Cohort (Scania\_PHC). In total, 6 202 of the participants were men (120).

#### **4.1.7 The Stockholm Public Health Cohort**

The Stockholm Public Health Cohort (Sthlm\_PHC) was set up within the Stockholm County Council public health surveys (121). The first survey, designed to recruit a cohort, was sent in 2002. It included a random sample of 50 000 Stockholm County residents aged 18 to 84 years. Respondents were asked to participate in follow-up surveys in 2007 and 2010. In the surveys, the respondents reported several lifestyle and social factors as well as anthropometric measurements such as height and weight. For the purpose of Study II, information from the 2002 baseline survey and the 2007 follow-up survey was used, whereas only the answers to the 2002 questionnaire were considered in Studies III and IV. The first survey had a response rate of 62% (n = 31 182) and 23 794 participated in both 2002 and 2007 (corresponding to a 76% retention rate), and 10 417 were men.

#### **4.1.8 The Work, Lipids, and Fibrinogen Study**

The Work, Lipids, and Fibrinogen Study (WOLF) was set up to investigate the relationship between psychosocial work environment and coronary heart disease as well as biological risk factors of coronary heart disease (122). Employees (ages 15-64 years) from nearly 60 companies were recruited through occupational health service units in Stockholm County from 1992 to 1995 and in Västernorrlands and Jämtlands counties from 1996 to 1998. Participants took part in a clinical examination that included anthropometric and blood pressure measurements. After completion of the examination, participants were given a questionnaire regarding their work environment, lifestyle, health, and social factors. Tobacco use included information on timing, duration, and intensity of use. The participation rate was 82% and 10 382 persons in total (7 146 men) contributed with complete information (122).

### **4.2 DEFINITION OF EXPOSURE AND IDENTIFICATION OF COVARIATES**

The definition of exposure varied somewhat between studies, as did the included covariates. In Studies I, III, and IV, exposure were assessed at baseline, whereas in Study II there were two measures of exposure five years apart. The questions used to assess snus use in the different studies are given in Table 2.

#### **4.2.1 Study I**

In Study I, use of snus was categorized as never, former, or current. Smoking status was classified the same way and those who never used tobacco were considered the reference group. Intensity of snus use was categorized as low (4 cans/week or less) or high (more than 4 cans/week) and total duration into short (less than 20 years) or long (20 years or more). Covariates of interest were age, BMI, education, alcohol intake, leisure time physical activity, type 2 diabetes, high blood pressure, and high serum cholesterol.

#### **4.2.2 Study II**

To categorize exposure in Study II, information from both the 2002 and 2007 questionnaires was used, and ten mutually exclusive exposure groups were created. Men who reported to never have used tobacco daily at baseline and at follow-up were categorized as never tobacco users, and this group constituted the reference category.

Snus users who did not report any smoking were grouped according to timing and stability of use. Snus users reporting use at both baseline and follow-up were considered stable current users, and stable former users were men who had quit more than six months prior to the baseline survey and reported still being former users at follow-up. Those who started using snus during follow-up were considered starters, and those who stopped using snus during follow-up were considered quitters. Exclusive smokers were grouped according to the same principles. Information on age, education, alcohol consumption, leisure time physical activity, frequency of eating breakfast, and consumption of fruit and berries was collected from the baseline questionnaire and considered possible confounders.

**Table 2.** Description of the Questions Regarding Current Use of Snus<sup>a</sup>

Cohort	Question	Possible answers
CWC	Do you use snus or chewing tobacco?	Yes/No
MDCS	Do you use snus?	Yes/No
MONICA	Have you ever used snus?	Yes, used snus earlier but not now Yes, less than 2 cans/week Yes, 2–4 cans/week Yes, more than 4 cans/week but less than 7 cans/week Yes, 7 cans/week or more No
NMC	How much have you smoked/used snus in different ages?	<i>Number of cans during different 5 or 10 year periods of life</i>
SALT	Have you ever smoked or used snus?	Use snus regularly Used snus regularly Use snus now and then (for example at parties) Used snus now and then (for example at parties)
Scania_PHC	Do you use snus?	Yes/No
Sthlm_PHC		
2002 survey	Do you use snus daily?	Yes/No
2007 survey <sup>b</sup>	Are you currently using snus more or less daily?	Yes/No
WOLF	Do you use snus?	Yes/No

<sup>a</sup> Other questions were used to categorize former snus use and duration and intensity of use

<sup>b</sup> Considered in Study II

### 4.2.3 Study III and Study IV

In Studies III and IV, snus use was primarily categorized into current and non-current use. The reference group consisted of participants who never smoked cigarettes and, included both never and former snus users. Current use was further categorized according to duration (less than 20 years, or 20 years or more), and intensity (less than

4 cans/week, 4–6 cans/week, or 7 cans/week or more) of use. In the cohorts with more detailed information on timing of use, non-current use was divided into never or former (see Table 1). Age, BMI, and educational level were considered possible confounders. Information collected on other covariates varied considerably between studies, and this is the reason why further data was not compiled.

### 4.3 FOLLOW-UP AND ASCERTAINMENT OF OUTCOME

#### 4.3.1 Cardiovascular disease

Baseline information was linked to the Inpatient Register and the Cause of Death Register using participants' unique personal identification numbers (123). These registers are coded according to the International Classification of Diseases (ICD) (59), and provide information on virtually all inpatient care and deaths in Sweden (124, 125). Participants in Study I were followed from entry (between 1998 and 2002) through 2003 in the Cause of Death Register and through 2005 in the Inpatient Register. Duration of follow-up varied from 5 to 29 years between the studies included in Studies III and IV. The specific lengths of follow-up are given in Table 1. When classifying outcome in Study I and Study III, primary and secondary admission diagnoses and both the underlying and contributing causes of death, were considered. In Study IV, primary and secondary admission diagnoses along with underlying cause of death were considered. Table 3 describes the ICD codes used to identify cases in Studies I, III, and IV.

**Table 3.** International Classification of Diseases Codes Used to Define Outcome in Studies of Cardiovascular Disease

Study	Outcome	Version of the International Classification of Diseases			
		7 <sup>th</sup> edition	8 <sup>th</sup> edition	9 <sup>th</sup> edition	10 <sup>th</sup> edition
Study I	IHD	420.00, 420.10, 420.17, 420.18, 420.20, 420.28	410, 411, 412.09, 412.99, 413, 414	410, 411, 413, 414	I20–I21, I24–I25 <sup>a</sup>
	Stroke	330–332, 334.00, 334.09	430–436	430–431, 433–436	I60, I61, I63, I64 G45
Study III	AMI	420.10, 420.17	410	410	I21
Study IV	Stroke				
	haemorrhagic	330–331 <sup>b</sup>	430, 431 <sup>c</sup>	430, 431	I60, I61
	ischemic	332	433, 434	434	I63
	unspecified		436	436	I64

<sup>a</sup> Not I25.2

<sup>b</sup> Not 331.10 or 331.11

<sup>c</sup> Not 431.01 or 431.91

#### 4.3.2 Weight gain and obesity

In Study II, outcome was assessed by comparing information on weight and height from the baseline questionnaire to information given at follow-up. Weight gain was defined as an increase in weight (kg) of more than 5% during follow-up, and incident obesity as having a BMI  $\geq 30$  kg/m<sup>2</sup> at follow-up among non-obese participants (BMI < 30) at baseline.

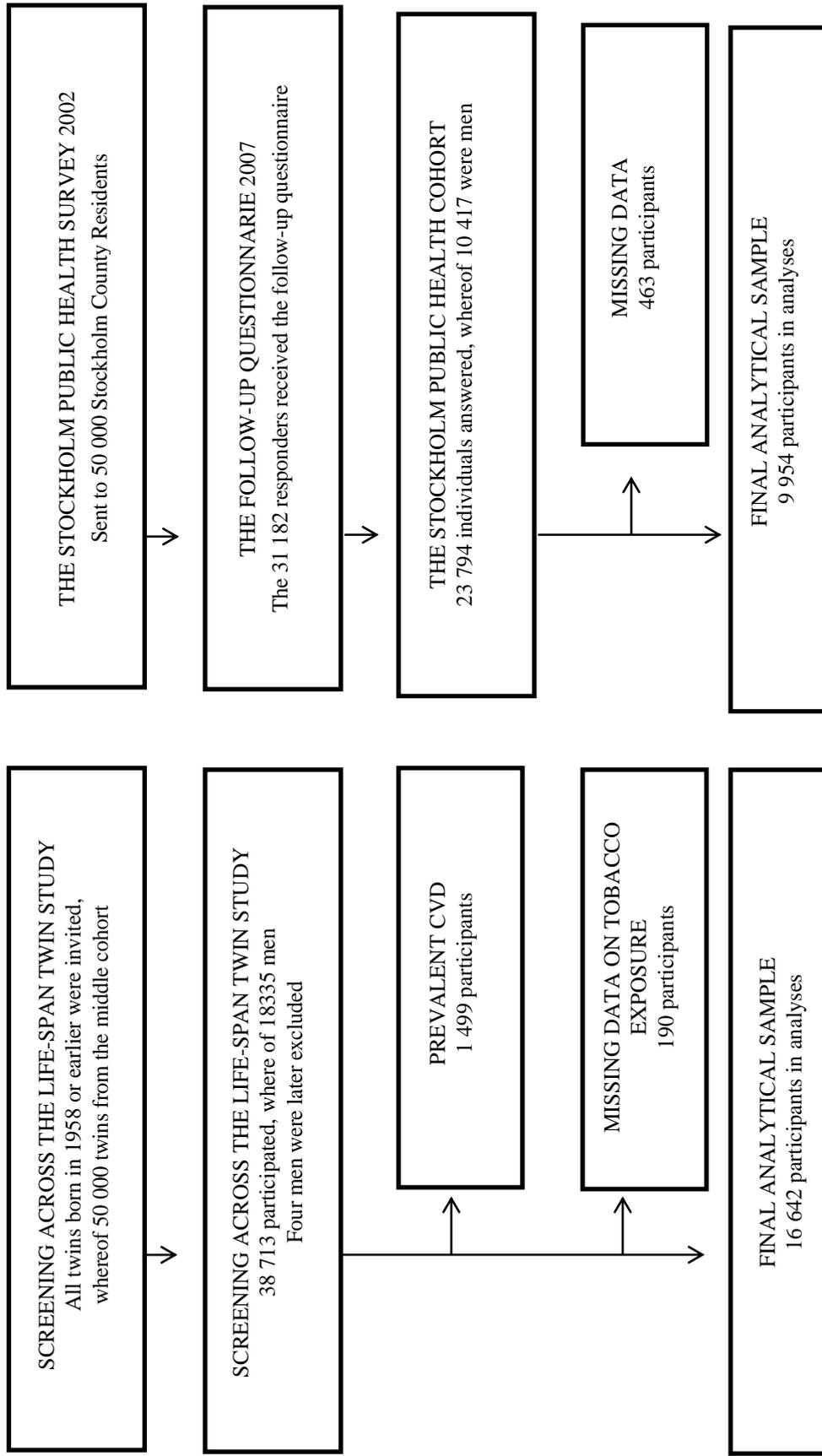
#### 4.4 STATISTICAL ANALYSES

Analyses were restricted to men aged 18 or older. Incomplete information on tobacco use led to exclusion in all studies and missing information on height or weight led to exclusion in Studies II-IV. In Studies I, III, and IV, prevalent cases of the respective CVD outcomes (defined as a primary- or secondary diagnosis in the Inpatient Register) were censored at baseline. The derivations of the analytical samples are described in Figures 1 and 2 for Studies I and II, respectively, and in Figure 3 for Studies III and IV. Other participants contributed person-time from date of entry in the respective study until diagnosis, death, or end of follow-up, whichever came first. Only the first registered relevant event was considered. Differences in age between exposed and unexposed participants were considered in all studies. All main analyses were conducted so that the effect from snus use could be presented without influence from smoking.

Besides age, none of the other possible confounders in Study I (BMI, education, alcohol intake, or leisure time physical activity) affected the regression coefficient by more than 10%, and these variables were, therefore, not included in the final model.

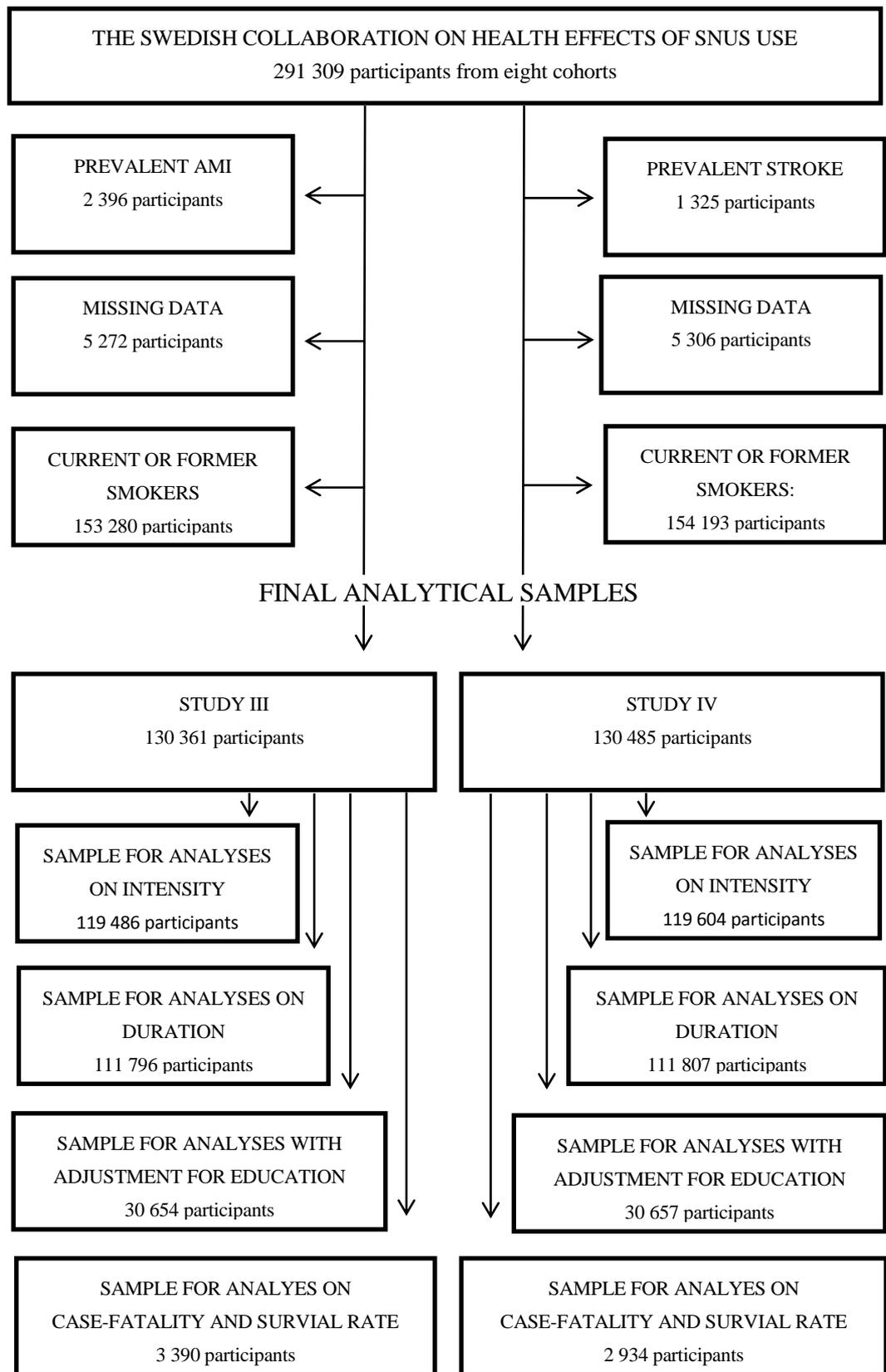
In Study II, age and baseline weight were included in the analyses as continuous variables, and the other covariates (alcohol consumption, physical activity, education, consumption of fruit and berries, and frequency of having breakfast) were included as categorical variables.

In Studies III and IV, age and BMI were considered confounders and were included in all models. Analyses were conducted for all current snus use, and separately for intensity and duration of use, in regards to case-fatality within 28 days of diagnosis, and for risk of death following diagnosis. Year of diagnosis were included in all analyses of case-fatality and risk of death after a stroke. Education level was included in sub-analyses with those cohorts for which this information was available. Further, the effect of including former snus users in the reference category was studied in separate analyses using men who never used any type of tobacco as reference. Also, the possibility of misclassification of exposure (and an attenuated association over time) was tested by restricting the length of follow-up to a maximum of ten years. Analyses were also stratified by period of recruitment (prior to and including December 31<sup>st</sup>, 1985 vs. January 1<sup>st</sup>, 1986 or later), and in Study IV an analysis was conducted in which secondary diagnosis during follow-up was censored. Additionally, all analyses were performed with and without the CWC, which constituted 76% of the total sample. In analyses of subtypes of stroke (Study IV) any registered event led to censoring irrespective of the outcome being studied.



**Figure 1.** Derivation of Analytical Sample in Study I

**Figure 2.** Derivation of Analytical Sample in Study II



**Figure 3.** Derivation of Analytical Samples in Study III and Study IV

In Studies I, III, and IV, the risk of CVD and risk of death following an event were estimated by Cox proportional hazards regression models, with attained age (or age at event) as the time scale, and presented as hazard ratios (HR) or relative risks (RR) with 95 % confidence intervals (CI). In Studies III and IV, study-specific and pooled HRs were presented. Heterogeneity in the results between cohorts in Studies III and IV was assessed with  $\chi^2$ -tests using a fixed-effect model. Further, to study the 28-day case-fatality, logistic regression was used and presented as odds ratios (OR) with 95% CI. In Study II, associations were studied using logistic regression models and results were presented as OR with 95% CI.

Analyses were mainly conducted using SAS version 9.1 and 9.2 (SAS Institute Inc., Cary, N.C., USA). In Study I, R version 2.6.0 (R Development Core team, Vienna, Austria) was used to a minor extent, and in Study III and Study IV heterogeneity in results between studies was tested using Epi-Sheet (126).

#### **4.5 ETHICAL APPROVAL**

Study I was approved by the Research Ethics Committee at Karolinska Institutet, Stockholm, Sweden (no. 00-132), and Studies II-IV by the Regional Ethical Review Board in Stockholm, Sweden (no. 2009/971-31/3).

## 5 RESULTS

### 5.1 STUDY I

Current snus use was reported by 16% of the 16 642 participants, and 6% were exclusive snus users. During a total of 80 775 person-years of follow-up, 1 119 participants suffered their first CVD, among whom 414 were never smokers and 32 were current exclusive snus users.

Exclusive current snus use was not associated with increased risk of CVD, IHD, or stroke after adjustment for age (Table 4). Additional adjustment for high blood pressure, high cholesterol, and type 2 diabetes had minor effect on estimates. Risk of CVD, IHD, and stroke among snus users were also estimated regardless of smoking status and the adjusted results did not differ from those in the main analyses.

Furthermore, duration of use was not associated with increased risk of any CVD among snus users. However, while intensity of use did not appear to affect risk of IHD, there was an apparent increase in risk of stroke among heavy users (>4 cans/week). The estimated HR was 1.80 (95% CI 0.99–3.29), after adjustment for age and smoking status.

**Table 4.** Relative Risks (RR) and 95% Confidence Intervals (CI) of Cardiovascular Disease According to Snus Use

Cardiovascular disease	No tobacco use		Current snus use	
	Cases	RR	Cases	RR (95% CI) <sup>a</sup>
Overall	382	1.00	32	1.01 (0.69–1.47)
Ischemic heart disease	246	1.00	18	0.85 (0.51–1.40)
Stroke	155	1.00	14	1.20 (0.69–2.11)

<sup>a</sup> Adjusted for age

### 5.2 STUDY II

In total, 9 954 men participated in both the baseline and follow-up questionnaires. At baseline, 18% of participants reported current snus use, and 6% were exclusive snus users. After reassessment of tobacco habits at follow-up, approximately 5% (n = 445) could be categorized as stable snus users.

Stable current snus use was associated with weight gain during follow-up (OR 1.31, 95% CI 1.04–1.65) after adjustment for age, baseline weight, alcohol consumption, physical activity, education, consumption of fruit and berries, and frequency of having breakfast. Stable current snus users were also more likely to become obese during follow-up (OR 1.93, 95% CI 1.13–3.30) compared to non-tobacco users in the full model.

Stable former use, quitting during follow-up, and starting using snus during follow-up appeared unrelated to weight gain, and neither stable former use nor cessation during follow-up seemed associated with development of obesity. No cases of obesity were observed among men who began to use snus during follow-up.

### 5.3 STUDY III

In total, 130 361 men who had never been regular smokers were included in the analytical sample. Twenty-five per cent ( $n = 32\ 560$ ) reported current snus use at baseline. During 2 262 333 person-years of follow-up, 3 390 incident cases of AMI were identified and 356 of these among snus users.

Current use of snus was not associated with risk of AMI when compared with non-current snus users. After adjustment for age and BMI, the pooled HR was 1.04 (95% CI 0.93–1.17). There was no significant heterogeneity between the results from the different studies ( $p = 0.23$ ), but some were based on small numbers. Further, there was no evidence of any dose-response relationship with risk of AMI according to either intensity or duration of snus use. When excluding the CWC, the age- and BMI-adjusted HR was 1.27 (95% CI 0.94–1.72) and additional adjustment for education resulted in a HR of 1.20 (95% CI 0.87–1.66). Results from all sensitivity tests are presented in Table 5.

**Table 5.** Pooled Hazard Ratios (HR) and 95% Confidence Intervals (CI) of Acute Myocardial Infarction According to Snus Use - Sensitivity Analyses in Study III

Type of analysis	Non-current snus use		Current snus use	
	Cases	HR	Cases	HR (95% CI) <sup>a</sup>
Excluding the CWC	712	1.00	47	1.27 (0.94–1.72)
Restricting follow-up to 10 years	1 187	1.00	125	1.20 (0.99–1.45)
Current snus use <sup>b</sup>	2 704	1.00	344	1.03 (0.92–1.15)
By period of recruitment				
1978–1984	1 976	1.00	240	1.01 (0.88–1.16)
1985–2004	1 058	1.00	116	1.12 (0.92–1.38)

<sup>a</sup> Adjusted for age and BMI

<sup>b</sup> Those who never used tobacco served as the reference group

There was a seemingly increased risk of incident AMI among snus users when restricting follow-up to ten years (HR 1.20, 95% CI 0.99–1.45) after adjustment for age and BMI. Exclusion of the CWC from this analysis resulted in a HR of 1.31 (95% CI 0.94–1.83), based on 39 exposed cases. Additional adjustment for education level reduced the HR to 1.23 (95% CI 0.88–1.72).

The OR of 28-day case-fatality and risk of death during total time of follow-up (up to 26 years) following an AMI appeared to increase among snus users. The OR of 28-day case-fatality was 1.28 (95% CI 0.99–1.68) adjusted for age and BMI. Without the CWC, the OR was 1.43 (95% CI 0.73–2.81) and changed negligible after inclusion of education in the model. HR of death during total follow-up was 1.39 (95% CI 1.18–1.65) among snus users after adjustment for age and BMI. Exclusion of the CWC and additional adjustment for education affected precision, but had only a modest effect on point estimates.

## 5.4 STUDY IV

Study IV included 130 485 men with no history of stroke or smoking, and of these 32 542 were snus users. A total of 2 934 cases of stroke were observed during 2 266 921 person-years of follow-up, and 304 of these occurred among current snus users.

Use of snus was not associated with risk of all incident stroke (HR 1.04, 95% CI 0.92–1.17) or any subgroup of stroke (Table 6) compared to non-current users after adjustment for age and BMI. There was no significant heterogeneity between the results from the different studies ( $p = 0.17$ ). Both intensity and duration of snus use seemed unrelated to risk of stroke.

**Table 6.** Pooled Hazard Ratios (HR) and 95% Confidence Intervals (CI) of Stroke According to Snus Use

Type of stroke	Non-current snus use		Current snus use	
	Cases	HR	Cases	HR (95% CI) <sup>a</sup>
All types of stroke	2 630	1.00	304	1.04 (0.92–1.17)
Ischemic stroke	1 758	1.00	195	1.06 (0.91–1.23)
Haemorrhagic stroke	510	1.00	71	0.94 (0.73–1.22)
Unspecified stroke	362	1.00	38	1.10 (0.78–1.54)

<sup>a</sup> Adjusted for age and BMI

In analyses excluding the CWC, the HR of stroke was 1.13 (95% CI 0.79–1.60) among snus users after adjustment for age and BMI. Additional adjustment for education changed HRs only marginally (HR 1.10, 95% CI 0.78–1.57 for all stroke). Results from other sensitivity analyses all provided HRs that differed only negligibly compared to the main analysis (Table 7).

**Table 7.** Pooled Hazard Ratios (HR) and 95% Confidence Intervals (CI) of All Stroke According to Snus Use - Sensitivity Analyses in Study IV

Type of analysis	Non-current snus use		Current snus use	
	Cases	HR	Cases	HR (95% CI) <sup>a</sup>
Excluding the CWC	757	1.00	35	1.13 (0.79–1.60)
Restricting follow-up to 10 years	1 033	1.00	94	1.00 (0.80–1.25)
Current snus use <sup>b</sup>	2 316	1.00	291	1.01 (0.89–1.14)
Primary admission diagnosis and underlying cause of death	2 630	1.00	304	1.00 (0.88–1.14)
By period of recruitment				
1978–1984	1 561	1.00	214	1.11 (0.96–1.29)
1985–2004	1 069	1.00	90	0.87 (0.69–1.10)

<sup>a</sup> Adjusted for age and BMI

<sup>b</sup> Those who never used tobacco served as the reference group

The OR of 28-day case-fatality after a stroke seemed increased in snus users compared to non-current users (Table 8). Without the CWC, adjusted for age, BMI and year of diagnosis, the OR was 1.43 (95% CI 0.52–3.92), based on 5 exposed cases and was slightly increased by the inclusion of education level in the model.

**Table 8.** Pooled Odds Ratios (OR) and 95% Confidence Intervals (CI) of Case-Fatality within 28 Days of a Stroke According to Snus Use

Type of stroke	Non-current snus use		Current snus use	
	Cases	OR	Cases	OR (95% CI) <sup>a</sup>
All types of stroke	285	1.00	41	1.42 (0.99–2.04)
Ischemic stroke	117	1.00	18	1.59 (0.93–2.71)
Haemorrhagic stroke	125	1.00	20	1.53 (0.85–2.76)
Unspecified stroke	43	1.00	3	0.65 (0.18–2.33)

<sup>a</sup> Adjusted for age, BMI, and year of diagnosis

When participants who suffered a stroke were followed during total time of follow-up, the HR of death from any cause was 1.32 (95 % CI 1.08–1.61). After exclusion of the CWC, and based on 10 exposed cases, HR of death was 0.93 (95% CI 0.46–1.88) adjusted for age, BMI and year of diagnosis. Further adjustment for education resulted in HR 0.87 (95% CI 0.43–1.77). Table 9 shows the subtype-specific HRs.

**Table 9.** Pooled Hazard Ratios (HR) and 95% Confidence Intervals (CI) of Death Following a Stroke During Total Time of Follow-up According to Snus Use

Type of stroke	Non-current snus use		Current snus use	
	Cases	HR	Cases	HR (95% CI) <sup>a</sup>
All types of stroke	882	1.00	115	1.32 (1.08–1.61)
Ischemic stroke	517	1.00	69	1.29 (1.00–1.67)
Haemorrhagic stroke	199	1.00	30	1.76 (1.16–2.67)
Unspecified stroke	166	1.00	16	0.92 (0.53–1.58)

<sup>a</sup> Adjusted for age, BMI, and year of diagnosis

## 6 DISCUSSION

### 6.1 MAIN FINDINGS

#### 6.1.1 Cardiovascular disease

No associations between snus use and incident AMI or all IHD were observed, and there was no indication of any dose-response relationship. These results are in agreement with prior studies of snus use and risk of AMI (8, 9, 11, 13, 14, 17) and IHD (12, 15). The strength of the studies presented here in relation to previous studies includes the prospective design and the large set of data that enable sub-analyses of dose-response associations. Some earlier studies were based on a limited number of exposed cases (11, 17), and three were conducted using case-control design (8, 9, 11). Consideration of covariates has differed between previous studies, and most have not been able to account for several lifestyle factors possibly associated with both snus use and AMI or IHD. All studies on snus use and incident AMI published during a 20-year period have failed to show an increased risk of incident AMI among snus users. The only indication of an increased risk was seen in the study of AMI included in this thesis, when follow-up was restricted to ten years. This finding suggests that misclassification of exposure can increase during follow-up and could result in an underestimation of the association. However, this needs to be confirmed in future studies.

OR of 28-day case-fatality and risk of death following an AMI were increased among snus users. These associations have previously been studied sparsely (9, 11, 13, 14) and interpretations of most previous studies are limited due to the low number of exposed cases (9, 11, 14). One large study did, however, report an increased risk among snus users when compared to non-tobacco users (13) similar to the risk estimate presented here. Note that this study was based on a cohort included in the Swedish Collaboration of Health Effects of Snus Use. After excluding this cohort (the CWC), the point estimate still indicated an increased risk, which decreased somewhat after adjustment for education. It is possible that residual confounding by socioeconomic position (SEP) or lifestyle factors could explain this association.

The results presented in this thesis suggest that snus users have the same risk as non-users of suffering a stroke. In Study I, a seemingly increased risk of stroke was observed among heavy users of snus, but such an association was not seen in Study IV. Overall, the results in this thesis support findings from previous research of a null association between snus use and risk of all incident stroke (10, 15, 17, 18) as well as risk of any stroke subtype (18). Interpretations of earlier research have often been difficult due to the small number of exposed cases (10, 15, 17), and the studies presented here, especially Study IV, add to the limited body of evidence by the large number of cases, which allowed for analyses of dose-response associations and analyses according to subtype of stroke.

Both higher odds of dying within 28-days and higher risks of death during total time of follow-up were observed among snus users. Sub-analyses indicated that mortality was increased following both ischemic and haemorrhagic stroke, and persisted after

adjustment for education. It cannot be excluded that confounding may explain these observed associations. Results of increased risk of death among snus users following any stroke and ischemic stroke are, however, in accordance with prior findings (18). However, the increased risk of haemorrhagic stroke was not. The understanding of snus use and risk of fatal stroke and risk of death following a stroke is still limited, but these results indicate a possible association.

### **6.1.2 Weight gain and obesity**

Snus users had an increased likelihood of gaining weight and becoming obese during follow-up compared to the non-tobacco users. An association between heavy snus use and onset of obesity has been described earlier (5), but results from prior studies on weight gain have been at odds with each other (6, 7). One of the strengths of the present study is the opportunity to take several confounders into account, especially eating habits, which has not been done prior to this. Based on the limited available information in regards to snus use and body fatness, potential metabolic effect of snus use cannot be excluded.

## **6.2 METHODOLOGICAL CONSIDERATIONS**

The results of the studies should be interpreted with the following methodological issues in mind.

### **6.2.1 Selection bias**

Selection bias can occur in cohort studies if non-participation is associated with the exposure, or when loss to follow-up is related to both the exposure and the outcome. That is, if snus users were more or less inclined to respond than non-users and if registration of CVD in national health registers would differ between individuals with regard to snus use.

Participation in health surveys is more common among people with less risky behaviour, as well as people with high SEP (127). Smoking (127, 128) is associated with non-response, but whether this is true for snus users as well has not yet been studied. There is also a possibility of another type of health selection in the cohorts included in Studies III and IV. Because the CWC and the WOLF study are occupational cohorts, there is a chance that participants are healthier than the general population, which contains people who are too sick to work. There is probably a similar selection in the NMC. On the other hand, people with symptoms of disease may be more motivated to participate in studies (127). Although none of the cohorts had as an objective to study the specific association between snus use and CVD or weight gain, the MONICA study aimed to investigate changes in risk factors for CVD. Also, the WOLF study investigated biological risk factors of coronary heart disease and the association between psychosocial work environment and coronary heart disease. In these cohorts, it is possible that men with symptoms of heart disease were more inclined to participate. Although these tendencies to respond might differ among exposed and unexposed, there is no reason to believe that loss to follow-up would be different when outcomes were assessed through health registers.

In Study II, participants were asked to answer two surveys with a five-year interval, and 48% of the initial study population answered both surveys. Because lifestyle and health behaviours are related to participation (127), as discussed above, it is possible that snus use was associated with willingness to respond to both baseline and follow-up questionnaires. Furthermore, those with greater weight gain might have been less inclined to respond. Hence, the possibility of selection bias cannot be excluded.

The men included in the studies do not constitute a representative sample of the Swedish male population. Only a few of the sampled cohorts were population-based, and in some a selection (or self-selection) of healthier participants is expected. There is, however, no reason to believe that any underlying biological mechanisms that could possibly increase body fatness or increase risk of death after CVD among snus users would differ between the studied group of men and rest of the male Swedish or Nordic populations. The results might even be applicable to other populations. The studies presented here do, however, only cover effects of snus, and it is not possible to draw any conclusions about the effects from other types of smokeless tobacco.

## **6.2.2 Information bias**

### *6.2.2.1 Classification of exposure*

Bias could have been introduced if snus users did not respond with correct exposure information or did not recall exposure. However, validation of self-reported snus use by measuring serum levels of cotinine has found good agreement between the two (84). Although misclassification of exposure can be expected to increase during follow-up, snus users are a stable group of tobacco users. Studies of stability of tobacco habits report 77–80% stability among snus users when followed for 5–13 years (39, 129). Misclassification of former snus users as current users would dilute the results towards the null. Such misclassification could potentially be the explanation for the observed null association between snus use and AMI during total follow-up and the increased risk during ten years of follow-up. The risk of misclassification of non-users of tobacco is likely to be negligible because it is likely that the studied population (with mean age at entry of 35 years) already established their tobacco habits before entering the studies. Indeed, studies of adults who have never used tobacco report 88–94% stability when followed for 5–13 years (39, 129). Any misclassification of exposure, snus users as non-users or vice versa, would likely result in a dilution of associations.

There seemed to be good agreement between interpretations of baseline and follow-up questions on snus use in Study II. When cross-tabulating snus use according to the questions, 74% of users at baseline reported current use at follow-up, 24% reported former use, and only 2% reported never having used snus.

### *6.2.2.2 Classification of outcome*

In Studies I, III, and IV, end-points were assessed using the Inpatient Register and the Cause of Death Register. They reached full national coverage in 1987 and 1961, respectively. A review of studies on the quality of CVD diagnoses registered in the Inpatient Register concluded that the validity overall is high for both AMI and stroke diagnoses (124). This has, however, varied over time. Findings from an examination

(with data from 1987–1995) of diagnostic information suggests a high positive predictive value and a high sensitivity for the ICD-9 code 410 in national registers (130). In a validation study of data from the late 1980s, Stegmayr and Asplund (131) reported that mortality statistics gave a good estimate of fatal stroke cases, but that the Inpatient Register did not reflect the incidence of stroke in an adequate way. Further, they reported that the proportion of unspecified stroke was considerable and varied over time. Additional validations of stroke in the Inpatient and Cause of Death Registers, with data from 1999–2000 reported high sensitivity and specificity (132). Strokes with low severity were less likely to be registered. Any misclassification of AMI, IHD, or stroke would likely be non-differential with regard to snus use.

In Study II, self-reported information on weight and height was used to define outcome variables. Self-reports on weight and height, however, tend to be under- and overestimates, respectively (133, 134). There is no data to suggest that snus users would differ from non-users in this respect and any bias would probably be non-differential. The  $\geq 5\%$  cut-off for overweight was adopted from a study by Stevens and colleagues (135). The authors suggested that this degree of weight gain could be considered to be clinically relevant. Obesity was defined as a BMI  $\geq 30$  according to the definition from the WHO (64). A limitation with BMI is that it does not distinguish between age, sex, or body composition. Measures of overweight and obesity based on visceral fat (WHR and WC) could be more appropriate measures to use on the individual level (136) and have been discussed as superior to BMI in predicting risk of CVD (65). However, BMI is a commonly used measure to identify overweight and obesity, and using BMI as an outcome enables comparisons with other studies.

### **6.2.3 Confounding**

As described in the background section, snus users differ from non-tobacco users in a number of lifestyle and social characteristics, some of which are also associated with CVD and adiposity. When possible, these differences were handled in analyses.

Mean age varied between snus users and non-users in all studies, and was, therefore, always adjusted for. All main analyses were conducted without smokers. The criteria were strict and all available information on smoking was considered. In Studies III and IV, this led to exclusion of more than 150 000 respondents.

In Study I, inclusion of BMI, physical activity, alcohol consumption, and level of education in the model had minor effect on estimates, and they were not included in the final model. Results are presented adjusted for age and, as a secondary approach, with the additional adjustment for high blood pressure, type 2 diabetes, and high levels of triglycerides. These three could be intermediates on the causal pathway from snus use to CVD. Adjustments of such factors could lead to over adjustment (137), but their inclusion had only minor effects on estimates.

The associations between snus use and weight gain and obesity (Study II) were studied with multiple potential confounders in the model. Energy intake was not available, but by adjusting for frequency of having breakfast and consumption of fruit and berries an attempt was made to handle differences in eating habits. No previous studies on snus

use and weight have attempted to adjust for any covariates related to eating habits or energy intake. Although, breakfast habits and fruit consumption have been associated with energy balance and weight stability (138), the possibility of residual confounding cannot be excluded.

The results in Studies III and IV are adjusted for differences in age and BMI, and in sub-analyses also adjusted for level of education. In analyses of case-fatality and overall survival after a stroke, year of diagnosis were included in the model in an attempt to handle that the prognosis after stroke have improved over time. In some of the included cohorts, more data on confounders was available but attempts to combine them were futile.

Failing to account for confounders may have led to underestimations or overestimations of associations. Socioeconomic or lifestyle factors associated with CVD and body fatness, may be, or may have been, more prevalent among snus users resulting in an overestimation of associations. Alternatively, certain lifestyle factors among snus users could have a protective effect, causing underestimation of relationships. Considering that non-tobacco users/non-current snus users served as the reference category, and given that this group are more health conscious than snus users, failing to account for confounders could have led to overestimation of associations. However, it is unlikely that the observed null association would be an overestimation and that snus use thereby would have a protective effect against CVD.

The social gradient needs to be carefully considered, because snus users have been reported to have a somewhat disadvantaged social profile (24, 25) and because AMI incidence (139) and mortality (140), as well as stroke incidence (140, 141) and mortality (141), are associated with low SEP. Level of education is often used as an indicator of SEP (142) and was accounted for in Studies I and II, as well as in a subset in Studies III and IV. Still, it must be noted that achieved education is only an indicator of SEP that covers the knowledge-related assets of an individual, not income or occupational factors, nor the life course SEP (142). Hence, residual confounding by SEP in the studies is possible. There is some evidence of an association between low SEP and stroke severity (141). If that is true, or if the social gradient is stronger for death than incidence, this could explain the observed results of increased risk of death without increased incidence among snus users.

#### **6.2.4 Pooled analyses**

With pooled analyses of individual data, the associations between snus use and AMI and stroke could be examined with greater power than in the individual studies. This allowed for sub-analyses that would not have been possible in the individual studies, for example, risk according to duration and intensity of snus use. The strengths also include the use of unpublished data, and thus no risk of publication bias. Further, it was possible to create unified definitions of confounders to adjust individual and pooled analyses. Limitations with pooling data include differences in data collection, and indeed some of the study-specific variables in the collaboration were not fully compatible. Attempts to unify data on covariates other than smoking, BMI, and education, were unsuccessful.

Tests revealed no heterogeneity between cohorts. However, such tests have low power and the possibility of heterogeneity cannot be excluded. It is, though, somewhat reduced by the uniform categorization of variables. Moreover, sensitivity tests were performed and resulted in estimates similar to those in the main analyses.

### **6.3 CONCLUSIONS**

Results from the studies presented in this thesis show that snus use was associated with weight gain and obesity. No relationship was observed between use of snus and any incident CVD during total follow-up time in any of the studies. Risk of AMI was, however, seemingly increased among users of snus compared to non-users when duration of follow-up was restricted to ten years. Snus use was associated with case-fatality and users who suffered an AMI or stroke had increased risk of death when followed for up to 26 years. Confounding may explain the observed associations with weight gain and obesity and could conceal increased risks of incident CVD or explain the observed association with case-fatality and risk of death. In conclusion, snus use seemed to affect weight, indicating the possibility of metabolic effects. Snus use also appeared to increase risk of death following a CVD, albeit a null association was observed between use and risk of suffering a CVD. These results of health effects of snus should be considered in the continued debate of the impact and role of snus in public health in Sweden and other countries.

To add to the existing evidence on snus use and CVD, future studies need to have extensive information on potential confounders. Initially, SEP and lifestyle factors such as alcohol consumption and physical activity are probably the most interesting factors that should be accounted for. The seemingly increased risk of death following a CVD among users of snus needs further investigation to infer on possible causal mechanisms. This needs to be studied both with epidemiological methods – with extensive control for confounding and by studies of the biological mechanisms that potentially increase vulnerability and lead to the increased mortality among snus-using CVD patients. Due to historically low prevalence, it has not been possible to estimate risk of CVD among female snus users, which now needs to be assessed. Changes in tobacco habits also need to be considered in future studies both with regard to restricted time of follow-up to limit misclassification and with regard to assessing risk among mixed tobacco users. Moreover, the metabolic effects of snus use among both women and men require additional investigation. Measures of visceral obesity are essential in these studies due to their association with insulin resistance and risk of CVD.

## 7 SAMMANFATTNING PÅ SVENSKA

I Sverige snusade 11 % av den vuxna befolkningen 2011 och internationellt ses ett växande intresse för produkten. Kunskaperna om hälsoeffekter av snusanvändning är till viss del begränsade men de höga halterna av nikotin som snusare får i sig gör att det finns anledning att tro att snusanvändning skulle kunna påverka hjärtkärlsystemet och metabolismen. Det övergripande syftet med avhandlingsarbetet var att studera hur snusanvändning påverkar risken att drabbas av olika typer av hjärtkärlsjukdom och risken för viktuppgång. Specifikt studerades risken att drabbas av ischemisk hjärtsjukdom (studie I), hjärtinfarkt (studie III), stroke (studie I och IV) samt sambandet mellan snusanvändning, viktuppgång och fetma (studie II). Eftersom snusanvändning historiskt varit ovanligt bland kvinnor inkluderades enbart män i studierna.

Studie I bygger på data från det Svenska Tvillingregistret och studie II på data från Stockholms folkhälsokohort. Studie III och IV är baserade på data från ett svenskt samarbetsprojekt, "Swedish Collaboration on Health Effects of Snus Use" och inkluderar kohorterna från studie I och II samt sex andra svenska kohorter. Samtliga innehåller information om tobaksanvändning vid baslinjen. I studie I, III och IV följdes deltagarna upp i nationella hälsoregister med avseende på de hjärtkärlsjukdomar som studerades i respektive studie. I studie II jämfördes vikt och body mass index (BMI) vid baslinjemätningen 2002 med vikt och BMI vid uppföljningen 2007. Risken att insjukna och sannolikheten att dö efter insjuknande i hjärtkärlsjukdom, samt sannolikheten att drabbas av fetma ( $BMI \geq 30$ ) eller viktuppgång ( $\geq 5\%$ ), beräknades med multivariata regressionsmodeller. Samtliga huvudanalyser genomfördes antingen utan rökare eller stratifierat på erfarenhet av rökning.

Resultaten visade att snusanvändning var associerat med viktuppgång och en ökad sannolikhet att drabbas av fetma, även när sambanden justerades för flera livsstilsfaktorer. Det fanns ingen skillnad i risk att drabbas av ischemisk hjärtsjukdom (justerat för skillnader i ålder), hjärtinfarkt eller en stroke (justerat för skillnader i ålder och BMI), bland snusare jämfört med personer som inte snusade. Snusarna som drabbats av en hjärtkärlsjukdom verkade dock ha en högre risk att dö, jämfört med de icke-snusare som insjuknat.

Sammanfattningsvis tycks snusare ha en ökad risk att gå upp i vikt och bli feta. Trots att detta är riskfaktorer för hjärtkärlsjukdom observerades inte någon ökad risk för att insjukna i detta bland snusare. Resultaten visade dock en överrisk för död bland insjuknade snusare. Det är möjligt att systematiska fel har påverkat resultaten och lett till under- eller överskattningar av sambanden men ett orsaksamband kan inte uteslutas. Mer forskning om snusets effekter på risken för hjärtkärlsjukdom behövs, där skillnader i livsstilsfaktorer och socioekonomiska omständigheter bör tas i beaktande. Vidare behövs ytterligare studier om det potentiella sambandet mellan snus och metabola sjukdomar. I den mån det är möjligt bör även dessa effekter undersökas separat för kvinnor.



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