Prepared for

RAI Services Company

Winston-Salem, North Carolina

Document type

Report

Date

September 2016

Prepared by

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Amherst, Massachusetts

A SYSTEMATIC, CRITICAL REVIEW OF THE LITERATURE PERTAINING TO THE RISKS OF ORAL AND LUNG CANCERS, CARDIOVASCULAR DISEASE AND RESPIRATORY DISEASES AMONG SNUS AND SMOKELESS TOBACCO USERS



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ACRONYMS AND ABBREVIATIONS

ABI	ankle-brachial index
AMI	acute myocardial infarction
ANOVA	analysis of variance
ARIC	Atherosclerosis Risk in Communities Study
BMI	body mass index
BP	blood pressure
BPM	beats per minute
CHD	coronary heart disease
CI	confidence interval
CIMT	carotid intima media thickness
COPD	chronic obstructive pulmonary disease
CPS	Cancer Prevention Study
CVD	cardiovascular disease
CWC	Construction Workers Cohort
EKG	electrocardiogram
FMD	flow-mediated dilatation
HR	hazard ratio
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
IHD	ischemic heart disease
MDC	Malmo Diet and Cancer cohort
MI	myocardial infarction
MONICA Study	Multinational MONItoring of trends and determinants in CArdiovascular disease
NHANES	National Health and Nutrition Examination Survey I
NHEFS	NHANES I Epidemiologic Follow-Up Study
OR	odds ratio
PIR	poverty index ratio
PMR	proportionate mortality ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QA/QC	quality assurance/quality control
RAIS	RAI Services Company
RE	risk estimate
SALLS	Swedish Annual Living Survey
SALT	Screening Across the Lifespan Twin Study
SCD	sudden cardiac death
SES	socioeconomic status
SBP	systolic blood pressure
DBP	diastolic blood pressure
ST	smokeless tobacco
STS	soft tissue sarcomas
ULF	Swedish Survey of Living Conditions
ULSAM	Uppsala Longitudinal Study of Adult Men
US	United States

VIP	Vasterbotten Intervention Program
WHO	World Health Organization

1 INTRODUCTION

Ramboll Environ was asked by RAI Services Company (RAIS) to conduct and document a systematic, critical review of the pertinent epidemiological literature on the risks of oral and lung cancers, respiratory diseases, and cardiovascular disease among users of snus and other smokeless tobacco (ST) products compared with cigarette smokers and never or non-users of tobacco products. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the conduct of this systematic review was documented in a detailed protocol that includes search and screening strategies, the criteria used to evaluate the quality of the individual studies, and the quality assurance/quality control procedures we employed. The protocol is provided in Appendix A, and search strategies are documented in Appendix B. Data from each study identified as relevant and of sufficient methodological quality were abstracted in a standard format. These data are provided in Appendix C.

Any overall conclusions regarding the health effects associated with use of smokeless tobacco products will require several important assumptions. For example, exposures to consumers in the US will differ due to differences in product composition, to methods of use (e.g., chewed vs. held in the mouth), and to typical portion sizes. Similarly, US products differ from Swedish snus, and snus products also may have changed over time. For an identified health effect to be pertinent, it must be assumed that differences are immaterial to risk. These assumptions are reiterated in each relevant section of the report, which is structured to address the research regarding specific product types, with a synthesis of the evidence supporting and not supporting associations between smokeless tobacco use and health effects included at the end of each section. Because of the etiological differences between each of the health outcomes of interest, no overall discussion section is provided.

Of note, much of the literature, especially the older literature, is methodologically weak, with limited ability to control for confounding by other exposures, such as alcohol use, and little or no information about changes in exposure over time. This report provides a discussion of such limitations. To assist in substantiating our assessments of the methodological quality of each included study, a general overview of epidemiological concepts and study designs is provided in the following section.

2 EPIDEMIOLOGY OVERVIEW

In order to conclude that a specific exposure or other risk factor is capable of causing a particular disease, the body of available relevant epidemiological evidence must be systematically critically evaluated. Results of high quality studies are weighted more heavily in synthesis of the evidence than weaker or flawed studies. Where a weight of evidence assessment of the studies of good quality demonstrates consistently and substantially increased relative risks that are statistically significant and precisely measured (i.e., have narrow confidence limits), and bias, chance and confounding can reasonably be excluded as explanations for the findings, the evidence is consistent with a causal connection.

The validity and strength of epidemiological study results depend on the research approach, study design and data quality and completeness. Factors determining the quality of epidemiological studies include the avoidance of bias, control for potential confounding and inclusion of sufficient numbers of exposed and non-exposed cases to reduce imprecision due to small numbers. Statistical results based on studies in which small numbers of cases are observed are not reliable, even if statistically significant. Results of any single study – especially if based on small numbers – carry limited weight in the assessment of causation.

The degree to which specific diseases are ascertained and studied, as well as the degree to which specific exposures or risk factors are measured also contribute to the validity of any associations observed between these exposures or risk factors and diseases. Combining or grouping diseases with different etiologies can result in various errors, including the dilution of true effects that pertain to one disease only, and creating false associations that do not validly reflect the true relationship between risk factors and a specific disease. Similarly, lack of specificity in estimating exposures can lead to inaccurate or invalid observed associations.

There are two basic epidemiological approaches to identifying associations between risk factors and disease: cohort studies in which disease rates are compared between groups of exposed persons and groups of unexposed persons; and case-control studies in which exposure history among individuals with disease (cases) is compared with exposure history among individuals without the disease (controls). These study designs allow for hypotheses to be tested by analyzing differences in disease rates (i.e., cohort studies) or exposure prevalence (i.e., case-control studies) between the study population and appropriate comparison populations.

Other general approaches include the cross-sectional study, such as disease prevalence surveys, in which exposure and disease outcome are simultaneously ascertained at a point in time and correlations between them evaluated, and proportionate mortality ratio (PMR) analyses. These approaches are simple and inexpensive, but subject to many potential sources of bias. Because these methods do not account for timing of exposure and disease onset, they may be useful for generating hypotheses but are generally unreliable for purposes of determining causation. Therefore, epidemiological evidence based on well-conducted cohort and case-control studies is stronger than evidence from cross-sectional (survey, PMR) and other approaches for purposes of evaluating causation.

In epidemiology, “bias” refers to systematic (or methodological) errors that lead to inaccurate and potentially invalid study results. Most forms of bias can be grouped into three broad categories: selection bias, information bias and confounding bias. The degree to which sources of systematic error leading to potential biases are identified and prevented in the study design, or addressed statistically (as with confounding bias), determine the validity of study results.

Selection bias results from incomplete and/or selective participation of certain subsets of individuals from a study target population, resulting in distorted or invalid results. The degree of bias depends on the type and severity of the selective forces acting upon the study sample.

Information bias results from systematic errors in questionnaire responses, other records including medical records, use of data from proxy respondents for some of the target population, or measured data. Information bias can lead to the misclassification of persons with respect to exposure level or disease status. Recall bias, a type of information bias, can occur when participants with exposures or diseases of interest remember or report their exposure and risk factor experiences differently than comparison participants. For example, mothers of children with birth defects may spend time ruminating on potential causes and therefore recall exposures and activities during pregnancy more completely than mothers of children without birth defects, generating a spurious association.

Reporting bias refers to the provision of selective or sometimes distorted information, and is of special concern for issues perceived as socially negative or embarrassing (e.g., details of illicit drug use or certain sexual behaviors). Interviewer bias can also occur, where persons performing data collection gather data in a different manner (consciously or subconsciously) for different exposure or disease groups. These types of biases are of particular concern when exposure or disease history is self-reported.

Confounding bias occurs due to the failure to account for other risk factors for the same disease outcome that are correlated with the exposure or risk factor of interest. For example, in evaluating the association between air pollution and lung cancer, one must take into account individual smoking histories so that the risks due to smoking are not inappropriately attributed to air pollution. This example of confounding will lead to substantial bias if air quality and smoking are correlated (positively or negatively). In contrast to other forms of bias, the effects of these other risk factors (i.e., confounders), if accurately identified and measured, can be controlled statistically, at least in part. Uncontrolled confounding and residual confounding can result in inaccurate or invalid study results.

Chance – or random or measurement error – also can lead to inaccurate or invalid results. Epidemiologists evaluate the probability that an observed result is due to chance by applying tests of statistical significance. Chance cannot reasonably be ruled out as an explanation for a reported association if the results are not statistically significant. Statistical tests are typically set to accept a 5% rate of committing a type I error, i.e., incorrectly identifying a result as statistically significant. Therefore, by definition, 5% of all statistically significant results arise by chance: even in the absence of a true underlying association, any single result, even if statistically significant, may not reflect a true underlying association. Therefore, statistical significance of a relative risk estimate does not necessarily indicate a valid or causal connection.

Confidence intervals (CIs) describe a range of values for an estimated parameter that are consistent with the study data. Wide confidence intervals indicate low precision in the estimated parameter, usually due to small sample size. Narrow confidence intervals indicate greater precision. Confidence intervals with a Type I error rate of 5% may be used to test statistical significance at the $p < 0.05$ level. Statistical significance is achieved when the 95% CI excludes the null value (for relative risks and odds ratios, this is 1.0). Likewise, if 1.0 falls within the 95% CI, the result is not statistically significant and chance cannot reasonably be ruled out. However, the confidence interval provides no direct indication of where the true parameter might lie (i.e., the validity of the estimated parameter and confidence interval). Furthermore, a large study with narrow confidence intervals that exclude the value 1.0 (i.e., indicating statistical significance) may produce invalid results due to bias in the study design: statistical significance is not an indicator of study validity.

3 METHODS

The PRISMA guidelines define a systematic review as a "review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review" (Moher et al. 2009). Ramboll Environ closely followed all relevant elements of the PRISMA guidelines in conducting this review, including preparation of a detailed study protocol (Appendix A). To facilitate this rigorous process, a 27-item checklist and four-phase flow diagram were created for researchers to use (see Figures A1 and A2 included in the protocol, Appendix A).

3.1 Literature identification

Prior knowledge about this research topic as well as exploratory searches of the National Library of Medicine's PubMed database were used to generate search terms that were as comprehensive and inclusive as possible. A final list of the exposure and outcome terms that were used is presented in Table 1. The Boolean operators "and" and "or" were used to combine search terms and focus results. Searches were completed on October 6, 2015. Filters were set in the PubMed search system to identify studies conducted in human subjects and studies published in the English language through December 31, 2015. In order to capture recently published articles, which might not have been indexed yet, searches were repeated without filters for articles published from January 1, 2015 through October 6, 2015.

We carried out supplemental searches of studies published between 2013 and 2015 whose outcome was indexed simply as "cancer" (i.e., not a specific type of cancer). To confirm that the search strategy successfully captured all relevant literature, the bibliographies of selected, recent review articles and meta-analyses were inspected; this included inspection of the bibliography of the 2002 UST report provided to us by RAIS (UST 2002). Finally, we selected three key studies (Hansson et al. 2012, Henley et al. 2005, Luo et al. 2007) and employed the 'similar article' search feature in PubMed. These had been published relatively recently and investigated all or some of the outcomes of interest in this review.

All search results were imported into ENDNOTE X5 where duplicates from the various search results were removed and references could be stored, labelled, and sorted.

3.2 Screening

The initial screening was split between three epidemiologists who reviewed the titles and abstracts of articles. Studies were considered eligible for inclusion if they: 1) presented primary epidemiological research; 2) examined oral and lung cancers, cardiovascular disease or respiratory diseases as endpoints; and 3) compared snus or smokeless tobacco users with either cigarette smokers or never or non-users of tobacco products. Studies were excluded if they only presented evidence for snus or smokeless tobacco use in those who were also current or former users of other tobacco products. Pertinent literature reviews were also identified.

Following a title and abstract review, each article was marked as relevant, potentially relevant, or not relevant. Articles determined to be not relevant were further marked with a reason. Reasons for exclusion, which were non-hierarchical, were: studies not conducted in humans, studies not published in the English language, duplicate articles (i.e., already identified), papers not presenting primary epidemiological research, studies focused on non-Western tobacco types, and studies with the wrong outcome, exposure, or comparison group. Papers describing literature reviews were marked as being a relevant review, potentially relevant review or not relevant.

Relevant and potentially relevant articles flagged for full text review were distributed randomly among five epidemiologists. Articles determined to be not relevant were assigned a reason for

exclusion. The methodological quality of relevant articles was assessed and articles were judged to be adequate, fair, or inadequate. Elements of each study that were considered in assigning a quality ranking include, in brief: clear and relevant statement of study objectives; adequate description and appropriate study methods that minimize bias; well-defined and accurately measured outcomes; well-defined and specific exposures; consideration of confounding; and use of appropriate analytic methods. Studies rated “adequate” tended to include large cohorts with a sufficient number of exposed and non-exposed participants and participants with the disease, or well-designed case-control studies with, for instance, good response rates; use of appropriate statistical methods; and appropriate control groups and adequate numbers of participants. Studies rated “fair” tended to include cohort and case-control studies with a small number of diseased or exposed individuals, and all cross-sectional studies. The “inadequate” category captured all other study designs including case series and studies that did not include a group of exclusive snus users. Cohort and case-control studies designed or executed with clearly identifiable biases or analyzed using inappropriate methods were also categorized as “inadequate”.

For each adequate or fair quality study, we tabulated the study’s characteristics, abstracted key data, and documented reasons for the methodological quality rating. Each inadequate study was marked as such with reasons.

3.3 QA / QC procedures

Each step in the screening process was coupled with a quality assurance/quality control (QA/QC) step in order to ensure: 1) Relevancy and quality of the literature identified; 2) Adherence to the study inclusion and exclusion criteria; and 3) Consistency of screening practices between the members of the review team involved in screening.

QA/QC procedures for the title and abstract screening process consisted of the selection of a random sample of at least 10% of the relevant or potentially relevant articles and at least 1% of the not relevant articles for review by an epidemiologist who did not participate in the initial screening. QA/QC procedures employed for the full text review and quality assessment were more rigorous than those used for the screening step. An *a priori* decision was made to re-assess at least 20% of adequate and fair quality articles, 5% of inadequate quality, and 5% of not relevant articles. Adequate and fair studies were QA/QC’ed using a ‘round-robin’ design, where each reviewer screened articles previously screened by a different reviewer, such that no reviewer was responsible for QA/QC of an article s/he had previously reviewed. Inadequate and not relevant studies were QA/QC’ed by a single epidemiologist.

All literature screening and QA/QC processes were conducted by trained epidemiologists. Disagreements among screeners identified during the QA/QC were resolved through team discussions and additional screening and QA/QC, as necessary. No formal statistical analysis of inter-reviewer agreement was conducted.

Additional screening documentation is provided in Appendix B.

4 RESULTS

4.1 Searches and Screening

An initial pool of 4,328 unique articles was identified through six processes: a main PubMed search (n=3,346), a search of PubMed without filters for articles published from January 1, 2015 through October 6, 2015 (n=331), a PubMed search using the broad term of cancer as an outcome for the years 2013 to 2015 (n=201), three similar article searches (n=292), a review of the bibliographies of relevant review papers (n=158) and the review of references from the UST report (2002) (no new articles identified, but the disposition of 2 changed). The counts in Figure 1 represent the final disposition of the articles following the screening, team discussions, and QA/QC processes.

Of the 4,328 articles, 3,856 were determined to be not relevant based on screening of titles and abstracts. These articles were excluded for the following reasons, which do not appear in Figure 1: 4 not published in English, 24 not conducted in humans, 593 not a primary epidemiological study, 643 conducted in a population where non-Western products tend to be used, 921 wrong outcome, 1,651 wrong exposure, 1 wrong comparison group, 16 inadequate quality (case report/case series), and 3 duplicates.

The full text of the remaining 472 relevant or potentially relevant articles were obtained and evaluated. Of these, 428 were excluded for the reasons specified in Figure 1. Fourteen studies were judged to be of adequate methodological quality and 30 studies were of fair quality; data abstracted from these 44 studies, and documentation to support their quality ratings, are provided in Appendix C.

Results are presented by health outcome. Within each outcome, evidence is presented separately for studies conducted in US populations and Scandinavian populations, because US and Scandinavian smokeless tobacco products are not identical. However, given the fact that Camel Snus is a Swedish-style snus product in regards to tobacco type, formulation, portion size, production methods, and comparative chemistry, the epidemiology regarding the health effects of snus for Swedish cohorts is considered relevant for evaluating health risks to US users of Camel Snus. In addition to presenting results comparing users of snus and other smokeless tobacco products to never or non-users of tobacco products, results comparing users of snus and other smokeless tobacco products to cigarette smokers are presented, when available.

In addition to discussing the 44 relevant primary epidemiological studies identified through this systematic review, selected literature reviews or meta-analyses published in peer reviewed journals or from documents published by authoritative bodies are discussed. While we did not aim to comprehensively identify and review published literature reviews and meta-analyses, consideration of recent and high-quality articles will help to place our findings and conclusions into context. The discussion of results from a few key meta-analyses will give the reader a quantitative summary of the relationship between smokeless tobacco and a given outcome. If heterogeneity of study population and/or design is properly accounted for, meta-analyses can increase study power and thereby allow examination of uncertainties between suspected relationships by combining data from several studies.

4.2 Respiratory disease

Emphysema, chronic bronchitis, and chronic airway obstruction are related pathological conditions that are commonly combined under the term “chronic obstructive pulmonary disease (COPD),” and are referred to in the proposed advertising for Camel Snus smokeless tobacco products as “respiratory disease.” COPD is characterized by pathophysiological inflammatory changes that result in airflow limitation and the destruction of essential tissue (i.e., lung parenchyma). Cigarette smoking is the dominant risk factor for the development of COPD, with attributable risks around 79%

(USDHHS 2014, p. 660). The incidence of COPD is highly associated with smoking history, and a strong dose-response relationship is consistently reported.

4.2.1 US Studies

Accortt et al. (2002) analyzed data on 14,407 US adults from the first National Health and Nutrition Examination Study (NHANES) conducted from 1971 to 1975, and its follow-up, the NHANES I Epidemiologic Follow-Up Study (NHEFS). Due to the small number of participants with ST use at baseline, ST use data from the 1982-1984 NHEFS were assumed to apply to the NHANES baseline assessment. All participants were followed through 1992 to determine causes of death. The authors reported no elevated risk of non-malignant respiratory disease mortality for either male (HR=0.9, 95% CI: 0.3-2.5) or female (HR=0.6, 95% CI: 0.1-2.3) ever ST users when compared to never tobacco users, adjusting for age, race, and poverty index ratio (Accortt et al. 2002).

Henley et al. (2005) evaluated mortality due to all respiratory system diseases, COPD, influenza, and pneumonia in two US male cohorts: the Cancer Prevention Study (CPS) I cohort and CPS II, and reported conflicting results. The CPS I cohort included 556 respiratory system disease deaths, including 378 deaths from influenza and pneumonia and 90 from COPD, identified during a 12 year (1959 – 1972) follow-up period among 77,407 men who reported never using tobacco or being exclusive chewing tobacco or snuff users at baseline. Adjusting for age, race, education, BMI, exercise, alcohol, fat consumption, fruit/vegetable consumption, and aspirin use, there was a statistically significant 28% increase (HR = 1.28, 95% CI: 1.03-1.59) in mortality from all respiratory system diseases for current ST users compared to the never tobacco users, mainly driven by an 86% increase in COPD mortality risk (HR=1.86, 95% CI: 1.12-3.06) (Henley et al. 2005). Mortality from influenza and pneumonia (combined) was not statistically significantly associated with current ST use (HR=1.16, 95% CI: 0.88-1.51).

The CPS II included 114,809 men who at baseline in 1982 reported never using tobacco or being exclusive current or former users of chewing tobacco or snuff. With 18 years of follow-up (1982 – 2000), there were 1,769 respiratory system disease deaths observed, including 972 from influenza and pneumonia (combined) and 289 from COPD (Henley et al. 2005). In this cohort, adjusting for the same factors as in the CPS I analysis, current ST users did not have statistically significantly elevated mortality risks due to all respiratory system diseases (HR=1.11, 95% CI 0.84-1.45), influenza and pneumonia (HR=0.85, 95% CI: 0.56-1.29), or COPD (HR=1.28, 95% CI: 0.71-2.32). In addition, there was no evidence of a dose-response relationship, a key component of causality determinations, for COPD mortality risk based on frequency or duration of smokeless tobacco use. Similarly, former ST use was not statistically significantly associated with death from all respiratory system diseases (HR=1.10, 95% CI: 0.75-1.62), influenza and pneumonia (HR=1.18, 95% CI: 0.73-1.92), or COPD (HR=1.88, 95% CI: 0.92-3.84) compared to never tobacco use (Henley et al. 2005).

The CPS I and II studies fall short in assessing ST use, which is determined only at baseline. Additionally, in CPS I, questions about former tobacco usage were not asked. Henley et al. (2005) report that they “excluded from the analyses men who volunteered information about former usage.” Moreover, the CPS I and II cohorts in this study were formed in 1959 and 1982, respectively, when the constituents of the ST products might have been different than those of contemporary products, rendering these results inapplicable to the present day. Both studies used a broad case definition that likely includes diseases with different etiologies, which would further reduce and dilute the power of the study. Lastly, as the investigators noted, “the participants in both cohorts reflect the demographic characteristics of the ACS volunteers and are more likely to be more educated, married, middle-class, and white than the general US population (at the time the cohort was formed)”, the results may not directly applicable to a general population (Henley et al. 2005).

The relatively small number of observed COPD deaths in both CPS cohorts could have led to the conflicting results by chance, and provided limited statistical power to detect an association between ST use and COPD mortality. In addition, there was a strong possibility of misclassification of exposure to ST and co-exposures in both Accortt et al. (2002) and Henley et al. (2005). Accortt et al. (2002), like Henley et al. (2005), only assessed ST use once and applied it throughout the duration of the follow-up period. Furthermore, for 10,560 of the 14,407 participants in Accortt et al. (2002), the authors retroactively applied ST exposure status gathered from the 1982-1984 NHEFS to about ten years of follow-up after NHANES enrollment, and also applied that exposure classification to the remainder of the follow-up interval (Accortt et al. 2002).

In summary, these two studies offer no consistent demonstration that smokeless tobacco use in the United States is associated with elevated risk for the respiratory diseases discussed above.

4.2.2 Scandinavian Studies

Epidemiological evidence is scarce regarding Swedish snus use and respiratory disease risk. In a cohort of 9,976 Swedish men aged 15 years or older at enrollment and followed from 1973 to 2002, ever daily users of snus at baseline who reached age 80 years or older during follow-up had a statistically significant increased risk of respiratory deaths compared with never users of snus after adjusting for age, alcohol use, and area of residence; the hazard ratio was 2.0 (95% CI: 1.2-3.4). In contrast, among those younger than age 80 years, there was no elevation in risk (HR=0.8, 95% CI: 0.2-30) (Roosaar et al. 2008). The very wide confidence interval suggests a small number of observed respiratory deaths among those under 80 years of age, indicating low statistical power and the possibility that the conflicting results occurred by chance. In addition, changes in Swedish snus manufacturing process and the likely reduced levels of N-nitrosamines over time could have resulted in the observed disparity in respiratory mortality risk, if the older members of the cohort had used higher risk snus products compared to modern products used by the younger men (Roosaar et al. 2008).

Bolinder et al. (1992) conducted a cross-sectional analysis of the Swedish Construction Workers Study using baseline data collected from 1971 to 1974. In this cohort at baseline, 5,014 daily snus users experienced statistically significantly higher prevalence of morning cough (OR=2.1, 95% CI: 1.8-2.4), breathlessness (OR=1.4, 95% CI: 1.3-1.6), and more than 3 months of coughing per year (OR=1.4, 95% CI: 1.1-1.7) when compared to 23,885 never users of tobacco and adjusted for age. In the same study, 8,823 smokers of at least 15 cigarettes per day experienced even greater prevalence of morning cough (OR=7.9, 95% CI: 7.2-8.5), breathlessness (OR=6.2, 95% CI: 5.5-6.8), and more than 3 months of coughing per year (OR=2.5, 95% CI: 2.2-2.7) compared to never users of tobacco (Bolinder et al. 1992). Though the authors did not discuss these respiratory symptom results, they suggested that the overall impression is that smokers faced more hazards for all symptoms and have a worse health profile compared to snus users (Bolinder et al. 1992). In the absence of information on other exposures and changes in exposure status during the follow-up period, it is possible that confounding or misclassification of smokers as snus users could explain the observed associations with snus use.

In summary, similar to the studies using the US population, these two studies provide inconsistent evidence regarding the association between snus use in Sweden and risk of respiratory diseases or symptoms.

4.2.3 Reviews

Given what is known about the pathobiology of COPD, there would seem to be no plausible mechanistic basis by which smokeless tobacco use would meaningfully contribute to the development of COPD (Foulds et al. 2003, LSRO 2008). To date, no review has examined this question.

4.3 Lung cancer

Limited epidemiological evidence exists regarding the possible risk of association between lung cancer (LC) and smokeless tobacco (ST) use. Three publications conducted in US populations (Accortt et al. 2002, Accortt et al. 2005, Henley et al. 2005) and four studies conducted in Scandinavian populations (Boffetta et al. 2005, Bolinder et al. 1994, Luo et al. 2007, Nordenvall et al. 2013) were identified and determined to be of adequate or fair quality.

4.3.1 US studies

Henley et al. (2005) evaluated mortality due to lung cancer in two US male cohorts: the Cancer Prevention Study (CPS) I cohort and CPS II cohort. The CPS I cohort included 134 lung cancer deaths, identified during the 12 year (1959 – 1972) follow-up period among 77,407 white men aged 30 years or older at enrollment and who reported via mailed enrollment questionnaire that they were never tobacco users or exclusive users of chewing tobacco or snuff. Compared to never tobacco use, lung cancer mortality risk was not statistically significantly associated with current smokeless tobacco use (HR=1.08, 95% CI: 0.64-1.83, 18 LC cases) in a model adjusted for age, race, education level, body mass index, exercise, alcohol consumption, fat consumption, fruit/vegetable intake, and aspirin use.

The CPS II included 114,809 men, who in 1982 were 30 years of age or older and reported never using tobacco or exclusive current or former use of chewing tobacco or snuff. In 18 years of follow-up (1982 – 2000), 418 lung cancer deaths were observed (Henley et al. 2005). Compared to the never tobacco users, there was a statistically significant increase (HR = 2.00, 95% CI: 1.23-3.24, 18 LC deaths) in lung cancer mortality risk for current smokeless tobacco users after adjusting for the factors included in the CPS I model (age, race, education level, body mass index, exercise, alcohol consumption, fat consumption, fruit/vegetable intake, and aspirin use) as well as employment status and type. Hazard ratios were similarly elevated in users of chew who never used snuff (HR=1.97, 95% CI: 1.10-3.54, based on 12 LC cases) and similar but not statistically significant in users of snuff who never used chew (HR=2.08, 95% CI: 0.51-8.46), among whom only 2 lung cancer cases were observed. Substantially elevated and statistically significant hazard ratios were observed for lung cancer in snuff users who were former chew users (HR=9.78, 95% CI: 3.58-26.7), but findings were based on only 4 lung cancer cases. Former smokeless tobacco use was not statistically significantly associated with lung cancer mortality (HR=1.17, 95% CI: 0.43-3.14, 4 LC cases). The limited number of cases available for the lung cancer analysis and the large number of covariates that were included in the models lead to concerns about over-controlling and loss of power (Hosmer et al. 2013, Vittinghoff and McCulloch 2007). Results from models adjusted only for age were similar, and more appropriate considering the small number of events. No clear exposure-response relationship was observed when risk of lung cancer death was examined by times per week spit tobacco was used or by years of use, though risk of death from lung cancer was statistically significantly elevated in those who had used spit tobacco for 30 or more years compared to never tobacco users (HR=2.96, 95% CI: 1.67-5.24, 13 LC cases).

Conflicting results between the CPS I and the CPS II may be explained by chance or by the relatively small number of observed lung cancer deaths in either cohort. Furthermore, non-differential misclassification of the exposure, leading to attenuation of the risk estimates towards the null, is a particular concern in the longest exposed group in each cohort. Tobacco usage was only gathered once, at enrollment in each study, and nothing is known about changes in habits that may have occurred during the 12-18 years of follow-up. Tobacco exposure information is also limited in the CPS I, where questions about former tobacco usage were not asked. Henley et al. report that they "excluded from the analyses men who volunteered information about former usage."

Accortt et al. examined mortality from lung cancer using data from the National Health and Nutrition Examination Survey I (NHANES I) and the NHANES I Epidemiologic Follow-Up Study (NHEFS)

(Accortt et al. 2002). Follow-up lasted for approximately 20 years (1971-75 to 1992) for 13,861 non-institutionalized US adults aged 45 or older, who reported no tobacco use, exclusive smokeless tobacco use, exclusive smoking, or both smokeless tobacco use and smoking (Accortt et al. 2002). Tobacco use was gathered once from a subsample of the population in 1971-75 and again from all participants in 1982-1984. The determination of ever use of smokeless tobacco was based on information reported at either of these time points by the participant or, in those who were deceased by 1982-84, a proxy respondent. Use of proxies for some, but not all, of the data collected may lead to information bias. Among women who were never smokers, a statistically significantly elevated hazard ratio for lung cancer death was observed in those who were ever smokeless tobacco users compared to never tobacco users (HR=9.1, 95% CI: 1.1, 75.4, 3 LC deaths) after adjusting for age, race, poverty index ratio, region of residence, alcohol use, recreational physical activity, and vegetable and fruit intake. Again, the limited number of cases and the large number of covariates that were included in the models lead to concerns about over-controlling and loss of power (Hosmer et al. 2013, Vittinghoff and McCulloch 2007). No lung cancer deaths were reported in men who never smoked, who were exclusive smokeless tobacco users.

In a later study, Accortt et al. examined incident lung cancer using data from NHANES I and the NHEFS (Accortt et al. 2005). A total of 6,779 white or black US adults aged 45 years or older were included and followed from 1971-75 until 1992. In women over the age of 65 years, risk of lung cancer was significantly increased in exclusive smokeless tobacco users compared to never tobacco users (HR=9.6, 95% CI: 1.8-51.2, 4 LC cases total; number of cases in women >65 years not provided) in a model adjusted for race and poverty index ratio. No statistically significant association was seen in those aged 45 to 64 years. No lung cancer cases were identified in male exclusive smokeless tobacco users.

Many of the limitations noted for the CPS I and II cohorts are observed again in the Accortt et al. (2005) analyses of the NHANES I and NFES analysis. Concerns about non-differential misclassification of the exposure result from lack of follow-up information on tobacco usage, and information bias likely stems from the use of proxies to gather information about a portion of participants. Additionally, the few cases available in either of Accortt et al.'s publications led to extremely wide and imprecise confidence intervals.

4.3.2 Scandinavian studies

Three studies evaluated the relationship between smokeless tobacco use and lung cancer incidence or mortality using data from the Swedish construction worker cohort (Bolinder et al. 1994, Luo et al. 2007, Nordenvall et al. 2013). Luo et al. (2007) examined lung cancer risk in an analysis that included 297,897 male Swedish construction workers. A total of 154 lung cancers were found using "essentially complete" nationwide population and health registers during follow-up from 1971 to 2004; information on snus use was gathered during the baseline visit. No increased risk of lung cancer was found in ever users of snus compared to never tobacco users among the 125,576 never-smoking men (RR=0.8, 95% CI: 0.5-1.3, 18 LC cases) after adjusting for age and body mass index. Similarly, no statistically significant associations were observed in former users or current snus users compared to never tobacco users. Furthermore, there was no exposure-response association based in examination of the amount of snus consumed per day (1 to 9 grams, ≥10 grams). Data for smokers were not useful for this portion of the report because of the strong possibility that smokers may have also been smokeless tobacco users.

An earlier study conducted in this population followed 84,781 male workers from 1974 to 1985 for lung cancer mortality, and reported no association with smokeless tobacco use in those aged 35 to 54 (HR=1.2, 95% CI: 0.2-9.1; 1 LC death) or aged 55 to 65 (HR=0.8, 95% CI: 0.1-3.9; 2 LC deaths) (Bolinder et al. 1994). Deaths were identified from the National Cause of Death Register. In contrast, current smokers had significantly higher risks of dying from lung cancer compared to never

users of tobacco in both age groups, and risk was particularly high in those who smoked more than 15 cigarettes per day (35-54 years: HR=21.4, 95% CI: 8.5-54.1, 43 LC deaths; 55-65 years: HR=30.6, 95% CI: 14.6-64.1, 57 LC deaths) versus less than 15 cigarettes per day (35-54 years: HR=8.1, 95% CI: 3.2-20.4, 16 LC deaths; 55-65 years: HR=11.9, 95% CI: 2.2-25.6, 36 deaths).

The most recent study conducted among the Swedish construction workers, published by Nordenvall et al. (2013), identified 40,230 incident cases of cancer among 336,381 male participants who had at least one study visit between 1971 and 1993. These incident cancer cases (median age of 67 at diagnosis) were identified from the Swedish National Cancer Register, which is 96-98% complete, and followed for mortality through 2007; deaths were identified from nationwide registers that are also highly complete. The authors report issues with imprecise mortality estimates for specific cancer sites because of small numbers of deaths. Compared to never users of any tobacco, there was no association between exclusive use of snus and lung cancer mortality (HR = 1.21, 95% CI: 0.71-2.08). The authors note that the point estimate for this non-statistically significant result was higher than that observed in smokers compared to never tobacco users (HR=0.98, 95% CI: 0.78-1.24). Models were adjusted for body mass index, age at diagnosis, calendar period at diagnosis, and cancer site.

A cohort study conducted by Boffetta and colleagues (2005) presented data on the relationship between use of snus and development of lung cancer in 10,136 men living in Norway and among relatives of Norwegian migrants to the US (age not specified). A total of 343 lung cancer cases were found during the more than 30 years of follow-up from 1966 to 2001. Cases were identified from national residence, cancer incidence and mortality registries. Snus use was determined by questionnaire responses at baseline, between 1964 and 1967. In never smokers, no association with lung cancer was observed in ever users of snus compared to never users of tobacco after adjusting for age (HR=0.96, 95% CI: 0.26-3.56; 3 LC cases, all never smokers).

Concerns about misclassification of the exposure, which plague the US studies, are also an issue in publications from the Swedish Construction Workers Study and in the cohort of Norwegian men described in Boffetta et al. (2005); in both studies, tobacco usage information was obtained at baseline. However, the long (over 30 years) duration of follow-up adds strength to the findings from Luo et al. (2007) and Boffetta et al. (2005), as the chances of identifying lung cancer cases, which have a decades-long latency interval, are higher with the longer follow-up. Additional detail and follow-up regarding tobacco usage would have further strengthened their findings. Bolinder et al. and Nordenvall et al. were limited by a small number of lung cancer cases in their efforts to examine lung cancer mortality and survival in incident cancer cases, respectively (Bolinder et al. 1994, Nordenvall et al. 2013). Nonetheless, neither results from these two studies nor the results from Boffetta et al. (2005) and Luo et al. (2007) provide evidence of an association between smokeless tobacco use and lung cancer.

4.3.3 Synthesis of findings

There is little to no evidence that lung cancer risk is associated with snus use based on the Scandinavian studies. The studies conducted in the US that suggest an association between lung cancer and ST use are limited by factors including potentially inadequate exposure assessment, which might have led to misclassification. For example, some of those who were exclusive smokeless tobacco users at baseline may have become smokers during the course of the study period, and some of those who were former smokers at baseline may have been incorrectly categorized as users of only smokeless tobacco according to their status at enrollment. If this misclassification occurred, it could have resulted in the apparent elevated lung cancer risk among nominal exclusive smokeless tobacco users. Additional methodological limitations of these studies include possible information bias, and limited statistical power due to few cases of lung cancer and over-controlled regression models.

4.3.4 Reviews and meta-analyses

Several recent, high quality literature reviews and meta-analyses have been published in peer-reviewed journals or were published by authoritative bodies. Colilla (2010) pointed out that problems with exposure assessment and the likely misclassification of smokers as exclusive smokeless tobacco users may have led to the sporadically observed association between smokeless tobacco use and lung cancer; the author concluded that "the relationship between ST use and lung cancer appears tenuous at best" (Colilla 2010).

In 2007, the International Agency for Research on Cancer (IARC) published a monograph on "the carcinogenic risks associated with the use of smokeless tobacco, including chewing tobacco and snuff" and concluded that "studies on cancers at other sites [including lung cancer] did not provide conclusive evidence of a relationship with smokeless tobacco use" (IARC 2007). The monograph references four epidemiological studies on this topic (Accortt et al. 2002, Boffetta et al. 2005, Henley et al. 2005, Williams and Horm 1977). As a note, we excluded the study published by Williams and Horm because its ST exposure group was not clearly restricted to exclusive users (Williams and Horm 1977). Differences between reviews in the material cited or emphasized can be expected as a result of differing scopes and other review parameters (Rosen and Suhami 2016).

Meta-analyses provide a quantitative summary of findings between an exposure and an outcome and can increase power and examine uncertainties between suspected relationships. Lee and Hamling's meta-analysis (Lee and Hamling 2009a) found no statistically significant increase in lung cancer risk in never smokers who used smokeless tobacco in either studies conducted in the US (RR/OR=1.38, 95% CI: 0.72-2.64) or conducted in Scandinavia (RR/OR=0.82, 95% CI: 0.52-1.28). Results were not substantially different when studies that reported results in smokeless tobacco users after adjusting for smoking were included. They report that there was "considerable heterogeneity" as a result of "the high RR of 6.80 (1.60–28.5) in never smokers in NHANES I (Accortt et al. 2005), the significant increase of 1.77 (1.14– 2.74) from CPS-II (Henley et al. 2005), and the low RR of 0.70 (0.60–0.70) for the Swedish construction workers study (Luo et al. 2007)." Again, as a note, we included five of nine studies Lee included (Accortt et al. 2005, Boffetta et al. 2005, Henley et al. 2005, Luo et al. 2007). The remaining four studies were judged to be inadequate for our review (Doll and Hill 1952, Williams and Horm 1977, Winn et al. 1982, Wynder and Stellman 1977).

A second meta-analysis that relied on a more limited body of the same literature (Boffetta et al. 2005, Henley et al. 2005, Luo at al. 2007) also did not observe a significantly elevated risk of lung cancer among smokeless tobacco users in studies conducted in the United States (RR=1.8, 95% CI: 0.9-3.5) or in studies conducted in Nordic countries (RR=0.8, 95% CI: 0.6-1.0) and reported that "results on lung cancer risk are inconclusive" (Boffetta et al. 2008). Lee and Hamling undertook an assessment of their review and meta-analysis process compared to that of Boffetta et al. (Lee and Hamling 2009b). Lee and Hamling concluded that they "cannot evaluate the lung cancer meta-analyses of Boffetta et al. due to their only providing four of the five individual RRs they used," but note that they "agree that an association has not been demonstrated" (Lee and Hamling 2009b).

Findings and limitations reported in these documents are consistent with the study design issues we noted in our discussion of individual studies.

4.4 Oral Cancer

The "oral cavity" is a heterogeneous tissue composed of a number of subsites. According to the World Health Organization (WHO), the oral cavity includes the lips, the inside lining of the lips and cheeks (buccal mucosa), the teeth, the gums, the front two-thirds of the tongue, the floor of the mouth below the tongue, the front, bony portion of the roof of the mouth (hard palate), and the area behind the wisdom teeth (retromolar trigone) (WHO 2005). The terms "oral cavity cancer" and "oral cancer" will be used synonymously. The oropharynx includes the base of the tongue (the back third

of the tongue), the soft palate (the back part of the roof of the mouth), the tonsils, and the side and back wall of the throat. Studies that report tobacco-related risks for cancer of the oral cavity and oropharynx have sometimes considered these sites separately. Other studies have combined these sites, and some have even included such unrelated sites as the larynx and esophagus.

4.4.1 US Studies

Eight published studies reported on the association between ST use and risks of oral cancers in the US, though each study defined endpoints differently, rendering it difficult to draw overall conclusions. Keller et al. (1970) was the first study to examine the relative risk of oral cancer among exclusive smokeless tobacco users. Using a 20% sample of the medical discharge data from over 160 veterans' (VA) hospitals, 304 histologically confirmed cases of basal or squamous cell carcinomas (SCC) of the extra-oral labial mucous membrane were matched with an equal number of cancer controls with SCC of the mouth, mesopharynx, or hypopharynx, and an additional control group representative of the VA hospital population. All controls were matched by age, race, and hospital site (Keller 1970). Restricting analyses to only white males, the authors reported that of the combined 602 oral cancer patients from both cases and the cancer controls with SCC of the mouth, mesopharynx, or hypopharynx, 12 reported exclusive ST use compared to 3 in 265 general hospital population controls. Though the authors did not report an estimate for exclusive ST use, an unmatched, unadjusted odds ratio and confidence interval can be calculated according to the authors' methods (OR=1.78, 95% CI: 0.50-6.35), indicating a non-statistically significant increase in risk of oral cancer among exclusive ST users compared to tobacco non-users.

In another study of male military veterans, Zahm et al. (1992) analyzed data from 248,046 veterans who provided ST use data on a mailed questionnaire in 1954 or 1957 (Zahm et al. 1992). Through 1980, there were no deaths due to soft tissue sarcomas (STS) of head, face, neck, trunk, upper and lower limbs, multiple, unspecified, and unknown sites among 2,308 exclusive ST users (Zahm et al. 1992). In contrast, there were 64 cases of STS mortality among 120,470 exclusive smokers compared with tobacco non-users, yielding a statistically significantly elevated risk of STS (RR=1.8, 95% CI: 1.1-2.9) (Zahm et al. 1992).

Data from two studies of women residing in rural counties of South Carolina suggest a statistically significant, positive association between current use of snuff (type not specified) and incidence of oral and pharyngeal cancer as a combined endpoint (Winn et al. 1981, Winn et al. 1984). Using hospital records and death certifications, 255 cases of oral and pharyngeal cancer cases were identified and matched with two female controls according to age, race, source of ascertainment (hospital or death certificate), and county of residence. Overall, there was a statistically significant increase in oral and pharyngeal cancer risk among current snuff users compared with non-users of tobacco (OR =3.8, 95% CI: 2.3-6.3) (Winn et al. 1984). When data were stratified by race/ethnicity, the association was observed among white (OR=4.2, 95% CI: 2.6-6.7) but not among African-American women (OR=1.5, 95% CI: 0.5-4.8) (Winn et al. 1981). In addition, the authors reported on patterns of risk associated with increasing duration of use. For cancers of gum and buccal mucosa, those who had used snuff for 1 to 24 years had a RR of 12.8 (95% CI: 1.9 to 98); the risks were similar for those who used snuff for 25 to 49 years (RR=12.6, 95% CI: 2.7 to 58.3); and RR for those with more than 50 years of snuff use was 47.5 (95% CI: 9.1 to 249.5), compared to non-users of tobacco. Although these are unstable estimates, they suggest increasing risks associated with longer duration of snuff use. Odds ratios for mouth and pharynx cancers, but not cancers of the gum or buccal mucosa, ranged from 1.7 to 3.8, with only the middle category of duration associated with a statistically significant increase in risk (25-49 years of snuff use, 95% CI: 1.5-9.6). In contrast, a consistently increasing exposure-response relationship was reported for smokers in the study, with odds ratios ranged from 1.1 – 4.6 for oral cavity cancers and 1.3-9.6 for pharyngeal cancers. These studies have been criticized for their failure to adequately control for other risk factors for oral

cancers, including alcohol consumption and possible use of smoked tobacco by snuff users (Colilla 2010, Rodu and Cole 2002, Weitkunat et al. 2007).

A later case-control study by Blot et al. (1988) reported a similarly increased risk for oral and pharyngeal cancers among women in urban centers the US, though they also did not control for alcohol consumption in their analyses of exclusive ST users. Gathered from cancer registries covering four metropolitan areas and the state of New Jersey, 1,114 cases of oral and pharyngeal cancers were frequency matched for age, sex, and race with 1,268 population controls from the same area. After adjusting for age, race, study location, and respondent status (self vs. next of kin), female exclusive ST users had over a 6 fold increase in odds of oral and pharyngeal cancers compared with non-users of tobacco (OR=6.2, 95% CI: 1.9-19.8). Comparisons of relative odds for ST users and smokers are not possible because all reported models of exclusive smokers additionally controlled for alcohol consumption. In addition, the effect estimate should be interpreted with caution as the analyses were based on approximately 14 female exclusive ST users in the study population, leading to unreliable estimates due to low statistical power (i.e., small numbers) and a model that contains too many covariates (Hosmer et al. 2013, Vittinghoff and McCulloch 2007).

In two publications, Accortt et al. (2002, 2005) linked data from the National Health and Nutrition Evaluation Study (NHANES) with the NHANES-Epidemiologic Follow-Up Study (NHEFS). In brief, 14,407 non-institutionalized US adults were gathered from 1971 to 1975 and followed up through 1992. Due to the small number of participants with ST use data at baseline, ST use data from the 1982-1984 NHEFS were retroactively applied to baseline exposure assessments. All participants were followed through 1992 (Accortt et al. 2002, 2005). At the end of follow-up, there were no deaths due to oral cancer among 505 exclusive snuff or chewing tobacco users compared to 0.8 expected. In contrast, there were 11 deaths due to oral cancer among 5,523 exclusive smokers compared to 3.8 expected (SMR=2.88, 95% CI: 1.42-4.80) (Accortt et al. 2002).

Henley et al. (2005) evaluated the risk of mortality due to oropharyngeal cancer among users of chewing tobacco or snuff vs. never users of tobacco in the first and second Cancer Prevention Studies (CPS I and CPS II). There were 13 observed deaths from oropharyngeal cancer among 77,407 men included in the CPS I during the twelve year follow-up period (1959 to 1972), and 46 in the CPS II cohort of 114,809 men who were followed for 18 years, from 1982 to 2000. In the CPS I cohort, there was a suggestive, but non-statistically significant two-fold increase (HR = 2.02, 95% CI: 0.53-7.74, 4 deaths) in oropharynx cancer mortality risk for current ST users, adjusting for age, race, education, BMI, exercise, alcohol, fat consumption, fruit/vegetable consumption, and aspirin use (Henley et al. 2005). However, adjusting for the same factors, current ST users in the CPS II cohort did not have elevated risk of oropharynx cancer (HR=0.90, 95% CI: 0.12-6.71) (Henley et al. 2005). The small number of deaths in both cohorts could have led to the conflicting results by chance, and provide limited statistical power to detect an association between ST use and oropharynx cancer mortality, if one exists. Overall, there appears to be no epidemiological evidence of an effect of ST use on oropharynx cancer mortality in these cohorts.

In the most recent study, Zhou et al. (2013) analyzed data from a case-control study of 1,046 cases of head and neck squamous cell carcinoma and 1,239 controls matched on age, sex, and town of residence gathered from the Greater Boston area. Mailed questionnaires gathered data on self-reported ST use (type not specified). Among never smokers, cases were over 4 times more likely to report ST use as compared to controls (OR=4.21, 95% CI: 1.01-17.57), controlling for age, sex, race, education, and alcohol consumption. This association was most pronounced among those who reported heaviest usage of ST, including those who reported using ST for 10 or more years (OR=13.21, 95% CI: 1.53-114.46, p for trend=0.018) or more than 7 times per week (OR=5.11, 95% CI: 0.47-55.94, p for trend = 0.142) (Zhou et al. 2013).

The strongest associations between ST use and oral cancers were reported by case-control studies (Blot et al. 1988, Winn et al. 1981, Winn et al. 1984, Zhou et al. 2013), which typically report higher risk estimates than cohort studies and are known to be susceptible to selection and recall biases. Information bias is a particular concern when data are collected through proxy interviews for a proportion of the study population, such as kin of the deceased. For example, given that the data for 51% of cases and 21% of controls from Winn et al. (1981, 1984) were obtained through proxy interviews, the possibility of misclassification of exposure both to ST and to potentially important co-exposures, such as smoked tobacco and alcohol, is high. All estimates from the case-control studies were unstable, being generated from a small number of cases and controls who were exclusive ST users. In addition, most of the estimates were unadjusted for potential confounding factors. By comparison, cohort studies of ST use and oral cancers (Accortt et al. 2002, Accortt et al. 2005, Henley et al. 2005, Zahm et al. 1992) included larger numbers of exclusive ST users, fewer numbers of cancer cases, and more inconsistent results. The small number of cancer cases in the NHANES-NHEFS and both CPS cohorts provided limited statistical power to detect an association and could have produced the conflicting results by chance. In addition, there was a strong possibility of misclassification of exposure to ST and co-exposures, as ST use was only assessed at baseline in all studies, and was assumed to remain consistent throughout the duration of the follow-up period. Furthermore, for 10,560 of the 14,407 participants in Accortt et al. (2002, 2005), the authors retroactively applied ST exposure status gathered from 1982-1984 to prior years of follow-up (Accortt et al. 2002, Accortt et al. 2005).

Overall, the epidemiological data are inconsistent in the exposures and outcomes evaluated, and reported inconsistent results regarding associations between head and neck cancers and ST use in the US. Despite the strong associations presented in the older case-control studies, methodological problems in most of the case-control studies and in the cohort studies preclude conclusive judgment. The methodologically strongest study in this group, (Zhou et al. 2013), suggests a positive association may exist between ST use and SCC of the head and neck, but one study is an insufficient basis for reaching a causal conclusion.

4.4.2 Scandinavian Studies

Lewin et al. (1998) completed a population-based case-control study of 1,361 Swedish men, aged 40 to 79 years during 1988-1991, including 605 cases of head and neck cancer and 756 controls matched on age and residential region. The authors reported elevated incidence of head and neck cancer among ever (OR =4.7, 95 % CI: 1.6-13.8) and current (OR = 3.3, 95% CI: 0.8-12) snus users compared with never users of tobacco, based on unadjusted analyses of nine cases and 10 controls (Lewin et al. 1998). The highest point estimate was observed for odds of incident oral cancer among former snus users vs. never users of tobacco (OR = 10.5, 95% CI: 1.4-117.8), suggesting that a diagnosis of oral cancer might encourage snus users to quit. In this population, risks of head and neck cancers associated with ever snus use (OR = 0.8, 95% CI: 0.5-1.2), current snus use (OR=0.6, 95% CI; 0.3-1.1), and former snus use (OR=1.0, 95% CI: 0.5-2.0) were unexpectedly similar to risks associated with cigarette smoking (Lewin et al. 1998).

Schildt et al. (1998) reported a small, non-statistically significant decrease in risk of squamous cell oral cancer among current snus users versus non-users (OR=0.7, 95% CI: 0.4-1.2), based on 19 cases and 23 controls within a population-based case-control study of 708 participants from 4 counties of Sweden. In contrast, active smokers had a statistically significant 70% increased risk of oral cancer compared to never tobacco users (OR=1.7, 95% CI: 1.1-2.6). The risk was increased among former snus users compared to never smokers (OR=1.8, 95% CI: 0.9-3.5), but it was not statistically significant. In fact, increased risks were observed for former snus users regardless of smoking habits, but only statistically significantly so if the subjects were also active smokers (OR=3.1, 95% CI: 1.4-6.8); there were only 3 cases and 1 control who reported such history.

A cohort of 9,976 Swedish men enrolled in 1973 and followed until 2002 identified 11 cases of oral and pharyngeal cancer among reported never smokers at baseline. Compared to never daily use of snus, ever daily use of snus was associated with a non-statistically significant increased risk of oral and pharyngeal cancer (HR=2.3, 95% CI: 0.7-8.3) after adjusting for age, alcohol use, and area of residence (Roosaar et al. 2008). The small number of head and neck cancer cases implies low statistical power and the possibility that the conflicting results occurred by chance.

Luo et al. (2007) conducted an analysis of 279,897 participants in the Swedish Construction Workers Study who reported tobacco use habits from 1971 to 1974. Followed up through 2004, 50 cases of oral cancer were observed among never tobacco users, 10 among ever snus users, and 198 among ever smokers. Compared to never users of tobacco, there was no increased incidence of oral cancer among ever (HR=0.8, 95% CI: 0.4-1.7), former (HR=0.7, 95% CI: 0.1-15.0), or current (HR=0.9, 95% CI: 0.4-1.8) snus users, adjusting for age and BMI. In addition, there was no evidence of a gradient in risk associated with daily use of snus less than vs. more than 10 grams. In this cohort, current smokers at baseline had significantly elevated risk of oral cancer (HR=2.5, 95% CI: 1.7-3.5) compared to never smokers.

Similar to studies in the US, the largest magnitude estimates of an association between snus use and oral cancers were reported by case-control studies (Lewin et al. 1998, Schildt et al. 1998). Both case-control studies also reported higher risk of oral cancers for former users of snus compared to current users, which suggests that disease symptoms prior to diagnosis may provoke a change in tobacco use habits. Cohort studies (Luo et al. 2007, Roosaar et al. 2008) reported no statistically significant elevated risk of oral cancers for exclusive snus users, but Roosaar et al. (2008) reported an elevated point estimate of effect. Overall, Scandinavian studies of oral cancer risk and snus use suggest, somewhat inconsistently, that Swedish snus may be associated with elevated risk for head and neck cancers (Lewin et al. 1998, Roosaar et al. 2008) and squamous cell oral cancers (Schildt et al. 1998).

4.4.3 Reviews and Meta-Analyses

Several high quality literature reviews (Colilla 2010, Critchley and Unal 2003, IARC 2007, Lee 2011, Lee 2013) and meta-analyses (Boffetta et al. 2008, Gross et al. 1995, Lee and Hamling 2009a, Rodu and Cole 2002, Weitkunat et al. 2007), evaluating the association between smokeless tobacco use and oral cancers have been published in peer reviewed journals or by authoritative bodies. These reviews have consistently highlighted that methodological issues, particularly low number of ST users or oral cancer cases, limit the ability of studies to demonstrate an association between smokeless tobacco use and oral cancer. In addition, several reviews pointed out that the strongest evidence for an association between ST use and oral cancer was provided by older studies, in which ST products provided higher levels of TSNAs compared with modern products (Colilla 2010, Critchley and Unal 2003, Lee and Hamling 2009a, Lee 2013).

Results from the meta-analysis of Boffetta et al. (2008) suggested important differences in risk for oral cancer among US smokeless tobacco users (various types of products) versus Norwegian or Swedish snus users. Analyses using 9 estimates from US studies indicated a statistically significantly increased mortality risk for oral cancer (RR= 2.6; 95% CI: 1.3-5.2). However, four estimates based on studies in Norway and Sweden did not show any increased risk of death from oral cancer among snus users (RR = 1.0, 95% CI: 0.7-1.3). No details were provided regarding the methodology of the meta-analysis, but it does include studies of mixed ST and cigarette users. Several older, similar meta-analyses of mixed users reported similar results indicating elevated oral cancer risk among ST users in the US, but not Norwegian or Swedish snus users (Gross, et al. 1995, Rodu and Cole 2002, Weitkunat et al. 2007).

The meta-analysis conducted by Lee and Hamling (2009a) of US. studies providing estimates of "oropharyngeal cancer" risk (which included studies of oral cancer) and smokeless tobacco use considered 29 studies providing 31 separate risk estimates (Lee and Hamling 2009a). Of the 31 estimates, 19 reported low but statistically significantly elevated risks for oropharyngeal cancer. Meta-analysis of the data from all 31 estimates suggested that , after adjusting for smoking, smokeless tobacco use is associated with an increased risk of oropharyngeal cancer (RR/OR=1.65; 95% CI: 1.22-2.25). Using the five estimates with never-smokers as referent group resulted in a risk estimate of RR/OR= 3.33 (95% CI: 1.76-6.32). Using the two estimates with never-smokers as the referent group, but adjusted for alcohol consumption, a statistically nonsignificant, but still elevated risk of RR/OR= 1.58 (95% CI: 0.52-4.81) persisted. Many of the higher risk estimates for oral cancer among smokeless tobacco users come from dated studies that either did not adjust for cigarette smoking or alcohol consumption, or reflected the use of either older products or dry snuff (e.g., Winn et al. 1981). In comparison, Scandinavian ST studies did not show an elevated risk of oropharyngeal cancers in snus users adjusted for smoking (RR/OR=0.97; 95% CI: 0.68-1.37; 7 studies), or when restricted to never smokers (RR/OR=1.01; 95% CI: 0.71-1.45; 4 studies) (Lee and Hamling 2009a, Lee 2011, Lee 2013).

A published comparison of the Boffetta et al., (2008) and Lee & Hamling (2009a) meta-analyses attributed the difference in findings to the use by Lee and Hamling of a more consistent approach for selecting between study-specific never-smoker and combined smoker/non-smoker estimates, the use of derived as well as published estimates. Lee and Hamling additionally contend that the Boffetta et al. (2008) meta-analysis included biased estimates Lee & Hamling (2009b), but the statement is not clearly substantiated and Boffetta et al. described their methods in insufficient detail to allow for comment Some differences between reviews, i.e., in the papers identified and estimates selected for emphasis, can be expected as a result of differing scopes and other review parameters, and should not immediately lead to the conclusion that one review is correct and the other incorrect (Rosen and Suhami 2016). Nonetheless, most meta-analyses suggest an increased risk of oral cancers associated with ST use in the US, but not Scandinavia.

In contrast to the sharp distinction between data from the US and Scandinavia highlighted in the reviews described above, IARC concluded that "The studies from the USA, Asia and Africa — in particular, one study from the USA and four studies from South Asia — provide sufficient evidence for a causal association of smokeless tobacco use with oral cancer." (IARC 2007, p. 129-191, 327). The working group continued to suggest that, while Swedish studies did not show the same level of risk associated with ST use, they are "not inconsistent" with positive studies from other regions (IARC 2007, p.327).

Overall, the authors of the reviews and meta-analyses identified the same study design issues we noted in the discussion of individual studies, above, and arrived at similar conclusions. Despite the inconsistent definition of oral cancers and mixture of exposures captured in the "ST" category in the US studies, there is suggestive evidence that risk of oral cancer is elevated among ST users, mostly driven by results of case-control studies. Results from Scandinavian studies follow the same trend, with case-control studies showing statistically significant associations while cohort studies generally have not reported elevated risks of oral cancer among snus users. The strongest evidence suggesting an effect of ST and snus use on oral cancer risk comes from older studies or cohort studies that included exposure to products that likely had higher levels of nitrosamines than are typically found in more modern products, especially snus.

4.5 Cardiovascular disease: overview

Cardiovascular disease (CVD) includes diseases of the heart and/or vascular (blood vessel) system, including hypertension, ischemic heart disease (IHD; also commonly referred to as coronary heart disease, CHD), cerebrovascular disease, atherosclerosis, aortic aneurysm (AA), and peripheral artery

disease (PAD). Clinical events that may result from these conditions include stroke (for cerebrovascular disease) and myocardial infarction (MI, for IHD or CHD). Epidemiological studies typically rely on reported clinical events rather than diagnoses of their underlying conditions since data on clinical events are more easily obtained.

Our review identified 33 studies that examined the association between use of smokeless tobacco (ST) and cardiovascular outcomes. Most of these studies were conducted in Sweden, while a handful were conducted in the US. The studies focused on the following cardiovascular system events: 1) "all CVD," which includes multiple and/or combined adverse cardiovascular events; 2) IHD/CHD; 3) MI; 4) blood pressure and hypertension; 5) stroke and cerebrovascular disease; and 6) changes in miscellaneous indicators of cardiovascular dysfunction, e.g., flow mediated dilatation and heart rate variability.

4.5.1 All cardiovascular disease

4.5.1.1 US studies

Two publications conducted in US populations examined CVD mortality (Accortt et al. 2002, Henley et al. 2005). These analyses were based on data from the National Health and Nutrition Examination Survey I (NHANES I), NHANES I Epidemiologic Follow-up Study (NHEFS), and the Cancer Prevention Study (CPS) I and II.

The definitions of CVD for results presented in this section are broad for both Henley et al. (2005) and Accortt et al (2002). In the CPS I analysis, Henley et al. (2005) included the International Classification of Diseases, Seventh Revision (ICD-7) codes 330-468 in their definition of CVD mortality. This range of codes included multiple sclerosis, other diseases of the nervous system and sense organs, rheumatic heart disease including fever, hypertension with heart disease, IHD, chronic disease of the endocardium, conductive disorder, other diseases of the heart, cerebrovascular disease, hypertension without heart disease, and diseases of the arteries, veins and lymphatic vessels. In the CPS II analysis, Henley et al. (2005) used a narrower range of outcomes to define CVD mortality by including the International Classification of Diseases, Ninth Revision (ICD-9) codes 390-459, which exclude multiple sclerosis and other diseases of the nervous system and sense organs, but include the other conditions listed above. Accortt et al. (2002) also included deaths coded 390-459 within ICD-9, but refers to this category as "diseases of the circulatory system". A third study conducted in a US population examined incidence of CVD (Yatsuya et al. 2010). These analyses of data from the Atherosclerosis Risk in Communities Study (ARIC) used a more focused definition of CVD defined as fatal coronary heart disease, hospitalized and/or electrocardiogram-confirmed MI, cardiac procedure, or stroke.

Henley et al. (2005) evaluated CVD mortality as defined above in two US male cohorts: the CPS I cohort and CPS II cohort. The CPS I cohort included 7,777 CVD deaths, identified during the 12 year (1959–1972) follow-up period among 77,407 white men aged 30 years or older at enrollment and who reported via enrollment questionnaire that they were never tobacco users or exclusive users of chewing tobacco or snuff. Compared to never tobacco users, CVD mortality was elevated and statistically significantly associated with current ST use (HR=1.12, 95% CI: 1.03-1.21, based on 1,399 deaths) in a model adjusted for age, race, education level, body mass index (BMI), exercise, alcohol consumption, fat consumption, fruit/vegetable intake, and aspirin use. Those who reported prevalent heart disease, diabetes, or stroke in 1959 were excluded from these analyses.

The CPS II included 114,809 men, who in 1982 were 30 years of age or older and reported never tobacco use or exclusive current or former use of chewing tobacco or snuff. In 18 years of follow-up

(1982–2000), 8,967 CVD deaths, defined above, were observed in the CPS II (Henley et al. 2005). Compared to the never tobacco users, there was a statistically significant increase (HR = 1.23, 95% CI: 1.09-1.39, 278 deaths) in CVD mortality risk for current ST users after adjusting for the factors included in the CPS I model (age, race, education level, BMI, exercise, alcohol consumption, fat consumption, fruit/vegetable intake, and aspirin use) as well as employment status and type. Hazard ratios were similarly elevated in users of chew who never used snuff (HR=1.26, 95% CI: 1.09-1.46, 186 deaths), of similar magnitude but not statistically significant in users of snuff who never used chew (HR=1.38, 95% CI: 0.99-1.92, 36 deaths), and in users who used both snuff and chew (HR=1.26, 95% CI: 0.91-1.75, 37 deaths). The smaller number of deaths in these subsets limits the statistical power to detect differences between users and non-users. Additionally, the regression models may be over-controlled, i.e., the number of covariates is too large for the number of cases, which would result in an underestimate of the actual association, if one exists (Hosmer et al. 2013, Vittinghoff and McCulloch 2007) No associations were observed in former users, chew users who were former snuff users, or snuff users who were former chew users. No clear exposure-response relationship was observed when risk of CVD death was examined by number of times per week spit tobacco was used or by years of use. Statistically significant elevations, though, were noted in those who used spit tobacco for 30 or more years (HR=1.24, 95% CI: 1.05-1.45, 160 CVD deaths) and in those who used it fewer than 7 times per week (HR=1.37, 95% CI: 1.03-1.82, 49 CVD deaths).

CPS I and CPS II provide a large number of CVD deaths to sufficiently examine the questions at hand and adjust models for a wide range of factors in the more common exposure groups and in overall analyses, but not in the less common exposure categories. As noted earlier, the study falls short in its assessment of ST use, which occurred only at baseline. Additionally, in CPS I, questions about former tobacco usage were not asked. Henley et al. (2005) report that they “excluded from the analyses men who volunteered information about former usage.” Moreover, the CPS I and II cohorts in this study were formed in 1959 and 1982, respectively, when the constituents of the ST products might have been different than those of contemporary products, again rendering these results inapplicable to the present day. Both studies used a broad case definition that likely includes diseases with different etiologies, which would further reduce and dilute the power of the study. Lastly, as the investigators noted, “the participants in both cohorts reflect the demographic characteristics of the ACS volunteers and are more likely to be more educated, married, middle-class, and white than the general US population (at the time the cohort was formed)”, the results may not directly applicable to a general population (Henley et al. 2005).

Accortt et al. examined mortality from diseases of the circulatory system using data from the NHANES I and NHEFS (Accortt et al. 2002). Follow-up lasted for approximately 20 years (1971-75 to 1992), and included 13,861 non-institutionalized US adults aged 45 or older, who reported no tobacco use, exclusive ST use, exclusive smoking, or both ST use and smoking (Accortt et al. 2002). Information on ST use was gathered once from a subsample of the population in 1971-75, and again from all participants in 1982-84. The determination of “ever use” of ST was based on information reported at either of these time points by the participant or, in those who were deceased by 1982-84, a proxy respondent. Compared to never tobacco users, there was no association between exclusive ST use and diseases of the circulatory system observed in men (HR=1.0, 95% CI: 0.7-1.5) or women (HR=1.2, 95% CI: 0.7-1.9) in models adjusted for age, race, and poverty index ratio. The specific number of circulatory disease deaths was not reported, but was noted to be at least 30. As with Henley et al. (2005), concerns about non-differential misclassification of the exposure result from lack of follow-up information on tobacco usage, and any association with cardiovascular disease, if one exists, will be diluted and likely attenuated due to use of a non-specific case definition. Additionally, tobacco habits other than smoking and ST use were not considered when

determining never tobacco use status. Lastly, the possibility of information bias stems from the use of proxies to gather information about a portion of participants.

Yatsuya et al. (2010) examined the association between incident CVD and ST use using data from the Atherosclerosis Risk in Communities (ARIC) Study cohort. Subjects in the ARIC Study cohort were selected by probability sampling from four US communities. At baseline (1987-1989), 15,792 men and women aged 45-64 were recruited; after exclusions, 14,498 subjects remained for analysis. Tobacco habits were assessed at baseline; the “smokeless tobacco” definition included both chewing tobacco and snuff. Subjects were followed for incidence of cardiovascular disease and stroke through 2005. The authors ran models stratified by current smoking status and adjusted for age, sex, race, study center, education, income, alcohol use, physical activity, never/past cigarette smoking (in current non-smokers), pack-years of smoking, pipe/cigar use, and exposure to secondhand smoke. The authors separately examined associations between never cigarette smokers and past cigarette smokers, noted that the results were “virtually identical,” and only presented results for the combined category including never and past cigarette smokers. Data for the combined category of never and former smokers are reported here. Among current non-smokers, former ST users did not show elevated risk of CVD and stroke (HR = 0.90, 95% CI 0.73-1.11) compared to currently non-smoking never ST users. However, current non-smokers who were current ST users showed a slightly elevated risk of CVD and stroke (HR = 1.31, 95% CI 1.06-1.61) compared to current non-smokers who never used ST. Models of the risk of CVD and stroke from cigarette smoking included ST users in all comparison groups, and are therefore not useful in comparing risks associated with ST use versus cigarette smoking. Again, this study is limited by measuring tobacco exposures only at baseline and by use of mixed categories of both exposure and outcome. Any specific associations between chewing tobacco or snuff and CVD, if they exist, will likely be attenuated towards the null in these analyses.

In spite of their methodological limitations, results from the CPS I and II and the ARIC study provide some suggestion of an association between ST use and CVD. All identified studies provide a sufficient number of cases, lengthy follow-up periods, appropriate age ranges, and adequate adjustment for confounding, at least in the exposure groups with larger numbers of cases. They fall short in their assessment of ST usage and use of non-specific case definitions, and differ in their definitions of both exposure and outcomes. Non-differential misclassification of the exposure is a particular concern in the longest exposed groups in each cohort, because tobacco usage was only assessed early in the study period and nothing is known about changes in habits that may have occurred during follow-up. Use of proxies to gather information about a portion of participants in the NHANES I and NHEFS study published by Accortt et al. may introduce information bias, particularly if proxy data were more commonly collected for cases and were more accurate or complete for certain exposure groups (including non-exposed) (Accortt et al. 2002).

4.5.1.2 Scandinavian studies

Two publications using data from the Swedish Construction Workers cohort have examined CVD (Bolinder et al. 1992, Bolinder et al. 1994). Bolinder et al. (1992) examined “cardiovascular diagnoses” obtained from the disability pension diagnoses from the Swedish National Social Insurance Board, but provided no information about the specific diagnoses included. A clearer definition is provided by Bolinder et al. in their 1994 publication, where CVD mortality is defined using underlying causes of death from International Classification of Diseases, 8th revision (ICD-8) codes 390-458 (rheumatic heart disease including fever, hypertension with heart disease, IHD, chronic disease of endocardium, conductive disorder, other diseases of the heart, cerebrovascular disease, hypertension without heart disease, and diseases of the arteries, veins, and lymphatic vessels). Two additional Swedish studies were identified on this topic, one conducted among Swedish twins who participated in the Screening Across the Lifespan Twin Study (SALT) (Hansson et al. 2009)

and one conducted in male residents of Uppsala county (Roosaar et al. 2008). Hansson et al. (2009) defined CVD as the first recorded ischemic heart disease (IHD) or stroke diagnosis, where IHD included hospitalization or death from MI or coronary revascularization procedures and stroke included hospitalization or death from acute ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, transient ischemic attack or unspecified cerebral hemorrhage. They note that main and contributing discharge diagnoses were used. Roosaar et al. (2008) defined CVD as deaths from ICD-8 or ICD 9 categories 390-458 or ICD-10 categories I00-I99, similar to the case definition used by Bolinder et al. (1994), Henley et al. (2005), and Accortt et al. (2002).

Bolinder et al. (1992) conducted a cross-sectional analysis of the Swedish Construction Workers Study using baseline data collected from 1971 to 1974. The cohort included 5,014 daily snus users, 23,885 never-users of tobacco, and 8,823 smokers of at least 15 cigarettes per day. Participants who were 56 to 65 years of age experienced statistically significant increased prevalence of CVD diagnoses (OR=1.5, 95% CI: 1.1-1.9, 69 cases) when compared to never-users of tobacco. The result was of similar magnitude, but not statistically significant, in those aged 46-55 (OR=1.6, 95% CI: 0.7-3.5, 8 cases). While ST users were not directly compared to cigarette smokers, results presented comparing cigarette smokers to never users of tobacco indicate no association in those who were 56-65 years of age (OR=1.3, 95% CI: 0.9-1.9, 33 cases) and an increased prevalence of having a CVD diagnosis in those aged 46-55 who were smokers (OR=2.2, 95% CI: 1.3-3.9, 22 cases), the opposite of what was reported in ST users. No additional covariates were included in the models. This cross-sectional analysis has limited ability to provide information about a causal association ST use and CVD, but does serve as useful indicator for associations that deserve examination using more rigorous approaches.

Bolinder et al. (1994) followed 84,781 Swedish male construction workers from 1974 to 1985 to identify all CVD deaths (n=2,263). Tobacco use was gathered once by questionnaire that was filled out with a nurse during an initial study medical exam. The authors reported a positive and statistically significant association with ST (presumed to be snus) use in those aged 35 to 54 (HR=2.1, 95% CI: 1.5-2.9; 44 deaths) and aged 55 to 65 (HR=1.1, 95% CI: 1.0-1.4; 174 deaths) after adjusting for age and region of origin when compared with never users of tobacco (Bolinder et al. 1994). In current smokers, risks of dying from CVD were statistically significantly elevated compared to never users of tobacco in both age groups and in both those who smoked fewer than 15 cigarettes per day (35-54 years: HR=2.7, 95% CI: 2.2-3.4, 164 deaths; 55-65 years: HR=1.5, 95% CI: 1.3-1.7, 272 deaths) or more than 15 cigarettes per day versus fewer than 15 cigarettes per day (35-54 years: HR=3.2, 95% CI: 2.6-3.9, 199 deaths; 55-65 years: HR=1.5, 95% CI: 1.3-1.7, 167 deaths). The magnitude of the associations observed in cigarette smokers compared to never tobacco users were slightly higher than those observed in ST users compared to never tobacco users.

Hansson et al. (2009) followed a cohort composed of 16,642 Swedish male twins born between the years 1926 and 1958 that were part of the Screening Across the Lifespan Twin (SALT) study for cardiovascular disease hospitalization or mortality. The SALT study, which was conducted between 1998 and 2002, when the participants were a mean age of 55.9 years, collected ever snus use (never, former, or current) information by telephone interview. A total of 1,119 incident CVD cases occurred during follow-up, which began at the time of the interview and lasted through 2003 for mortality and 2005 for hospitalizations. In never smokers, there was no association with CVD hospitalization or mortality observed in former (RR=1.21, 95% CI: 0.75-1.97, 19 cases) or current (RR=1.00, 95% CI: 0.69-1.46, 32 cases) snus users compared to never users after adjusting for age, diabetes mellitus, high blood pressure, high cholesterol, and twin status through the use of a frailty component. BMI, exercise, education, and alcohol use were assessed but did not appreciably change the risk estimates. In never snus users, on the other hand, risk of CVD was statistically

significantly elevated in current smokers (RR=1.86, 95% CI: 1.56-2.22, 230 CVD cases) and was of borderline statistical significance in former smokers (RR=1.17, 95% CI: 1.00-1.38, 318 CVD cases) compared to never users after adjusting for the same factors.

A cohort of 9,976 Swedish men from Uppsala county who were aged 15 years or older at enrollment and recruited initially to participate in a population-based survey about oral lesion prevalence was used to examine snus use and CVD death (Roosaar et al. 2008). Among never smokers, ever daily users of snus at baseline were not at a statistically significantly increased risk of cardiovascular disease death during follow-up (from 1973-74 through 2002) compared with never users of snus after adjusting for age, alcohol consumption, and area of residence; the hazard ratio was 1.15 (95% CI: 0.97-1.37, number of cases not reported). The results of sensitivity analyses restricted to never smokers over the age of 25, an age after which the authors report that it would be rare to start smoking, were reported to be very similar to the results of the main analysis (Roosaar et al. 2008). The authors report lack of available information on dietary patterns, physical activity and socioeconomic status to be an important limitation of their work. In addition, snus use was only assessed once at the start of follow-up.

The findings presented by Roosaar et al. (2008) and Hansson et al. (2009) point to no association between ST use and CVD while Bolinder et al.'s two analyses of the Construction Workers Study suggest a positive association (1994, 1992). Evidence from Bolinder et al.'s first study, however, is particularly weak as a result of its cross-sectional design (Bolinder et al. 1992). Findings from Bolinder et al. (1994), Hansson et al. (2009) and Roosaar et al. (2008) are strengthened by their prospective study designs. Of note, however, is the fact that the follow-up times used in each study were quite different, with Hannson et al. following subjects for up to approximately 7 years, Bolinder et al. for up to approximately 11 years, and Roosaar et al. for up to approximately 29 years. The use of Swedish health registries, which provide comprehensive coverage of the population, is another noteworthy strength. The Swedish studies, as with the US studies, fall short in their exposure assessment of ST usage and differ in their definitions of "cardiovascular disease" outcomes. Non-differential misclassification of the exposure is a particular concern in the longest exposed groups in each cohort, because tobacco usage was only assessed early in the study period and nothing is known about changes in habits that may have occurred during follow-up.

4.5.2 Reviews and meta-analyses

Cardiovascular disease risks associated with ST use have also been examined in three recent systematic reviews and meta-analyses conducted by Lee (2007, 2011, 2013).

Lee (2007) examined the evidence regarding an association between ST use and circulatory disease, and specifically focused on chewing tobacco and snuff. Based on three studies (Accortt et al. 2002, Bolinder et al. 1994, Henley et al. 2005), Lee reported a statistically significantly elevated combined estimate for all circulatory disease (RR=1.25, 95%CI: 1.13-1.37) with "no marked heterogeneity" between studies. Lee notes that much of the association was driven by the CPS I and CPS II data, which contributed 68.2% and 18.5%, respectively, of the weight of the estimate. The publications by Roosaar et al. (2008) and Hansson et al. (2009) that we included had not yet been published when Lee conducted his literature searches; each of these studies found no evidence of an association between snus use and cardiovascular disease deaths or hospitalization. The first Bolinder et al. (1992) publication was not included in the Lee meta-analysis because it represents the baseline population used in the later publication by Bolinder et al. (1994).

Swedish snus was the focus of Lee's next publication, in 2011, which added four studies (Haglund et al. 2007, Hansson et al. 2009, Janzon and Hedblad 2009, Roosaar et al. 2008) in addition to Bolinder et al. (1994). Results from Haglund et al. (2007) will be discussed in the next section, in which the focus is specifically on IHD and CHD. Janzon and Hedblad (2009) presented results separately for MI

and stroke and will be discussed in each of those sections. As a result of this update, Lee (2011) concludes that while a "weak effect of snus use on CID [circulatory disease] remains possible, the overall data are certainly consistent with no effect" and notes that the only study reporting an increase is an early publication conducted in the Swedish Construction Workers cohort (i.e., Bolinder et al. 1994). Lee notes that earlier publications from the Swedish construction workers cohort, including Bolinder et al.'s 1994 paper, used data collected before 1978; no information was gathered on snus or smoking during 1976-77 data collection period and questionnaires used before this were "limited for snus and ambiguously coded for smoking." Starting in 1978, personal interviews were used to gather this information and later researchers using the Swedish Construction Workers cohort data have excluded data from the earlier period. Lee also concludes that "there is convincing evidence that the risks of cancer and circulatory disease are much lower for snus users" compared to smokers.

4.5.3 Synthesis of findings

Evidence regarding a relationship between ST use and CVD is mixed. Two of the three large US cohorts suggest a positive association, but employed non-specific definitions of both exposure and outcome. One of the three large Swedish cohorts reported a positive association between snus use and CVD. Adequate exposure assessment of ST usage is lacking in all of the studies discussed and the differing definitions of "cardiovascular disease" used in each study complicate conclusions that can be drawn from this body of literature. The following sections examine the evidence regarding associations between more specifically defined cardiovascular disease outcomes and ST use.

4.6 Coronary heart disease / Ischemic heart disease

This review identified six cohort studies, two conducted in US populations and four in Swedish populations, examining the association between ST use and IHD mortality or incidence. In some studies, the term coronary heart disease (CHD) is used instead of IHD; despite the difference in nomenclature, these two terms refer to the same outcome. For the purposes of this discussion, the term "IHD" is used, except where the authors specifically investigate CHD. Across all studies, IHD was defined using the International Classification of Diseases, Eighth Revision (ICD-8) codes 410-414, ICD-9 codes 410-414, or ICD-10 codes I20-25.

4.6.1 US Studies

Accortt et al. (2002) examined IHD mortality associated with exclusive smokeless tobacco use in the NHANES and NHEFS. The cohort and the study methodology used have been described earlier, within the "All CVD" discussion. After adjusting for age, race, alcohol, poverty index ratio, exercise, blood pressure and fruit and vegetable intake, the study found no increased risk of IHD mortality in exclusive ST users compared to never tobacco-using men (HR=0.6, 95% CI: 0.3-1.2) or women (HR=1.4, 95% CI: 0.8-2.2). In comparison, male exclusive smokers had a statistically significantly increased risk of IHD mortality (HR=1.5, 95% CI: 1.1-2.1) compared to never-tobacco users. This result appears to be driven by risk among current smokers, who had twice the risk of IHD mortality (HR = 2.0, 95% CI: 1.4-2.8), while no association was observed in former smokers (HR=1.2, 95% CI: 0.8-2.0). As noted before, there is a possibility of misclassification of exposure due to tobacco usage ascertainment early in the study period only, and concerns about information bias stem from the use of proxies to gather information about some participants.

Henley et al. (2005) reported results for CHD as part of their analysis of health outcomes in relation to ST use, based on CPS I and CPS II data, described previously in the "All CVD" section. In the CPS I, the investigators reported 799 deaths from CHD among 7,745 current, exclusive ST users, and 4,035 deaths from CHD among 69,662 never tobacco users. A slightly elevated, but statistically significant mortality risk of 1.12 (95% CI: 1.03-1.21) was reported for current, exclusive ST users compared to never-tobacco users after adjusting for age, race, education, BMI, exercise, alcohol, fat, fruit and vegetable intake, and aspirin use.

In the CPS II, among 111,482 men who reported never using any form of tobacco, 4,920 deaths were attributed to CHD while 172 and 44 CHD deaths were reported in 2,488 current and 839 former ST users, respectively. Similar to the CPS-I cohort, a statistically significantly increased CHD mortality risk was reported for current, exclusive ST users (HR=1.26, 95% CI: 1.08-1.47, 172 CHD deaths) compared to never tobacco users. These elevations were observed in both exclusive chew tobacco users (HR = 1.25, 95% CI: 1.03-1.51, 111 CHD deaths) and exclusive snuff users (HR =1.59, 95% CI: 1.06-2.39, 24 CHD deaths). Former use of ST was associated with a statistically significantly reduced risk of CHD mortality (HR = 0.70, 95% CI: 0.52-0.95, 44 CHD deaths). In addition to the covariates applied in CPS-I, estimates in this cohort were also adjusted for employment status and type. The limited number of cases available for some, but not all of these analyses, and the large number of covariates that were included in the models lead to concerns about over-controlling and loss of power (Hosmer et al. 2013, Vittinghoff and McCulloch 2007).

General concerns about the CPS I and II have been discussed in previous sections. These concerns include generalizability issues as a result of recruiting friends and family members of the ACS to be participants; non-differential exposure misclassification as a result of tobacco assessment only once at enrollment; and changes in the constituents in tobacco products, which may render these results inapplicable to the present day.

4.6.2 Scandinavian studies

Bolinder et al. (1994) conducted one of the earliest studies identified by our review to examine the association between ST use and IHD (Bolinder et al. 1994). This study has been previously described, within the “All CVD” section. During the 12 years of follow-up from 1971-75 until 1985, 552 deaths due to IHD were reported in the 35-54 age group and 1,180 were reported in the 55-65 age group. Among exclusive ST users, the risk of IHD mortality was statistically significantly elevated for both the 35-54 year age group (HR=2.0, 95% CI: 1.4-2.9) and 55-65 age group (HR = 1.2, 95% CI: 1.0-1.5) compared to never tobacco users. For comparison, this study also examined current and former smokers, stratified both by duration of smoking and cigarettes per day (CPD), to the same referent group of non-tobacco users. In the 35-54 year age group, the investigators found statistically significant elevated risk of IHD mortality both for those currently smoking fewer than 15 CPD (HR = 2.6, 95% CI: 2.1-3.4) and more than 15 CPD (HR = 3.3, 95% CI: 2.6-4.2). Similarly, in the 55-65 age group, there were statistically significant elevated risks of mortality for those currently smoking fewer than 15 CPD (HR = 1.7, 95% CI: 1.4-1.9) or greater than 15 CPD (HR = 1.4, 95% CI: 1.2-2.8). Among former smokers, the risks were elevated in those who had quit smoking 1-5 years prior in both the 35-54 (HR = 1.4, 95% CI: 1.0-2.1) and 55-65 year age groups (HR = 1.3, 95% CI: 1.1-1.6). The risk of IHD also was elevated in those who quit more than five years previously in both age groups, but this risk was not statistically significant.

Johansson et al. (2005) followed 3,120 males between the ages of 30 and 74 years as part of the Swedish Annual Level of Living Survey (SALLS) cohort, from 1988-89 to 2000. This study identified first-time CHD, fatal or non-fatal, from the Swedish National Hospital Discharge Register and the Cause of Death Register, among 1,036 non-tobacco users, 793 exclusive smokers and 107 exclusive snus users. The investigators concluded that, after controlling for age, physical activity, BMI, and a diagnosis of diabetes and/or hypertension, the risk of a first incidence of CHD among snus users compared to non-tobacco users was elevated (HR=1.41, 95% CI: 0.61-3.28), though the result was not statistically significant. In contrast, current smokers had two fold risk compared to non-tobacco users (HR=2.3, 95% CI: 1.66-3.19) and the risk remained elevated among former smokers (HR=1.47, 95% CI: 1.07-2.03). The relatively small sample size, restriction of the results to males, and the small number of outcomes, evidenced by the wide confidence intervals, limit the application of the results to a larger population group.

Haglund et al. (2007) followed 5,002 men aged 16-74 years identified from the Swedish Survey of Living Conditions (ULF), conducted in 1988-89, for 14-16 years until 2003, and included 2,579 men never exposed to tobacco and 721 daily users of snus. Compared to never tobacco users, the daily snus users did not have elevated risk of incident IHD (HR=0.77, 95% CI: 0.51-1.15) or IHD mortality (HR=1.15, 95% CI: 0.54-2.41), based on 28 incident cases and 8 deaths. In contrast, incidence of IHD (HR=1.74, 95% CI: 1.41-2.14) and deaths due to IHD (HR=1.98, 95% CI: 1.41-2.14) were statistically significantly elevated among 1,185 exclusive smokers when compared to never tobacco users, based on 153 incident cases and 52 deaths.

Hansson et al. (2009) followed a retrospective cohort composed of 16,642 Swedish male twins born in the period 1926-1958; the results of this study are described previously in the "All CVD" section. From 1998-2002 to 2003-2005, there were 630, 60, and 70 IHD-related hospitalizations or deaths reported among 12,525 non-tobacco users, 1,456 former snus users, and 2,661 current snus users, respectively. Similar to other studies, risk of IHD was elevated for current (RR=1.99, 95% CI: 1.59-2.5, 155 IHD hospitalizations or deaths) and former (RR=1.34, 95% CI: 1.1-1.64, 229 IHD hospitalizations or deaths) smokers, but not for current (RR=0.85, 95% CI: 0.51-1.41, 18 IHD hospitalizations or deaths) and former (RR=1.07, 95% CI: 0.56-2.03, 11 IHD hospitalizations or deaths) snus users, compared to never tobacco users. All models were adjusted for age, diabetes, blood pressure, cholesterol, and twin status through the use of a frailty component. BMI, exercise, education, and alcohol use were assessed but did not appreciably change the risk estimates.

4.6.3 Reviews and Meta-Analyses

Our review did not identify any reviews or meta-analyses that specifically discussed the association between ST use and risk of CHD/IHD as a separate, defined category. However, some publications reviewed results for CHD/IHD together with myocardial infarction (MI), and these will be discussed in the MI section below.

4.6.4 Synthesis of findings

The literature identified does not provide any clear evidence of an association between ST use and IHD mortality or incidence. Of the six studies identified, only two studies (Bolinder et al. 1994, Henley et al. 2005) provide any indication of a positive association between ST use and IHD. Both of the studies reporting positive associations assessed tobacco use many years ago, and it is possible that the constituents of the ST products used then differ from those found in modern products. Accortt et al. (2002) identified no association within their study, and ST users would have used these older products. In addition, findings from all six studies were limited by their tobacco usage assessments, as tobacco usage was assessed either at baseline or once during follow-up, and nothing is known about changes in habits that may have occurred during each study's respective follow-up period. Results from the study with the shortest follow-up and whose methods were least likely to be substantially impacted by misclassification (Hansson et al. 2009) indicate no association between snus use and IHD hospitalization and deaths.

In contrast to the conflicting results for ST, the evidence for a positive association between smoking and risk of IHD was clear and consistent. All five studies identified by this review to include exclusive smokers reported approximately a two-fold risk of CHD/IHD incidence or mortality for current smokers, compared to never tobacco users (Accortt et al. 2002, Bolinder et al. 1994, Haglund et al. 2007, Hansson et al. 2009, Johansson et al. 2005). Thus, from the available evidence, it is clear that smoking carries substantially higher risk of CHD/IHD compared to exclusive ST use.

4.7 Myocardial infarction

This review identified four case-control studies, two prospective cohort studies, a pooled analysis, and a meta-analysis conducted in Swedish populations examining the association between ST use

and myocardial infarction. An additional prospective cohort study conducted in a US population examined myocardial infarction as one of a larger group of CVD outcomes.

4.7.1 US study

Yatsuya et al. (2010), described previously in the "All CVD" section, examined the association between incident CVD and smokeless tobacco use using data from the ARIC Study cohort. MI was not addressed as a specific endpoint in this study; it was included in a larger grouping of CVD outcomes. However, because there are currently no other quality studies specific to MI and ST in a US population, Yatsuya et al. (2010) provides relevant information. Subjects in the ARIC Study cohort were selected by probability sampling from four US communities. At baseline (1987-1989), 15,792 men and women aged 45-64 were recruited; after exclusions, 14,498 subjects remained for analysis. Tobacco habits were assessed at baseline; "smokeless tobacco" includes both chewing tobacco and snuff. Subjects were followed for incidence of CVD through 2005; the CVD definition included fatal coronary heart disease, hospitalized and/or electrocardiogram-confirmed MI, cardiac procedure, or stroke. The authors ran models stratified by current smoking status and adjusted for age, sex, race/study center, education, income, alcohol, physical activity, never/past cigarette smoking (in current non-smokers), pack-years of smoking, pipe/cigar use, and exposure to secondhand smoke. Among current non-smokers, former ST users did not show elevated risk of CVD (HR=0.90, 95% CI: 0.73-1.11) compared to current non-smoking never ST users. However, current non-smoking subjects who were current ST users had a slightly elevated risk of CVD (HR=1.31, 95% CI: 1.06-1.61) compared to currently non-smoking never ST users. Among current cigarette smokers, neither former nor current ST use contributed to any additional risk of CVD (former HR=0.86, 95% CI: 0.65-1.13; current HR=1.09, 95% CI: 0.74-1.60) compared to current smokers who never used ST. Models demonstrating the CVD risk from cigarette smoking included ST users in all comparison groups, and are therefore not useful in comparing risks associated with ST use versus cigarette smoking. This study is limited by measuring tobacco exposures only at baseline; actual exposures may have changed over the many years of follow-up. Furthermore, as MI was not examined as a specific endpoint, the risk estimates in this study are not directly comparable to estimates of MI risk found in the other studies discussed below.

4.7.2 Scandinavian studies

Studies of Swedish snus use and MI have shown mixed results. Several studies of snus use in Sweden have identified no statistically significant association between snus use and MI (Hergens et al. 2005, Huhtasaari et al. 1992, Huhtasaari et al. 1999, Janzon and Hedblad 2009, Wennberg et al. 2007). One study that utilized data from the Swedish Construction Workers cohort (Hergens et al. 2007) found possible evidence of increased risk of fatal, but not nonfatal, MI. A pooled analysis (Hansson et al. 2012) which included data from the Swedish Construction Workers Study and several other cohorts also found no association of current snus use with increased risk of incident acute MI; however, this analysis found evidence of increased risk of fatality among current snus users who experienced MI. These studies are discussed in more detail below.

Huhtasaari et al. (1992) conducted a case-control study of Swedish men aged 35-64 years selected from the population being followed by the Northern Sweden Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project. All men aged 35-64 years who experienced a first acute MI from April 1989 to April 1991 were eligible cases; 585 (93%) had data on tobacco consumption and were included in analyses. Controls were randomly selected from the same geographic area by age group; after refusals and exclusions, 589 (81.2%) participated. Tobacco consumption was assessed by interviews conducted by trained nurses; for deceased subjects, family members answered questions about the subject's tobacco use. In age-adjusted analyses, current snus use was not associated with increased risk of MI incidence compared to non-tobacco users (OR=0.89; 95% CI: 0.62-1.29), whereas current cigarette smokers did have an

increased risk of MI incidence compared to non-tobacco users (OR=1.87, 95% CI: 1.40-2.48). The small sample size prevented an analysis of MI mortality by tobacco use. Misclassification of exposure and information bias could have resulted from the use of proxy interviews for deceased subjects, some of whom were identified as MI cases, because proxies might not report tobacco use as accurately as living subjects. Because proxies were used only for deceased cases and not for controls, the measured exposure of cases might be less accurate as a whole than the measured exposure of controls. Results of this study are also limited by the inclusion of occasional cigarette or snus users (less than once per day) in the "non-tobacco users" comparison group, leading to possible misclassification of exposure which could bias results towards the null.

Huhtasaari et al. (1999) later published another case-control study of Swedish men, also selected from the population of the Northern Sweden MONICA study. In this study, all cases of first acute myocardial infarction (AMI) occurring in the Northern Sweden MONICA population among men aged 25 to 64 from May 1991 through December 1993 were eligible as cases; controls were selected from population registers and matched by county of residence and date of birth. The calendar dates used to define eligible cases suggests minimal or no overlap between this study and the earlier study (Huhtasaari et al. 1992). After refusals and exclusions, 687 matched pairs were available for analysis (78.2% of eligible pairs). Data on snus use were collected by oral interview; for deceased subjects, data were collected from family members by written questionnaire. Matched controls of deceased subjects received the same written questionnaire as provided to proxies for the cases, thus minimizing information bias. In models adjusted for "multiple risk factors" (not clearly specified), there was a slightly reduced risk of fatal and nonfatal AMI combined among regular snus users compared to non-tobacco users (OR=0.58, 95% CI: 0.35-0.94), and no association of regular snus use with fatal AMI only (OR=1.50, 95% CI: 0.45-5.03). In contrast, among regular cigarette smokers, there was a substantially increased risk of fatal AMI compared with non-tobacco users (OR=8.57, 95% CI: 2.48-30.3). This study is limited by its unclear description of the analysis methods used and the likely inclusion of occasional cigarette or snus users (less than once per day) in the "non-tobacco users" comparison group; this misclassification of exposure could bias results towards the null.

As in Huhtasaari et al. (1999), Wennberg et al. (2007) performed a case-control study of MI and sudden cardiac death using participants in the Northern Sweden MONICA study and the (Northern Sweden) Vasterbotten Intervention Program (VIP). Eligible cases participated in one of the two studies and were identified by the Northern Sweden MONICA incidence registry as having experienced MI or sudden cardiac death between January 1985 and December 1999. Controls were randomly selected from the MONICA and VIP populations and matched on sex, age, geographical region, and date of health survey. After exclusions, 525 cases and 1,798 controls were available for analysis; of these subjects, 65 cases and 210 controls had also been included in the studies conducted by Huhtasaari et al. (1992) and (1999). Data on tobacco use was collected by a questionnaire at baseline; current use was defined as daily smoking and/or snus use. In models adjusted for BMI, physical activity, educational level, and cholesterol level, there was no increased risk of MI in current exclusive snus users (OR=0.82, 95% CI: 0.46-1.43) or in former exclusive snus users (OR=1.18, 95% CI: 0.82-1.70) compared to never tobacco users. Former smokers showed no increased risk of MI (OR = 1.18, 95% CI 0.82-1.70) compared to never tobacco users; however, current smoking was statistically significantly associated with increased risk (OR=2.60, 95% CI: 1.91-3.54). Additional models examined the association of tobacco use with fatal MI (within 28 days), sudden cardiac death (SCD) with survival time less than 24 hours, and sudden cardiac death with survival time less than 1 hour; these models were also adjusted for BMI, physical activity, educational level, and cholesterol level. Compared to never tobacco use, current snus use showed no increased risk of fatal events (fatal MI OR=1.12, 95% CI: 0.38-3.29; SCD less than 24 hours

OR=1.18, 95% CI: 0.38-3.70; SCD less than 1 hour OR=0.38, 95% CI: 0.08-1.89). Former snus use similarly showed no elevated risk of fatal cardiac events (fatal MI OR=0.64, 95% CI: 0.13-3.18; SCD less than 24 hours OR=0.70, 95% CI: 0.14-3.64; SCD less than 1 hour OR=0.35, 95% CI: 0.03-4.56). In contrast, compared to never tobacco use, current cigarette smoking, but not former cigarette smoking, was statistically significantly associated with all three fatal outcomes (current smoking fatal MI OR=3.53, 95% CI: 1.83-6.84; SCD less 24 hours OR=3.12, 95% CI: 1.53-6.33; SCD less than 1 hour OR=4.54, 95% CI: 1.55-13.25). This study is limited by the collection of tobacco use data at baseline only; actual exposures may have changed during the years of follow-up. Statistical power was limited, and risk estimates are unstable, as evidenced by the wide confidence intervals. In contrast to the Huhtasaari case-control studies (1992) and (1999), this study defined its referent category as “never tobacco users”, and therefore had less possibility of misclassification of occasional tobacco users as non-users.

Another case-control study evaluating Swedish snus use and MI was published by Hergens et al. (2005). Cases included all first AMI events occurring from 1992 to 1994 among men aged 45-70 years, identified from all hospitals in Stockholm, and the discharge and mortality registers at Statistics Sweden. Male controls were randomly selected from the two-county study base and matched by age and hospital catchment area. The participation rate was 77% among cases and 78% among controls; a total of 1,432 cases (1,173 nonfatal, 259 fatal) and 1,810 controls were included in analyses. Data on tobacco use was collected by mailed questionnaire followed by telephone interview; for fatal cases, the questionnaire was answered by next of kin. Models adjusted for age and hospital catchment area found no statistically significant elevated risk of all first AMI among current snus users compared to never tobacco users (OR=0.73, 95% CI: 0.35-1.5) or among former snus users compared to never tobacco users (OR=1.2, 95% CI: 0.46-3.10). When broken down by nonfatal versus fatal AMI, there was still no statistically significant association seen among current snus users compared to never tobacco users (nonfatal AMI OR=0.59, 95% CI: 0.25-1.4; fatal AMI OR=1.7, 95% CI: 0.48-5.5). Similarly, there was no association found between nonfatal or fatal AMI among former snus users compared to never tobacco users (nonfatal AMI OR=1.2, 95% CI: 0.43-3.2; fatal AMI OR=1.7, 95% CI: 0.21-13.6). The authors reported that adjustment for diabetes, hyperlipidemia, hypertension, overweight, physical inactivity, and job strain did not meaningfully alter these risk estimates. By contrast, current exclusive smokers showed elevated risk of both nonfatal AMI (OR = 2.7, 95% CI 2.2-3.3) and fatal AMI (OR = 3.6, 95% CI 2.4-5.2).

Janzon and Hedblad (2009) examined the association of snus use and MI in a prospective cohort study using the Malmo Diet and Cancer (MDC) cohort, which included men and women aged 45-73 who lived in Malmo, Sweden and who participated in a health examination between March 1991 and February 1996. Approximately 40% of the eligible population chose to participate; after exclusions, 16,754 women (mean age: 57.4 years) and 10,473 men (mean age: 59.1 years) were included in analyses and followed up through December 2004. Smoking and snus habits were assessed at baseline by self-administered questionnaire. Because none of the women who experienced a MI were snus users, analyses of snus and MI were restricted to male subjects. Adjusting for BMI, age, smoking habits, diabetes, hypertension, physical activity, marital status, and occupation, there was no association with MI seen among current snus users compared to never-smoking non-snus users (RR = 0.75, 95% CI 0.3-1.8). This study was limited by assessing tobacco use only at baseline; actual exposures may have changed during follow-up. On the other hand, the exposure categories were defined more specifically in this compared with other studies, which would improve the validity of the estimates by reducing one source of exposure misclassification.

In contrast to the above studies, which identified no association between current or former snus use and fatal or nonfatal MI, one prospective study conducted using data from the Swedish Construction Workers cohort demonstrated a possible association between snus use and fatal cardiac events.

Hergens et al. (2007) looked specifically at risk of MI among this large cohort of Swedish construction workers. Because the data on tobacco use collected prior to 1978 in this cohort were limited, Hergens et al. (2007) restricted their analyses to participants who were registered between 1978 and 1993. After other exclusions, 118,395 male Swedish construction workers with no previous history of cigarette smoking or MI (mean age at baseline: 31.5 years) were available for analyses. Subjects were followed up through 2004 using national disease and death registries, with a mean duration of follow-up of 19 years. Models were adjusted for age, BMI, and region of residence. For all cases of MI, there was no elevated risk among former snus users (RR=0.76, 95% CI: 0.55-1.05) or current snus users (RR=1.02, 95% CI: 0.92-1.14) compared to never users. There was also no elevated risk of nonfatal MI among former snus users (RR = 0.70, 95% CI 0.48-1.02) or current snus users (RR = 0.94, 95% CI 0.83-1.06) compared to never users. For all MI and nonfatal MI combined, there was no association seen with any category of amount of snus used, including the highest category of ≥50g/day. When fatal cases of MI were analyzed separately, there was no association among former snus users compared to never users (RR = 1.00, 95% CI 0.54-1.88). However, there was a slightly elevated risk of fatal MI among current snus users compared with never users (RR = 1.32, 95% CI 1.08-1.61). There was no clear exposure-response relationship with categories of increasing daily snus amount; only the bottom (12.5g/day) category and the top (≥50g/day) category showed an association with increased risk of fatal MI. However, the highest point estimate of association was seen in the highest category of daily snus use (≥50g/day; RR = 1.96, 95% CI 1.08-3.58). This study is limited by the assessment of snus use at baseline only; however, its strengths include its large size, lengthy follow-up, use of multiple national registries for outcome assessment, and reduction of confounding by smoking through the exclusion of those who smoked at baseline. There is still some possibility that men categorized as snus users at baseline switched to cigarette smoking during the study period, which would have inflated the apparent risks between snus and MI.

4.7.3 Reviews and meta-analyses

Hansson et al. (2012) performed a pooled analysis of eight Swedish cohort studies, including several cohorts used in the studies discussed above: the Swedish Construction Worker cohort (Hergens et al. 2007), the MONICA cohort (Huhtasaari et al. 1992, Huhtasaari et al. 1999, Wennberg et al. 2007), the Malmo Diet and Cancer cohort (Janzon and Hedblad 2009), the Swedish Twin Registry (Hansson et al. 2009), discussed previously in detail within the “All CVD” section; MI was not a specifically defined endpoint), and four sets of previously unpublished data on snus use and cardiovascular disease. The pooled cohort consisted of 130,361 male never smokers recruited and followed for 5 to 29 years from 1978 to 2004, of whom 32,560 were current snus users at baseline. During follow-up, there were 3,390 incident cases of acute myocardial infarction (AMI). No statistically significant association was found between either intensity of snus use (cans/week) or duration of snus use (years) and incident AMI. However, current snus users had an elevated risk of excess fatality from AMI within the first 24 hours ($p < 0.05$; no risk estimate reported), and the 28-day case fatality from AMI was 1.28 (0.99-1.68), adjusted for BMI and age and based on 97 cases. Sensitivity analyses excluding data from the Swedish Construction Workers Cohort yielded similar results.

A 2011 review by Lee (Lee 2011) discussed cardiovascular outcomes related to snus, including the studies discussed above in his analyses (Bolinder et al. 1994, Hergens et al. 2007, Huhtasaari et al. 1992, Huhtasaari et al. 1999, Wennberg et al. 2007). Lee (2011) includes Haglund et al. (2007) in his analyses of cardiovascular outcomes; in this report, Haglund (2007) is included in discussions of general ischemic heart disease and stroke, as MI was not a specific endpoint in this study. A 2013 review by Lee (Lee 2013) updated the earlier Lee review (Lee 2011) by adding the eight cohorts used in the Hansson et al. (2012) pooled analysis. Because one of the cohorts in Hansson et al. (2012) had no cases (the National March Cohort), Lee used data from the other 13 study cohorts

(Bolinder et al. 1994, Haglund et al. 2007, Hergens et al. 2007, Huhtasaari et al. 1992, Huhtasaari et al. 1999, Wennberg et al. 2007) and the seven cohorts with cases in his meta-analysis (Hansson et al. 2012). Incorporating individual RR/OR estimates from all 13 cohorts, Lee found a combined fixed effect estimate of 1.07 (95% CI 0.98-1.16) for risk of circulatory disease in non-smoking male snus users compared with non-smoking men who did not currently use snus. However, his analysis showed heterogeneity among the studies (p=0.06), suggesting that the effect estimates in this group of studies might be more dissimilar than would be expected by chance. To account for this heterogeneity, Lee used a random-effects model and estimated a combined RR/OR = 1.06 (95% CI 0.91-1.23). The main contributor to the heterogeneity among the 13 studies was the Bolinder et al. (1994) study of the Swedish Construction Workers cohort, in which data on snus use collected during the early years of the study (1971-1974) were limited. Furthermore, Bolinder et al. (1994) was the only study in this analysis which relied on fatal rather than incident cases of ischemic heart disease (a group of cardiovascular outcomes including MI). Removing the data from Bolinder et al. (1994) from his analysis, Lee found a fixed effect estimate of RR/OR = 1.00 (95% CI 0.91-1.10) for nonfatal circulatory disease among non-smoking male snus users versus non-smoking men who did not currently use snus, indicating no difference in risk. There was no statistical evidence of heterogeneity between studies when the data from Bolinder et al. (1994) were removed.

In a separate analysis of the five studies reporting fatal cardiac outcomes (Haglund et al. 2007, Hergens et al. 2005, Hergens et al. 2007, Huhtasaari et al. 1999, Wennberg et al. 2007), Lee found a combined RR/OR estimate of 1.31 (95% CI 1.09-1.58) for fatal cases and RR/OR = 0.9 (95% CI 0.79-1.00) for non-fatal cases among nonsmoking male snus users versus nonsmoking men who did not currently use snus, with no evidence of heterogeneity. Lee concluded that current snus use in male never smokers might be associated with an increased risk of fatal AMI/ischemic heart disease (IHD), but also may be associated with a slightly decreased risk of nonfatal AMI/IHD. However, he also wrote that further investigation into possible confounding is necessary, and that any increased risk of AMI from snus use is less than the increased risk from smoking.

4.7.4 Synthesis of findings

The evidence for an association between ST use and MI is mixed. The study of US ST (chewing tobacco and snuff) is limited by the failure to impose a specific case definition. The one available study (Yatsuya et al. 2010), which examined MI as part of a larger group of cardiovascular outcomes, found a slightly elevated risk of CVD associated with ST use among current, but not former, chewing tobacco and snuff users. Using ST in addition to smoking was not associated with any additional risk of cardiovascular disease. The design of this study did not allow a direct comparison between ST use and cigarette smoking as cardiovascular risk factors.

Among Swedish studies, the available evidence points to a possible association between current snus use and elevated risk of fatal MI; no association is seen with non-fatal MI. Individual analyses of the five available studies of Swedish populations found no association between snus use and risk of non-fatal or fatal MI (Hergens et al. 2005, Huhtasaari et al. 1992, Huhtasaari et al. 1999, Janzon and Hedblad 2009, Wennberg et al. 2007), and one study using data from the Swedish Construction Workers cohort found a positive association with fatal, but not non-fatal MI (Hergens et al. 2007). However, a pooled analysis, which included many of the above cohorts and previously unpublished data, found no elevated risk of nonfatal MI (Hansson et al. 2012); this same pooled analysis found that current snus users had a higher risk of fatality from MI within the first 24 hours. Results of the pooled analysis were similar when data from the Swedish Construction Worker cohort were excluded. Another meta-analysis which used a broader grouping of cardiovascular outcomes (Lee 2013) found a slightly reduced risk of cardiovascular disease among current snus users, but a slightly higher risk of fatality from AMI/ischemic heart disease. Although the evidence for elevated risk of MI among snus users in Swedish studies is mixed, all four of the above studies that assessed cigarette smoking

(Huhtasaari et al. 1992, Huhtasaari et al. 1999, Wennberg et al. 2007) showed a significantly elevated risk of MI among current smokers.

4.8 Blood pressure and hypertension

The studies investigating the relationship between ST use and blood pressure and/or hypertension are largely limited to nine studies utilizing either US (Ernster et al. 1990, Ksir et al. 1986, Siegel et al. 1992, Squires et al. 1984) or Swedish populations (Bolinder et al. 1992, Bolinder and de Faire 1998, Eliasson et al. 1991, Hergens et al. 2008b, Rohani and Agewall 2004).

4.8.1 US studies

Two US cross-sectional studies involve the same population of Arizonan professional baseball players. In the first study, which reports results from the first year of study, 1,109 participants were asked to complete a questionnaire which included “detailed” questions “concerning patterns of [ST] use” (Ernster et al. 1990). The majority (77%) of participants were between ages 20 and 29 years. Based on the responses to the questionnaire, participants were classified as either “nonusers” (i.e., those who had never used ST or had used ST in the past but never more frequently than once a month), “former users” (i.e., those who had used ST more than once a month in the past but had not used ST within the previous month), and “current users” (i.e., those who had used ST more frequently than once a month and who had used ST within the previous month). After adjusting for age, race, smoking, serum caffeine level, and immediate physical activity, the researchers did not identify a relationship between ST use and measured systolic or diastolic blood pressure. Results were similar in the second study, which includes reporting from both the first and second year of study, but were limited to the most complete or most recent data for each man: there was no statistically significant difference between the systolic or diastolic blood pressures of non-users and users of ST (Siegel et al. 1992). These studies are strengthened by the large size and consideration of relevant covariates; however, given that this population consists of young, professional athletes, the results may not be applicable to the general population (Ernster et al. 1990).

In an experimental study of five male college athletes who use 1.5-3.0 cans of Copenhagen moist snuff per week, each volunteer used and retained their “normal ‘pinch’” of Copenhagen snuff prior to exercise and during different intensities of exercise (Ksir et al. 1986). At rest, the group’s mean systolic blood pressure was approximately 4 mmHg higher on snuff use days (i.e., test days), compared to non-snuff use days (i.e., control days). Additionally, the group’s mean systolic blood pressure was higher across three exercise intensities (i.e., 300, 600, and 900 kg/min) on test days compared to control days. These differences between test and control days were statistically significant ($p<0.05$). However, there was no statistically significant difference in 1) the group’s mean diastolic blood pressure at any time point, or 2) systolic blood pressure during a 15-minute recovery period, on test and control days. This study, while providing information collected under controlled conditions, is limited due to its small size and focus on young, male, athletes, and the lack of information regarding the athletes’ cigarette smoking histories (Ksir et al. 1986).

A second experimental study involved twenty men, at a mean age of 20 years, who abstained from nicotine use for at least 72 hours and were asked to use 2.5 g of oral ST for 20 minutes (Squires et al. 1984). All men were non-users of cigarettes, though 10 men were chronic oral ST users and 10 men were non-users of oral ST. Compared to baseline (i.e., at pretest before ST use), ST use elevated both the mean systolic and diastolic blood pressures of the group; these differences were statistically significant ($p<0.05$). Specifically, the mean systolic blood pressure increased from 118 mmHg at baseline to 129 mmHg during the 20 minutes of ST use, while the mean diastolic blood pressure increased from 72 mmHg at baseline to 79 mmHg during the same time. Five minutes following 20 minutes of ST use, mean systolic blood pressure remained significantly elevated (126 mmHg) compared to baseline, while mean diastolic blood pressure did not remain elevated (Squires

et al. 1984). Like Ksir et al. (1986), this study is limited by its small size and restriction to young men, but is strengthened by its collection of information under controlled conditions.

4.8.2 Scandinavian studies

Of the five Swedish studies investigating the relationship between ST use, presumably snus, and blood pressure and/or hypertension, two studies utilized data from the Swedish Construction Workers Study cohort, a cohort of approximately 390,000 construction workers who were 1) registered between 1971 and 1993, and 2) linked to several national registers, including, but not limited to, the Inpatient Register and the Causes of Death Register (Bolinder et al. 1992, Hergens et al. 2008b). The other three studies utilized data from firefighters in the Stockholm City Fire Brigade (Bolinder and de Faire 1998) or volunteers (Eliasson et al. 1991, Rohani and Agewall 2004).

Bolinder et al. (1992) conducted a cross-sectional analysis of the Swedish Construction Workers Study using baseline data collected from 1971 to 1974. In this cohort at baseline, 5,014 daily snus users experienced statistically significant increased prevalence of diagnosed hypertension (OR=3.0, 95% CI: 1.9-4.9) when compared to 23,885 never-users of tobacco and adjusted for age. In the same study, there was no difference in prevalence of diagnosed hypertension among 8,823 smokers of at least 15 cigarettes per day (OR=0.9, 95% CI: 0.4-1.9) compared to never-users of tobacco (Bolinder et al. 1992). In detailed analyses of blood pressure effects, cohort members additionally were stratified by age (16-35 years, 36-45 years, 46-55 years, and 56-55 years) and obesity status (thin, normal, and obese). Overall and independent of obesity status, there was a statistically significant association between ST use in the 46-55 and 56-65 year old age groups (OR=1.8, 95% CI: 1.5-2.1 and OR=1.3, 95% CI: 1.1-1.4, respectively) and diastolic blood pressure greater than 90 mmHg, compared to non-tobacco users. The findings for the 46-55 year old age group remained statistically significant when limited to individuals with “normal” BMI. Similar findings were reported for these same age groups in the systolic blood pressure analyses: 46-55 (OR=1.7, 95% CI: 1.3-2.1) and 56-65 year old (OR=1.2, 95% CI: 1.1-1.4) ST users had a higher prevalence of systolic blood pressure greater than 160 mmHg compared to non-tobacco users. Blood pressures were not elevated in other ST user age groups, nor among smokers who reported smoking at least 15 cigarettes per day (Bolinder et al. 1992). In the absence of information on other exposures and changes in exposure status during the follow-up period, it is possible that confounding or misclassification of smokers as snus users could explain the observed associations with snus use.

In an expanded analysis of the Swedish Construction Workers Study cohort, which included 120,930 non-smokers followed between 1978 and 1993, individuals with “high blood pressure” included those who had measured systolic blood pressure greater than 160 mmHg and diastolic blood pressure greater than 100 mmHg (Hergens et al. 2008b). Within the cohort, there were statistically significant associations between “ever use” and “current” use of snuff and high blood pressure. Specifically, prevalence of high blood pressure was higher among “ever users” compared to “never users” of snuff (OR=1.23, 95% CI: 1.15-1.33), and among current snuff users compared to “never users” of snuff (OR=1.25, 95% CI: 1.16-1.35). These associations were generally consistent and statistically significant regardless of stratification of the cohort by age at baseline. When stratifying the cohort by both age at baseline and amount of snuff used per day (<12.5 g/day; 12.5-24.9 g/day; 25-49.9 g/day; and ≥ 50 g/day), there was a statistically significant exposure-response relationship in the 50-54 year age group; namely, increased snuff use was associated with an increased prevalence of high blood pressure in this age group, but not in older or younger men (Hergens et al. 2008b).

Separate analyses also investigated those diagnosed with “hypertension,” as identified in the Inpatient Register using relevant ICD codes. “Ever” snuff use and was positively and statistically significantly associated with prevalence of hypertension diagnosis (OR=1.36, 95% CI: 1.07-1.72), as was “current” snuff use (OR=1.43, 95% CI: 1.12-1.83), use of 12.5-24.9 g/day of snuff (OR=1.43, 95% CI: 1.01-2.02), and use of 25-49.9 g/day of snuff (OR=1.77, 95% CI: 1.08-2.90) compared

with “never” use of snuff. Both the blood pressure and hypertension analyses were adjusted for age at cohort entry, BMI, and region of residence within Sweden. Strengths of this study included its large size, its prospective cohort design, and its use of verified medical records for ascertainment of hypertension. Limitations, as mentioned previously, include limited data on exposure assessment and the resulting possibility of misclassification (Hergens et al. 2008b).

The last two Swedish studies were cross-sectional in design and utilized Stockholm City Fire Brigade data (Bolinder and de Faire 1998) and data from university-based volunteers (Eliasson et al. 1991). Bolinder et al. (Bolinder and de Faire 1998) used the 24-hour ambulatory blood pressure recordings of 135 men ages 35 to 60 years to “investigate whether the use of ST among healthy middle aged men is associated with any alteration in blood pressure… during daytime and nighttime, compared with smokers and nonusers of tobacco…”. In ST users, investigators observed a statistically significant correlation between blood cotinine values (an indicator of exposure to nicotine, presumably from tobacco use) and 24-hour systolic ($p<0.001$) and diastolic ($p=0.005$) blood pressure values; data for smokers did not yield such correlations. Further, compared to tobacco non-users, ST users had elevated mean 24-hour systolic blood pressure readings ($p<0.05$) and elevated mean systolic blood pressure readings during the day ($p<0.05$). The other blood pressure comparisons (i.e., casual systolic and diastolic blood pressures, mean 24-hour diastolic blood pressure, mean daytime diastolic blood pressure, mean night-time systolic and diastolic blood pressures) were not statistically significantly different between the exposure groups. Comparisons of cigarette smokers to non-users of tobacco yielded similar findings: smokers had some blood pressure measurements that were higher than non-users’ measurements, but these elevations were few in number and inconsistent (Bolinder and de Faire 1998). This study is limited by its small sample size and possible lack of adequate power to test the hypothesis in question.

In a study of 58 male university-affiliated volunteers, the participants consisted of 18 never tobacco users, 21 daily snuff (presumably, snus) users, and 19 daily cigarette smokers (Eliasson et al. 1991). The study participants were questioned about their tobacco use, and each was tested for his blood pressure twice. Overall, there were no differences in the systolic blood pressure readings between non-tobacco users, snuff users, and smokers. Further, there were no differences in the diastolic blood pressure readings between non-tobacco users and snuff users. Smokers’ diastolic blood pressures were statistically significantly ($p<0.05$) elevated compared to non-tobacco users. In addition to its small sample size, this study is limited by its lack of generalizability, due to the investigators’ recruitment practices; volunteers were identified in the study by newspaper ads. Further, the manner in which relevant covariates were accounted for is unclear (Eliasson et al. 1991).

Finally, a study by Rohani and Agewall (2004) assessed systolic and diastolic blood pressure in a group of 20 healthy habitual snuff users. These parameters were also tested in ten of the participants exposed to a placebo, in order to obtain a crossover sample for comparison. At 20 minutes after administration of snuff, the study found a statistically significant increase in both systolic and diastolic blood pressure (SBP: 109 at baseline to 111 at 20 min, DBP: 74 at baseline to 78 at 20 min). No significant differences were detected 35 minutes after administration. No significant changes in blood pressure were detected in the placebo group. Due to the limitations of this study (low statistical power, restricted applicability of the results), these findings do not provide clear evidence of an association between ST use and blood pressure and should be considered suggestive, only.

4.8.3 Reviews

Peter Lee has reviewed the literature on the association between ST use and blood pressure (Lee 2007, Lee 2011). The bibliography considered in Lee 2007 overlaps with the material considered in Lee 2011, and also includes articles not directly relevant to the question of an association between ST use and blood pressure (Lee 2007). Lee (2011), which included several publications we identified, but did not include (Ahlbom et al. 1997, Angman and Eliasson 2008, Eliasson et al. 1995, Hergens et al. 2005, Hirsch et al. 1992, Janzon and Hedblad 2009, Johansson et al. 2005, Wallenfeldt et al. 2001, Wennmalm et al. 1991), identified Bolinder et al. (1992) and Hergens et al. (2008b) as the only two of fourteen publications suggesting a positive association between ST use and elevated blood pressure (Lee 2011). Based on this limited body of literature, Lee concluded, “The overall evidence does not demonstrate a chronic effect of snus on blood pressure” (Lee 2011).

4.8.4 Synthesis

Overall, the literature investigating the relationship between ST use and blood pressure yields mixed results. Studies in the US were generally small in sample size, and utilized non-generalizable populations, such as athletes. The studies measured different blood pressure parameters, according to different protocols. The two studies of professional baseball players in the US were larger, and did not identify an association between ST use and elevated measured blood pressure (Ernster et al. 1990, Siegel et al. 1992), while two smaller, experimental studies reported some statistically significant findings between immediate ST use and acute blood pressure readings. Three smaller Swedish studies generally did not identify consistent associations between ST (presumably, snus) use and measured blood pressures, though these studies were limited by their small sample sizes (Bolinder and de Faire 1998, Eliasson et al. 1991, Rohani and Agewall 2004). The two strongest Swedish studies, which utilized the Swedish Construction Workers Study cohort, identified modest but consistent and statistically significant associations between ST use and prevalence of elevated blood pressure, but questions remain regarding potential misclassification of exposures (i.e., failure to account for potential changes in tobacco use over time) assessed only at baseline (Bolinder et al. 1992, Hergens et al. 2008b).

Only two studies investigated the prevalence of formally defined hypertension in ST users (Bolinder et al. 1992, Hergens et al. 2008b). These two studies, strengthened by their use of the large Swedish Construction Workers Study cohort, suggest that ST use may be associated with increases in hypertension prevalence. However, these findings need to be confirmed by additional and similarly strong studies in different populations.

4.9 Cerebrovascular disease (stroke)

The epidemiological evidence regarding the association between exclusive smokeless tobacco (ST) use and cerebrovascular disease is relatively sparse. Almost all of the studies reviewed below evaluate this association as part of a broader examination of the association between ST use and cardiovascular disease or atherosclerotic vascular changes. The studies that have reported results on carotid intima media thickness, carotid bulb and carotid body lumen diameter have also been included in this review. For perspective, an estimate of the risk among smokers in the same cohort, either compared to the same referent group as ST users or to ST users themselves, has also been discussed, if the studies themselves included these results.

4.9.1 US Studies

Two US studies investigated the association of ST use with stroke outcomes, as part of their investigation into a broader association with cardiovascular disease. Both of these studies have been discussed earlier, in relation to other cardiovascular outcomes. The earliest study conducted in a US population identified by our review was by Accortt et al. (2002) who examined mortality associated with exclusive smokeless tobacco use in the First National Health and Nutrition Examination Survey (NHANES I) and the follow-up NHANES I Epidemiologic Follow-up Study (NHEFS) cohort, formed in

1971-75 and followed up until 1992. This study identified 414 exclusive smokeless tobacco users and 2,751 exclusive smokers, each of whom were compared to 2,986 men who reported no tobacco use at the time the cohort was formed. After adjusting for age, race, alcohol, poverty index ratio, exercise, blood pressure and fruit and vegetable intake, the study found no association of stroke mortality with exclusive smokeless tobacco use in either males or females among those aged 45 years and older. However, as mentioned previously, the relatively small size of the study sample on which the analysis was conducted makes the results unreliable. Additionally, there is a possibility of misclassification of exposure due to ascertainment of exposure at only one time point.

Stroke mortality risks associated with US smokeless tobacco use based on CPS-I and CPS-II data have also been reported by Henley et al. (Henley et al. 2005). Exposure in this study was defined as the use of either chew tobacco or snuff, together referred to as spit tobacco. The details of the cohort for both CPS I and II, as well as assessment of exposure to spit tobacco and estimation of outcomes, have been previously described. Investigators identified 460 deaths attributed to cerebrovascular disease among 7,745 current, exclusive spit tobacco users, and 1,451 deaths among 69,662 non-users in this cohort, suggesting a 46% increased risk of death due to cerebrovascular disease (HR = 1.46, 95% CI: 1.31-1.64) after adjusting for age, race, education, BMI, exercise, alcohol, fat, fruit & vegetable intake, and aspirin use.

The CPS-II cohort was formed in 1982 and followed 114,809 men who reported either never having used tobacco (n = 111,482), or being current exclusive (n =2,488) or former users (n = 839) of spit tobacco at the time the study was initiated. Risk of mortality due to cerebrovascular disease was calculated for each of these subgroups, with the non-users acting as the referent group in each case. In addition to the covariates applied in CPS-I, estimates in this cohort were also adjusted for employment status and type. After 18 years of follow-up, 1,858 deaths were observed in the referent group, 71 deaths among current users and 29 deaths among former users. These resulted in estimated mortality risks of 1.40 (95% CI: 1.10-1.79) among current users of any spit tobacco (either chew or snuff) compared to never-users. Exclusive users of snuff had a stroke mortality risk of 0.62 (95% CI: 0.23-1.67), while risk among users of chew tobacco only was 1.38 (95% CI: 1.02-1.86). Mortality risk for current users of both forms of ST was 2.57 (95% CI: 1.59-4.17), though only 17 deaths were recorded for this group. Among former users of either form of spit tobacco, the risk of mortality was not statistically significantly elevated compared to never users (HR= 1.21; 95% CI: 0.83-1.76). Thus, the increased risk of stroke mortality seems to be driven by risks among current users and risk among users of only chew or chew plus snuff. Forty-five of the 71 observed deaths occurred among exclusive users of chew tobacco, compared to 4 deaths among exclusive snuff users.

The results reported by Henley based on analyses of data from CPS I and CPS II do suggest a reasonably strong, positive association between spit tobacco use and cerebrovascular disease. However, some limitations of this study highlighted in the discussion of cardiovascular outcomes apply here as well including, for example, the possibility of non-differential misclassification of the exposure and the issues associated with generalizability of these results, both across time periods, and to the general population.

4.9.2 Scandinavian studies

Six Swedish studies were identified that evaluated the risk of stroke/cerebrovascular disease in male snus users: five that utilized large prospective cohorts formed over different periods, one nested case-control study, and one that pooled these and other cohorts. The exposure in each of these studies was moist snuff, or snus. All of these studies follow a similar design in exposure and outcome assessment, utilizing questionnaires administered by trained interviewers to record tobacco habits and using mortality and morbidity registries to obtain their outcome data. Outcomes were reported as hazard ratios, adjusted for similar potentially confounding health and lifestyle factors.

Bolinder et al. (1994) followed 84,781 men from the Swedish Construction Worker cohort from 1974 to 1985, including 32,546 men who never used tobacco and 6,297 exclusive smokeless tobacco users. The referent group was composed of individuals who reported never using tobacco. This study recorded 86 deaths in never-tobacco users and 30 in exclusive smokeless tobacco users. After controlling for age, area of domicile, BP (measured), BP medication, BMI (calculated), diabetes and previous CVD symptoms, the reported relative risk of death in exclusive snuff users due to cerebrovascular disease was 1.9 (95% CI: 0.6-5.7, based on four deaths) in the 35-54 age group and 1.2 (95% CI: 0.7-1.8, based on 26 deaths) in the 55-65 year age group, suggesting that no association existed between smokeless tobacco use and risk of mortality due to stroke. In contrast, risk of stroke mortality was almost three times higher for current exclusive smokers in the 35-54 age group, when compared to never-tobacco users. No association was seen for those smoking <15 CPD, while the association was marginal for those smoking >15 CPD in the 55-65 age group. No association was found in former smokers.

Asplund et al. (2003) conducted a nested case-control study based on the MONICA and Vasterbotten Intervention Project cohorts. There were 276 cases of fatal or non-fatal stroke identified among the male participants in these studies between 1985 and 2000 in these cohorts. Five hundred and fifty-one controls, matched for age, geographic area, year of baseline examination and cohort were selected for comparison. The analyses were adjusted for diagnosis of hypertension, diabetes and/or high cholesterol, level of education and marital status. Compared with the reference group of never users of tobacco, odds of stroke, either fatal or non-fatal, were reported to be 1.05 times among exclusive snus users (95% CI: 0.37-2.94), while the odds among exclusive smokers were elevated by more than two (OR = 2.21, 95% CI: 1.29-3.79). The small sample size and the possibility of non-differential misclassification of exposure, due to exposure having been measured only once in both the cohorts, which biases the result towards the null, affect the interpretability, generalizability and the power of this study.

The study by Haglund et al. (2007) followed a cohort of 5,002 men aged 16-74 years identified from the Swedish Survey of Living Conditions (ULF) to investigate the association between snus use and IHD, and also reported outcomes for fatal and non-fatal stroke. This study did not find an association between snus use and incidence of stroke events (IRR = 1.07; 95% CI: 0.65-1.77), although an association was found when exclusive smokers were compared to never-tobacco users (IRR = 1.4 95% CI: 1.03-1.91); in other words, risk of mortality or hospitalization due to stroke was not associated with exclusive snus use, but was associated with exclusive smoking, when compared to never-users. All analyses were controlled for age, SES, residential area, self-reported health, number of chronic illnesses and physical activity.

Age-standardized rates and hazard ratios were reported for both incidence of and mortality from hemorrhagic and ischemic stroke in 118,465 male, never smoking, former and current exclusive snus users registered with the Swedish Construction Workers cohort between 1978 and 1993 (Hergens et al. 2008a). Among approximately 84,110 never tobacco users, 2,369 former snus users and 31,986 current snus users, there were 2,805, 31 and 412 cerebrovascular events (all types of strokes, both fatal and non-fatal) recorded. For all types of stroke combined, no associations between ever, former or current snus use and all types of stroke combined, fatal or nonfatal, were identified. However, an increased risk of fatal ischemic stroke was identified in ever (RR=1.63, 95% CI: 1.02-2.62) and current exclusive (RR=1.72, 95% CI: 1.06-2.78) snus users compared to never tobacco users. An increased risk of unspecified stroke type (fatal and nonfatal combined) was also reported in current exclusive snus users compared to never tobacco users (RR=1.35, 95% CI: 1.02-1.80). No clear dose response patterns were identified according to amount of snuff used and risk of stroke.

Results based on the Screening Across the Lifespan Twin Study (SALT), which included 12,525 never snus users, 1,456 former exclusive snus users, and 2,661 current exclusive snus users, also found no association between current or former snus use and cerebrovascular disease compared to never tobacco users. A statistically significant association in current exclusive smokers (aRR = 1.61, 95% CI: 1.22-2.13) compared to never tobacco users was reported (Hansson et al. 2009). Participants were followed for an average period of 4.9 years, between 1998-2002 and 2003-2005.

Janzon and Hedblad (2009) investigated a prospective cohort of 10,743 males and 16,754 females between 45 and 73 years of age, formed as part of the Malmo Diet and Cancer study, with baseline recruitment from 1991-1996 and follow-up through 2004. However, since only one case of stroke was observed among 75 women who were snus users at baseline, effect estimates were reported for male participants only. Among 136 male exclusive snus users, 4 cases of stroke were reported. Adjusting for age, BMI (calculated), a diagnosis of diabetes mellitus and/or hypertension, physical activity, marital status and occupation, the authors reported a relative risk of 0.59 (95% CI: 0.2-1.5) compared to never-tobacco users, suggesting no association of snus use with risk of stroke.

Given the long duration of follow-up and single ascertainment of the exposure, the possibility of non-differential misclassification of the exposure cannot be ruled out in each of these studies, which, if present, under-estimates the true effect size. Another source of misclassification of exposure in Haglund et al. was the lack of delineation between exclusive snus users and users of both snus and cigarettes.

In addition to these studies, two studies, one from Sweden and one from the US, evaluated the association of biomarkers of atherosclerotic vascular disease with smokeless tobacco use. Both these studies investigated changes in the carotid intima media thickness (CIMT) and carotid bulb diameter as a surrogate marker for general atherosclerotic disease. The results of these studies are discussed here because the results directly apply to the risk of ischemic stroke, given the anatomical location of the carotid artery.

In some cases of ischemic stroke, atherosclerosis and occlusion of the lumen of the common carotid is an antecedent event, and measuring the degree of this occlusion helps quantify the risk of ischemic stroke in these individuals. Bolinder et al. (1997) examined the effect of snus use on carotid intima media thickness and the diameter of the common carotid artery. This cross-sectional study recruited 143 male firefighters 35-60 years of age from Stockholm, among whom 40 were never tobacco users and 28 were exclusive snuff users. Ultrasonographic images of the right common carotid artery were used to assess wall thickness and luminal diameter, both of the artery and the carotid bulb. No statistically significant differences were identified in smokeless tobacco users compared to never tobacco users; however, the small sample size and lack of adjustment for other confounders limits the interpretability of these results. This study also reported results based on comparisons of lumen diameter in 29 smokers and 40 never-tobacco users, but the smoker group includes 5 subjects who were dual users; for this reason, results pertaining to smokers are not discussed here.

A more recent investigation of the biomarkers of atherosclerotic disease was undertaken by Nordskog et al. (2015). A total of 168 males 26-49 years of age were recruited into a single-center, single site, age-stratified, intervention study: 60 were exclusive smokers, 48 were moist snuff users, and 60 were non-tobacco users. Biomarkers of atherosclerosis were estimated after exposure to the participants' usual brand and form of tobacco. Results from two-way ANOVA did not suggest a significant difference when comparing the three groups as a whole. However, pairwise comparisons, stratified by age, suggested a statistically significant difference in the mean CIMT between the smoking group and the moist snuff users group in the 44-49 age group. In those who were 44-49 years of age, mean CIMT was 0.73 mm among the smokers and 0.63 mm for the moist snuff users

(p-value = 0.02). A comparison of the mean CIMT between moist snuff users and non-tobacco users (mean = 0.69 mm) was not statistically significant (p = 0.35) nor was the comparison between smokers and non-tobacco users (p = 0.38). None of the pairwise comparisons in the other age-categories nor the overall pairwise comparisons reached statistical significance. In this case too, the small study size precludes interpreting these results as strong evidence of an association, at least in the context of cerebrovascular disease. The similarity of CIMT for non-tobacco users compared to smokers suggests the possibility of selection bias influencing the results: study subjects were recruited voluntarily through advertisements, and may have volunteered due to personal or family health concerns related to stroke risk.

The studies reviewed above provide inconsistent evidence suggesting an association between ST use and increased risk of mortality due to stroke in both Swedish and US studies, when all types of stroke are considered. The evidence for this association, however, is not unequivocal, with results from two large cohorts supporting it and a number of smaller studies refuting it. Among US studies, the results from Henley et al. most strongly support this association, particularly among current users of smokeless tobacco. This study estimated the magnitude of the increased risk among current users to lie between 10-79%; among former users, this excess risk was 21% and it was not statistically significant. Stratified analysis of the data from CPS-II suggests that use of chew tobacco contributes more to this risk than snuff use. One of the largest Swedish studies to examine stroke risk associated with snus use also supports this association (Hergens et al. 2008a). The results from this study suggest the risk of mortality from all strokes combined to be about 38% higher, though not statistically significantly so, in snus users versus non-users; this risk is highest among current snus users, in whom a large proportion of the risk of mortality is contributed by mortality from ischemic stroke. The prospective nature of each of these cohorts and their large sample sizes suggest that these studies have reasonable statistical power to support their conclusions, and are also generalizable to adult men who are exclusive snus users. It must be pointed out that neither of these studies found a significant exposure-response or a duration of use-response relationship with either stroke incidence or mortality.

Very few of these studies have offered direct comparisons of either mortality or incidence risks for smokers compared to ST users. One way of achieving this is by relying on indirect comparisons of each individual exposure with a common referent group. Three studies, by Bolinder et al. (1994), Asplund et al. (2003) and Haglund et al. (2007), permit this kind of comparison. Results from Bolinder et al. (1994) suggest an association of stroke mortality among current smokers, particularly those in the 35-54 year age group; the risk is nearly three times that observed in never-users of tobacco, while snus use is not significantly associated with stroke mortality when compared to the same referent group. However, the small number of deaths recorded among smokers should be taken into account before concluding in favor of a strong association. The results from Asplund et al. (2003) and Haglund et al. (2007) suggest an increased risk of stroke mortality in smokers compared to non-tobacco users; Haglund et al. suggest an approximately 40% increased risk for incidence of stroke in smokers compared non-tobacco users, while they reported a non-statistically significant increase of 7% in the risk of death among snus users compared to non-tobacco users. According to Asplund et al. (2003), the risk of all stroke events among exclusive smokers, compared to never-users of tobacco, are elevated more than twice. While statistically significant, the small sample sizes and small number of outcomes observed in these studies prevent drawing causal conclusions about the excess risk of mortality due to stroke from smoking.

4.9.3 Reviews and meta-analyses

A pooled analysis by Hansson et al. (2014), which drew from some of the cohorts included in the above studies, did not find any elevated risk of mortality from all types of stroke in snus users; this result is pertinent because of the statistical power achieved by the pooled sample. A total of 130,485

Swedish males were available for this analysis. Compared to never tobacco users, the HR for overall stroke was 1.01 (95% CI: 0.89–1.14, based on 291 exposed cases) among current users and 0.88 (95% CI: 0.64–1.22, based on 39 exposed cases) among former users. Similar hazard ratios were observed for stratified analyses of individual types of stroke, duration and amount of snus use. The results were adjusted for BMI, year of diagnosis and socio-economic position; however, other potential confounders such as physical activity were not controlled, which might have resulted in some residual confounding in this analysis. Of note, Hansson et al. included the Construction Workers Cohort, the Malmo Diet and Cancer Study, MONICA, the National March Cohort, the SALT study, the Stockholm Public Health Cohort, the Scania Public Health Cohort, and the Work, Lipids, and Fibrinogen Study in their analysis (Alfredsson et al. 2002 Bellocco et al. 2010, Carlsson et al. 2006, Eriksson et al. 2011, Hansson et al. 2011, Hergens et al. 2007, Lichtenstein et al. 2006, Manjer et al. 2001). To our knowledge, results related to snus and stroke have not been published previously from the National March Cohort, the Scania Public Health Cohort, the Stockholm Public Health Cohort or the Work, Lipids, and Fibrinogen Study. Snus and stroke findings from the Swedish Construction Workers Cohort, the Malmo Diet and Cancer Study, MONICA, and the SALT study were included in this review and were discussed earlier.

In contrast, results from two large meta-analyses of cohort studies discussed above did suggest an association between snus use and mortality from all types of stroke. Based on four of the eight publications reviewed above (Accortt et al. 2002, Asplund et al. 2003, Bolinder et al. 1994, Henley et al. 2005), Lee (2007) estimated the risk of mortality from all types of stroke among ever users of snus compared to never users to be 1.42 (1.29-1.57). On the basis of the studies conducted in the US by Henley et al. (2005) and Accortt et al. (2002), Lee also estimated that the risk of stroke death for current ST users compared to never-users was 1.41 (95% CI:1.17-1.71). Risk was not statistically significantly elevated in the Swedish studies (1.17, 0.80-1.70). There was no statistical evidence of heterogeneity in the studies included in this analysis (p=0.29).

A later meta-analysis by Boffetta and Straif (2009) identified a non-statistically significant increased risk of mortality due to stroke of all types among ever-users of ST compared to never users, with the excess risk estimated to be around 19% (HR = 1.19, 95% CI: 0.97-1.47). For current ST users, the risk was 1.28 (95% CI: 1.00-1.64), while for former users, the risk was 0.93 (95% CI: 0.56-1.55). Heterogeneity was reported for all three risk estimates. Smokeless tobacco use was associated with an increased risk of any stroke in US studies (RR=1.39, 95% CI: 1.22-1.60), but not the Swedish studies (RR=1.02, 95% CI: 0.93-1.13). For fatal stroke, risk was statistically significantly increased in ever ST users (RR=1.40, 95% CI: 1.28-1.54) and current users (RR=1.44, 95% CI: 1.31-1.59), but not former users (RR=0.86, 95% CI: 0.26-2.79). Risk for fatal stroke was statistically significantly elevated in the US studies (RR=1.39, 95% CI: 1.22-1.60) and elevated, but not statistically significantly, in the Swedish studies (RR=1.25, 95% CI: 0.91-1.70).

4.9.4 Synthesis of findings

On balance, while the evidence is not conclusive, results from large, population-based cohort studies and pooled analysis of these cohort studies support a substantially positive association of stroke mortality with ever having used snus, especially among current users. The evidence for an association with stroke incidence and ST is not as well supported.

4.10 Indicators of cardiovascular dysfunction

4.10.1 Peripheral artery disease

An important component of cardiovascular atherosclerotic changes is peripheral arterial disease (PAD). The results from two studies identified in our review, one conducted in the US and one in Sweden, are briefly described here in order to round out the discussion of atherosclerotic changes in association with smokeless tobacco.

The study by Nordskog et al. (2015) has been previously described. This study also examined anklebrachial pressure index (ABI), an indicator of the degree of occlusion of lower-limb arteries, and variation in flow-mediated dilatation (FMD) of the brachial artery (a surrogate for endothelium mediated dilatory response) between smokers, moist snuff users and non-tobacco consumers. No statistically significant differences in FMD or ABI were identified in smokers compared to moist snuff users or moist snuff users compared to non-tobacco consumers. On day 1 of the study, following a 45 minute tobacco abstention and then use of the experimental product, ABI was statistically significantly lower in smokers compared to non-tobacco consumers, but this difference was not observed on day 2, following tobacco abstention overnight. An earlier study, by Rohani and Agewall (2004), also assessed FMD and reactive hyperemia, a measure of vascular compensation in response to ischemia, in a group of 20 healthy, habitual snuff users. These parameters were also tested in ten of the participants exposed to a placebo, in order to obtain a crossover sample for comparison. At 35 minutes after administration of snuff, the study found a statistically significant decrease in FMD from baseline. No change was found in the placebo group, and no significant changes in reactive hyperaemia were found. Taken together, the results from these studies do not support an association between ST use and peripheral artery disease, but given the limitations of both of these studies (low statistical power, restricted applicability of the results), this evidence should be considered suggestive, only.

4.10.2 Heart rate variability

Along with blood pressure, heart rate is the most direct indicator of cardiovascular activity. The importance of investigating an association of snus / snuff with these outcomes lies in the fact that even a relatively small change in the heart rate, can directly affect systolic blood pressure and myocardial oxygen demand. Five US studies investigated an association between smokeless tobacco use and either heart rate or variations in heart rate in humans (Ernster et al. 1990, Ksir et al. 1986, Morente-Sanchez et al. 2015, Siegel et al. 1992). Two Swedish studies also examined heart rate variations associated with snus use (Bolinder and de Faire 1998, Eliasson et al. 1991). All but one of these studies (Morente-Sanchez et al. 2015) has been discussed in detail in the section on blood pressure and will not be described at length here.

4.10.2.1 US studies

Squires et al. (Squires et al. 1984) reported the results of an experiment designed to ascertain whether use of ST had a short-term influence on cardiovascular hemodynamics. The study observed statistically significant changes in heart rate in twenty individuals, without any prior history of hypertension or other cardiovascular impairments, before, during and a short time after administering 2.5 g of moist snuff orally. Specifically, the mean heart rate changed from 69 beats per minute (bpm) at the pre-experiment baseline, to 89.3 bpm after administration of moist snuff, and remained elevated, compared to baseline, 20 minutes after removal of the exposure at 84.6 bpm. Although this study collects information under controlled conditions, it is limited due to its small sample size and restriction to young men.

Ksir et al. (1986) followed five college baseball players, who were users of Copenhagen snuff, and asked them to use and retain their “normal ‘pinch’” of Copenhagen snuff prior to exercise and during different intensities of exercise. This study reported a statistically significant difference in heart rate before and after administration of snuff, both while at rest and during all but the highest effort phases of a graduated exercise program. Again, while this study is conducted under controlled conditions, it is limited by its small size, focus on young, male athletes, and lack of information regarding the athletes’ cigarette smoking histories.

Two additional US studies recruited male professional baseball players to study the effects of smokeless tobacco use on hemodynamic variables. Both of these studies employed a cross-sectional design with a single point of contact at which exposure (i.e., smoking status, duration and dose of

smokeless tobacco use) and outcome (SBP, DBP, resting heart rate) were measured, and differed only in the number of participants. The study by Ernster et al. (1990) reported no difference in blood pressures (n=282) and resting heart rate (n=279) comparing current ST users with 119 former users or 118 nonusers after adjusting for age, race smoking, and caffeine level. Among 116 current users who had used ST within the last week, no associations between blood pressure and duration of use or time since last use were found. However, ST use within the hour before the examination was associated with a significantly higher pulse rate (72 vs. 64 beats per minute) compared to those who used ST more than 24 hours before ($p<0.01$). Another study conducted in the same population of professional baseball players was published by Siegel et al. (1992). Utilizing a cross-sectional study design, this study compared mean pulse rates between 175 non-tobacco chewing baseball players and 126 tobacco chewing players, adjusting for age, race, alcohol use and serum caffeine levels. This study did not find a statistically significant association. The possibility of confounding also remains high in the study.

The most recent investigation of variations in heart rate come from a double-blind, randomized, crossover trial conducted by Morente-Sanchez et al. (2015). The exposure in this study was snus, and the participants also were trained athletes, college football players. This study differed from the other studies in employing a washout period between snus use and placebo exposure. Different aspects of the EKG of the participants were assessed during exposure to placebo and snus. The study reported a statistically significant interaction between exposure (snus or placebo) and the time of measurement (before or after exposure and performance of physical activity), for almost all aspects of the EKG measured: average R-R interval, instantaneous beat-to-beat variability and root mean square of successive differences in length of the QRS complex, all of which suggest a high degree of inconsistency in heart rhythm after exposure to snus.

All of these studies share limitations that do not permit any interpretation of the results. The results are not generalizable due to the non-representativeness of the sample populations; acute effects of tobacco exposure may differ considerably in habitual vs. non-habitual users of smokeless tobacco products; several, but not all, of the studies were restricted to trained athletes; and the exposure to “smokeless tobacco” is not uniform between the US and Swedish studies.

4.10.2.2 Scandinavian studies

Two Swedish studies (Eliasson et al. 1991, Bolinder and de Faire 1998), employed cross-sectional designs to study the effect of moist snuff, presumably snus, on the dynamics of the cardiovascular system. The study by Eliasson et al. (1991) included 58 male volunteers who were either exclusive smokers (n = 19), exclusive snus users (n = 21) or non-tobacco users (n = 18). Measurements of heart rate, among other physiological hemodynamic measurements, were obtained during a single point of contact. The results for pulse rate were not shown, but the investigators reported that no differences were found in pairwise analysis of the three groups. A small sample size, lack of generalizability as a result of the use of newspaper ads to recruit volunteers, and lack of detail about covariates limit the utility of these findings.

The study by Bolinder and de Faire (1998) monitored blood pressure in 135 male firefighters in Stockholm, of whom 59 were non-tobacco users, 29 were smokers and 47 were exclusive snuff users, over a 24 hour period. The study found a statistically significant increase in the mean heart rate over 24 hours, mean heart rate during daytime, mean heart rate during nighttime and variation in the mean heart rate between day and nighttime among snuff users compared to never-tobacco users, though the actual magnitude of change was relatively small and of uncertain clinical significance (between 2 and 6 bpm over all four comparisons). For comparison, a statistically significant increase in the mean heart rate over 24 hours, mean heart rate during daytime, and mean heart rate during nighttime was also found in smokers compared to never-tobacco users, and the actual magnitude of change was larger (between 4 to 11 bpm over all three comparisons). The

results were adjusted for age, BMI, waist-to-hip ratio, physical fitness levels and alcohol consumption.

These two studies suffer from similar methodological issues observed in the US studies. Even accounting for these issues, none of the studies (US or Swedish) provide evidence for an association between ST use and an effect on heart rate.

4.10.3 Atrial fibrillation

The only study identified that provides evidence on the potential relationship between ST use and arrhythmias was by Hergens et al. (2014), who investigated the association between snus and the risk of incident diagnoses of atrial fibrillation in a pooled analysis of seven large, previously formed cohorts in Sweden, consisting of 274,882 men in total. The hazard ratio of atrial fibrillation among never-smoking, current users of snus compared to non-current users of snus was 0.97 (95% CI 0.71-1.33, 425 cases), after adjusting for age, BMI and level of education, suggesting no increased risk of atrial fibrillation with current snus usage. The inclusion of former snus users in the reference group likely minimized the difference between the two groups and potentially biased the results towards the null.

4.10.4 Heart failure

One study examined the association between snus use and heart failure (Arefalk et al. 2012). This study combined data from two different cohorts in Sweden, the Uppsala Longitudinal Study of Adult Men (ULSAM), formed in 1970-73, and the Construction Workers Study, formed in 1969. For this study, ULSAM was updated from 1991-95 through 2002 and included 995 participants without a history of myocardial infarction. The results from the ULSAM are not discussed here as this cohort did not make a distinction between exclusive snus users and users of both cigarette and smokeless tobacco. The Construction Workers Study, on the other hand, included subjects who used snus exclusively, without concomitant use of cigarettes. The cohort was followed from 1978, when adequate ST use data were available, through 2003, and included 118,425 participants. During follow-up, the study recorded 464 cases of heart failure among 83,705 never-users, 75 cases among 32,281 current users, and 6 cases among 2,439 former users. After adjusting for age, BMI, region of residence, systolic and diastolic blood pressures, and myocardial infarction during follow-up, current (HR =1.24, 95% CI: 0.97-1.59) and former (HR=0.99, 95% CI: 0.44-2.22) snus users did not have statistically significant elevated risk of heart failure compared to never-tobacco users. No significant trend was detected by the amount of snus used per day (p=0.90), though this may be due to lack of power in the usage groups. Sensitivity analyses restricted to non-ischemic heart failures reported similar results for current snus users compared to never tobacco users (HR=1.28, 95% CI: 0.97-1.68). The results of this study do suggest that there is an association between current snus use and heart failure, though results from one study are inadequate for causal inference. Limitations, particularly related to exposure assessment, in the Construction Workers Study have been discussed previously.

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TABLES

Table 1: Search terms used to identify literature on oral and lung cancers, respiratory diseases and cardiovascular disease among users of snus and other smokeless tobacco products compared with cigarette smokers and never or non-users of tobacco products

Exposure terms[2]	(("Oral" AND "tobacco") OR ("chew" AND "tobacco") OR ("alternative" AND ("nicotine" OR "tobacco")) OR ("plug" AND "tobacco") OR "potential reduced exposure products" OR preps OR ("spit" AND "tobacco") OR "non-cigarette tobacco" OR ("chew" AND "plug") OR ("chewing" AND "tobacco") OR dip OR "dissolvable tobacco" OR dissolvable OR dissolvable OR "dry snuff" OR "non-combustible PREPs" OR ("smokeless tobacco") OR snuff OR snus OR ("spit" AND "tobacco") OR ("spitless" AND "tobacco" AND "lozenges") OR ("loose" AND "leaf" AND "chew") OR ("moist" AND "plug") OR ("personal" and "vaporizers") OR "non-cigarette tobacco").
Outcomes[3]	
Cancer	(To be combined with terms identifying site): cancer, neoplasm, carcinoma.
Oral cancers	Oral, oropharyngeal, buccal, “buccal cavity”, mouth, “head and neck”, laryngeal.
Lung cancers	Lung, pulmonary, bronchial, respiratory, bronchogenic.
Non-cancer Respiratory Diseases	Asthma, “chronic obstructive pulmonary disease”, “COPD”, bronchiectasis, bronchitis, emphysema.
Cardiovascular diseases (CVD)	"Cardiovascular disease", "angina pectoris", "fatal myocardial infarction", "nonfatal myocardial infarction", “acute myocardial infarction”, "myocardial infarction", "cardiac arrhythmia", "peripheral vascular disease", "ischemic events", "heart disease", "rapid heartbeat", tachycardia, "heart attack", "cardiac arrest", "Irregular heartbeat", "heart palpitations", "high blood pressure", hypertension, stroke, “brain attack”, “cerebrovascular accident”, “transient ischemic attack”

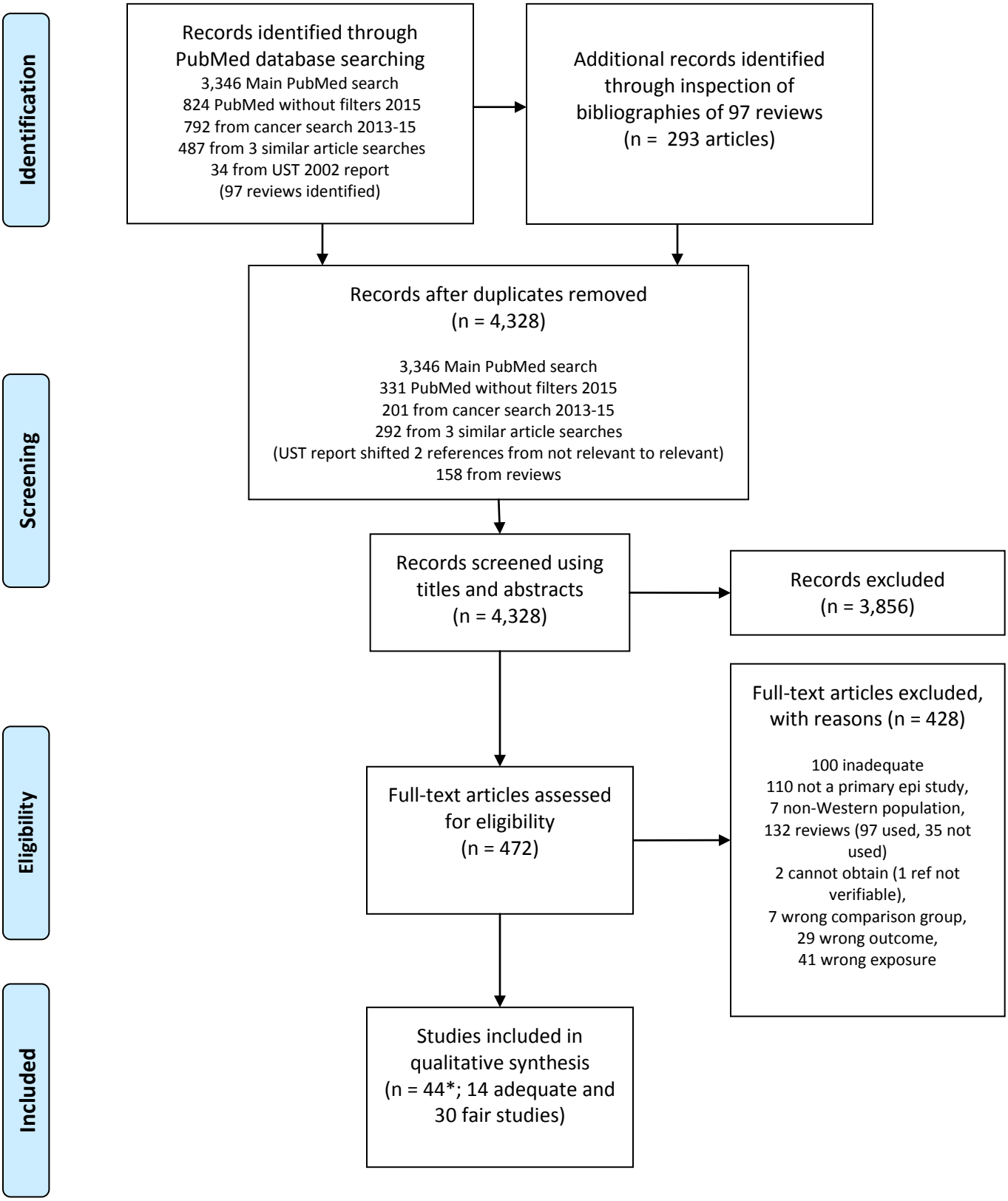
[1] Quotes ("") ensure strings are searched as phrases, and not as individual words.

[2] The search terms for the exposure were used en bloc and were paired, using boolean operators, with each possible combination of the outcome terms.

[3] All associated MeSH terms for each outcome were included as search terms.

FIGURES

Figure 1. Data identification and acquisition



*The two publications including pooled analyses are discussed with the reviews and meta-analyses.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

APPENDIX A
PROTOCOL

Prepared for:
RAI Services Company
Winston-Salem, North Carolina

Document type:
Protocol Report

Prepared by:
Ramboll Environ
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Date:
October 7, 2015

Finalized:
April 8, 2016

PROTOCOL FOR A SYSTEMATIC, CRITICAL REVIEW OF THE LITERATURE PERTAINING TO THE RISKS OF ORAL AND LUNG CANCERS, CARDIOVASCULAR DISEASE AND RESPIRATORY DISEASES AMONG SNUS AND SMOKELESS TOBACCO USERS



RAMBOLL ENVIRON

CONTENTS

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FIGURES

1 INTRODUCTION

Ramboll Environ was asked by RAI Services Company (RAIS) to provide consulting support as they prepare to submit an application to the Food and Drug Administration (FDA) for a modified risk tobacco product (MRTP) order for Camel Snus, a moist snuff product. Specifically, Ramboll Environ has been asked to conduct and document a systematic, critical review of the pertinent epidemiological literature on the risks of oral and lung cancers, respiratory diseases and cardiovascular disease among users of snus and other smokeless tobacco products compared with either cigarette smokers or never or non-users of tobacco products. See section 6.1, modification 1.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines defines a systematic review as a "review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review" (Moher 2009 PRISMA). To facilitate this rigorous process, a 27-item checklist and four-phase flow diagram were created for researchers to use (see Figures A1 and A2). Ramboll Environ will closely follow all relevant elements of the PRISMA guidelines in conducting this review, with particular attention to guidelines for documenting procedures and decisions.

2 LITERATURE IDENTIFICATION

Relevant publications will be identified from the National Library of Medicine's PubMed database. Specific search terms, the dates of searches, and the number of publications identified will be tracked using a standardized documentation sheet (Table A1). Searches will be limited to studies conducted in humans and published in the English language. See section 6.2, modification 2.

Prior knowledge about this research topic as well as exploratory searches of PubMed will be used to generate search terms. Search strategies will be developed in a team setting. A preliminary list of terms that will be tested is presented in Table A2. Boolean operators will be used to combine search terms and focus results. An example of the search strategy that will be implemented in PubMed is as follows:

a) Search ("lung cancer") OR ("lung neoplasms")

b) Search snus OR "moist snuff" OR ("smokeless tobacco")

c) Search (("lung cancer") OR ("lung neoplasms")) AND (snus OR "moist snuff" OR ("smokeless tobacco"))

combine a AND b = c

See section 6.2, modification 3.

To confirm that the final search strategies successfully captured all relevant literature, the bibliographies of previously published, relevant literature reviews will be examined to confirm the completeness of the search results. See section 6.2, modifications 4-8.

3 SCREENING

Inclusion and exclusion criteria

Studies eligible for inclusion will: 1) present primary epidemiological research; 2) examine oral and lung cancers, cardiovascular disease or respiratory diseases as endpoints; and 3) compare snus or smokeless tobacco users with cigarette smokers and never or non-users of tobacco products. See section 6.3, modifications 9 and 10. Only users of Western types of snus and other smokeless tobacco products will be included. The disposition of each excluded article will be documented with reasons. Reasons for exclusion will include studies not conducted in humans, studies not published in the English language, duplicate articles, papers that do not present primary research, studies with the wrong outcome, exposure, or comparison group, and studies of inadequate quality; see section 6.3, modification 11. Refinements to the criteria for including or excluding potentially relevant articles and reports will be determined based on the material that is identified and the result of its ongoing review, and documented.

A figure tallying this process, as shown in Figure 2 of the PRISMA guidelines, will be prepared at the end of the screening process.

Screening and Study Ranking

A preliminary screening of the titles and abstracts of all articles identified will be conducted and used to categorize studies as likely relevant, of questionable relevance, or not relevant. The full text of articles categorized as being of likely or questionable relevance will be obtained and a second round of screening and review will be conducted. See section 6.4, modification 12.

The second round of screening, where full text articles are reviewed, will allow us to confirm the relevance of studies categorized as likely relevant and determine the disposition of studies categorized as being of questionable relevance. Again, the disposition of each article will be documented with reasons and used to prepare a summary figure (see Figure A2). See section 6.4, modification 13.

All relevant studies will be carefully critiqued and ranked for quality. Relevant studies will be ranked as adequate, fair, or poor quality. See section 6.4, modification 14. The elements of the study that will be considered in assigning a ranking are presented in Table 3 and include, in brief: clear and relevant study objectives; adequately described and appropriate study methods that minimize bias; well defined and accurately measured outcomes; well defined and specific exposures; consideration of confounding; and use of appropriate analytic methods. Judgment and discussion will be necessary in determining a ranking for some studies. Reviewers will document the decision-making process leading to their final judgment.

Studies rated “adequate” will tend to include large cohorts with a sufficient number of exposed and non-exposed participants and participants with the disease, or strong/large case-control studies with, for instance, good response rates; appropriate statistics; and appropriate control groups.

Studies rated “fair” will tend to include cohort and case-control studies with a small number of diseased or exposed individuals, small cohort studies, and all cross-sectional studies. The “inadequate” category will capture all other study designs including case series and studies

that do not include exclusive snus users. See section 6.4, modification 15. Cohort and case-control studies designed or executed with clearly identifiable biases or analyzed using inappropriate methods will also be categorized as “inadequate”.

Quality Assurance / Quality Control

To assess the accuracy of the initial quality assessment, a random sample of all articles identified through database searches and bibliography reviews will be re-screened for relevance and inclusion. Another random sample of articles excluded at initial screening or categorized as being of questionable relevance will also be re-screened. See section 6.5, modification 16.

If the quality control procedures indicate corrections to the screening process or guidelines are needed at this stage, additional samples of included and excluded articles will be selected for review to assess the accuracy of the subsequent screening. The total number of articles and reports selected for re-screening will depend on the accuracy of the initial screening process and the number of articles identified through the literature searches, and will be documented in the final protocol. A minimum of 2% - 5% of included and excluded articles will be re-screened. See section 6.5, modification 17.

The quality assessment and re-screening of articles will be conducted by an epidemiologist who did not participate in the initial review process. See section 6.5, modification 18. Disagreements, when necessary, will be discussed with a third epidemiologist. All literature screening and QA/QC processes will be conducted by trained epidemiologists.

4 DATA EXTRACTION

Key study characteristics and results from all studies of adequate or fair quality will be extracted into tables. The elements that will be extracted are the full study reference, first author, publication year, country, study name, study design, study population, study period, specific exposure (snus or type of smokeless tobacco product and brand name, if available), disease endpoint, number of cases/controls or exposed/unexposed, covariates, risk estimate, confidence intervals, p values, apparent biases, study quality ranking, limitations, rationale for any ranking other than “adequate”, and any additional comments.

Prior to data extraction, three to five studies will be selected for training purposes. All team members will review the training studies, abstract key information and rate their quality, and results will be compared. Additional studies will be included in the training process until consensus is achieved.

Quality assurance/quality control procedures will be built into the data extraction process. A random sample of studies will be selected for review by a different member of the project team. See section 6.6, modification 19. Inter-rater reliability will be assessed qualitatively (i.e., no statistics will be calculated) and used to identify problems of understanding or interpretation. Additional assessments of inter-rater reliability will be carried out as needed.

5 REPORTING

The results of each step of the literature search and evaluation process will be documented. The protocol and the bibliography resulting from the literature review will be provided to RAIS as a deliverable.

As a consequence of completing the systematic literature search and critical review on the health effects associated with use of smokeless tobacco products, we will identify a body of literature that is complete and relevant to the research questions at hand and can be used to prepare written material that is scientifically valid and accurate. See section 6.7, modifications 20-23.

The conclusions we are able to draw from the literature on the health effects associated with use of smokeless tobacco products will require making several important assumptions. For example, there are likely differences in the exposures experienced by users of various types of smokeless tobacco products used by consumers in the US due to differences in product composition, methods of use (e.g., chewed vs. held in the mouth), and typical portion sizes. The results of the literature review will be structured to address the research regarding specific product types, and it will provide a synthesis of the evidence supporting and not supporting associations between smokeless tobacco use, in general, and health risks. The final report will provide clear and careful documentation of the search and critical review process and a discussion of the gaps in and limitations of the literature.

6 MODIFICATIONS

This section lists modifications to the protocol. Underlining shows text added for clarification. Modifications shown without underlining represent new material. Strikethroughs show text that has been removed.

6.1 Introduction

1. Specifically, Ramboll Environ has been asked to conduct and document a systematic, critical review of the pertinent epidemiological literature on the risks of oral and lung cancers, respiratory diseases and cardiovascular disease among users of snus and other smokeless tobacco products <u>compared with either cigarette smokers or never or non-users of tobacco products.</u>

6.2 Literature Identification

2. In order to capture recently published articles, which might not have been indexed yet, searches will be repeated without filters for articles published in the latter part of 2015.
3. We will also carry out supplemental searches of studies published between 2013 and 2015 whose outcome is indexed simply as “cancer” i.e., not a specific type of cancer.
4. To confirm that the final search strategies successfully captured all relevant literature, the bibliographies of ~~key articles and any~~

previously published, relevant literature reviews and meta-analyses will be examined to confirm the completeness of the search results.

5. Because we expect to identify many reviews, each reviewer will exercise his or her judgment in determining which reviews are most pertinent. High quality reviews with focused research questions examining epidemiological literature will be selected over lesser quality publications.
6. Three key studies will be selected and the 'similar article' search feature in PubMed will be employed.
7. All PubMed searches will include references published through 10/6/2015, except for the 2013 to 2015 "cancer" search where publications through 10/26/2015 will be included.
8. All search results will be imported into ENDNOTE X5 where duplicates from the various search results will be removed and references will be stored, labelled, and sorted.

6.3 Literature Screening: Inclusion and exclusion criteria

9. Studies eligible for inclusion will: 1) present primary epidemiological research; 2) examine oral and lung cancers, cardiovascular disease or respiratory diseases as endpoints; and 3) compare snus or smokeless tobacco users with either cigarette smokers or never or non-users of tobacco products.
10. Studies will be excluded if they only present evidence for snus or smokeless tobacco use in those who are also current or former users of other tobacco products.
11. Reasons for exclusion will include studies not conducted in humans, studies not published in the English language, duplicate articles (i.e., already identified), papers that do not present primary epidemiological research, studies focused on non-Western tobacco types, studies with the wrong outcome, exposure, or comparison group, and studies of inadequate quality.

6.4 Literature Screening: Study Ranking

12. A preliminary screening of the titles and abstracts of all articles identified will be conducted and used to categorize studies as likely relevant, potentially relevant, or not relevant. The full text of articles categorized as being relevant or potentially relevant will be obtained and a second round of screening and review will be conducted.
13. The second round of screening, where full text articles are reviewed, will allow us to confirm the relevance of studies categorized as likely relevant and determine the disposition of studies categorized as being potentially relevant. Again, the disposition of each article will be documented with reasons and used to prepare a summary figure (see Figure A2).

14. All relevant studies will be carefully critiqued and ranked for quality. Relevant studies will be ranked as adequate, fair, or inadequate quality.
15. The “inadequate” category will capture all other study designs including case series and studies that do not include exclusive snus or smokeless tobacco users.

6.5 Literature Screening: Quality assurance / quality control

16. The “inadequate” category will capture all other study designs including case series and studies that do not include exclusive snus or smokeless tobacco users.
17. A minimum of 10% of included and 1% of excluded articles will be re-screened.
18. The quality assessment of articles will be conducted by an epidemiologist who did not participate in the initial review process.

6.6 Data Extraction

19. Following the full text review, a random sample of at least 20% of adequate and fair quality articles, 5% of inadequate quality, and 5% of not relevant articles will be selected for review by a different member of the project team.

6.7 Reporting

20. Results will be presented by health outcome. Within each outcome, evidence will be presented separately for studies conducted in US populations and Scandinavian populations, because US and Scandinavian smokeless tobacco products are not identical. However, given the fact that Camel Snus is a Swedish-style snus product in regards to tobacco type, formulation, portion size, production methods, and comparative chemistry, the epidemiology regarding the health effects of snus for Swedish cohorts is considered relevant for evaluating health risks to US users of Camel Snus.
21. The results of this literature review will provide a synthesis of the evidence supporting and not supporting associations between smokeless tobacco use, in general, and health risks.
22. The final report will provide clear and careful documentation of the search and critical review process and a discussion of the gaps in and limitations of the literature.
23. The results of the literature review will be structured to address the research regarding specific product types.

Figure A1. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Figure A2. PRISMA 2009 exclusions diagram

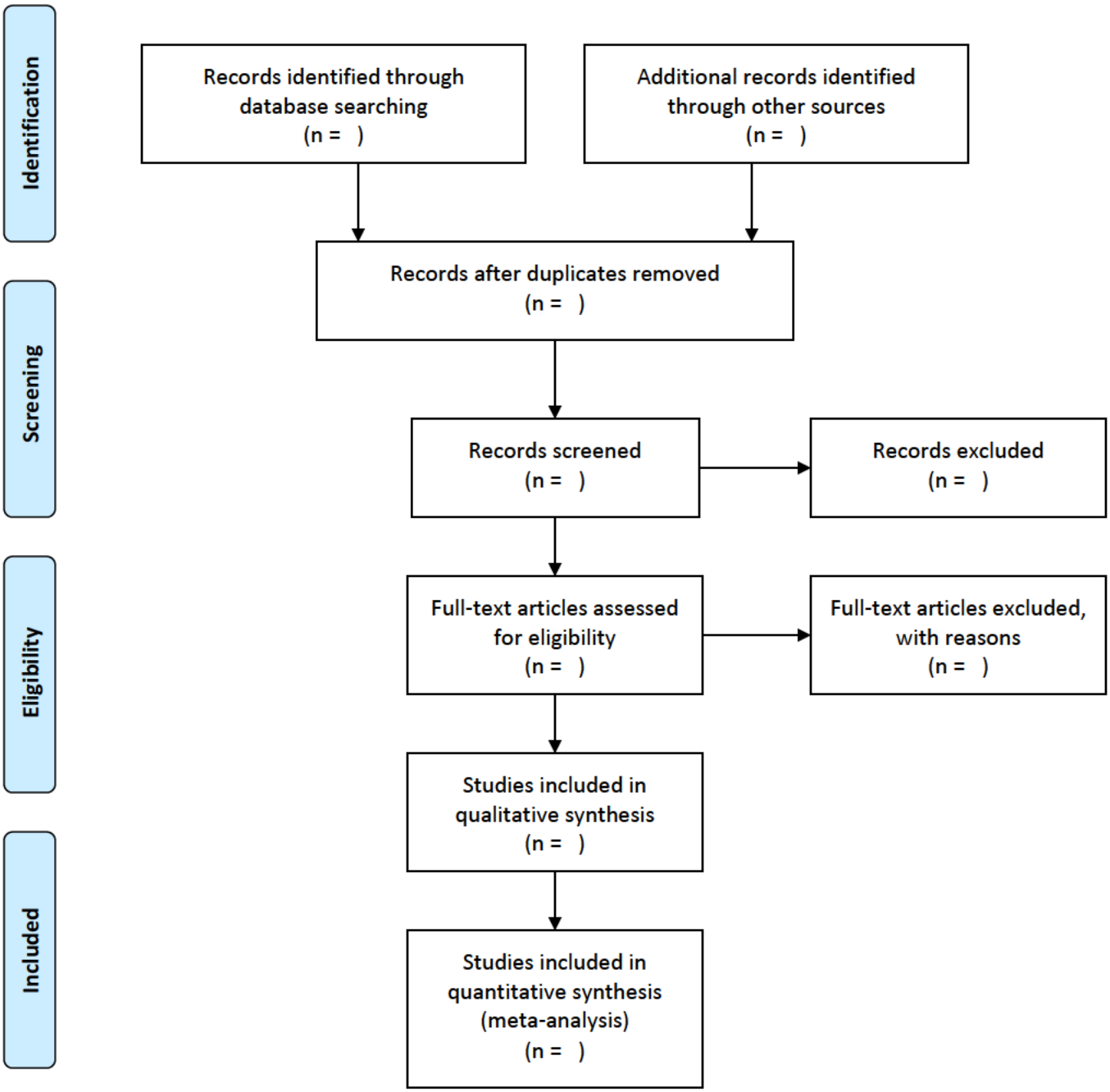

Table A1. Summary of Literature Searches

Literature Sources Searched:	
PubMed	☑
HSDB	☐
ToxNet	☐
IRIS	☐
CICADs	☐

I. Search of PubMed (standard site):
Note: All searches were limited to **human subjects and English language**. Other terms were not restricted by field unless indicated.

No.	Search terms	Results (#)	Saved File	Notes
	"XXX" AND "Case control"			
	"XXX" AND "Cohort"			
	"XXX" AND "Risk"			
	"XXX" AND "Exposure"			

Table A2: Preliminary search terms used to identify literature on oral and lung cancers, respiratory diseases and cardiovascular disease among users of snus and other smokeless tobacco products compared with cigarette smokers and never or non-users of tobacco products.

Exposure terms	(("Oral" AND "tobacco") OR ("chew" AND "tobacco") OR ("alternative" AND ("nicotine" OR "tobacco")) OR ("plug" AND "tobacco") OR "potential reduced exposure products" OR preps OR ("spit" AND "tobacco") OR "non-cigarette tobacco" OR ("chew" AND "plug") OR ("chewing" AND "tobacco") OR dip OR "dissolvable tobacco" OR dissolvable OR dissolvable OR "dry snuff" OR "non-combustible PREPs" OR ("smokeless tobacco") OR snuff OR snus OR ("spit" AND "tobacco") OR ("spitless" AND "tobacco" AND "lozenges") OR ("loose" AND "leaf" AND "chew") OR ("moist" AND "plug") OR ("personal" and "vaporizers") OR "non-cigarette tobacco").
Outcomes	
Cancer	(To be combined with terms identifying site): cancer, neoplasm, carcinoma.
Oral cancers	Oral, oropharyngeal, buccal, “buccal cavity”, mouth, “head and neck”, laryngeal.
Lung cancers	Lung, pulmonary, bronchial, respiratory, bronchogenic.
Non-cancer Respiratory Diseases	Asthma, “chronic obstructive pulmonary disease”, “COPD”, bronchiectasis, bronchitis, emphysema.
Cardiovascular diseases (CVD)	"Cardiovascular disease", "angina pectoris", "fatal myocardial infarction", "nonfatal myocardial infarction", “acute myocardial infarction”, "myocardial infarction", "cardiac arrhythmia", "peripheral vascular disease", "ischemic events", "heart disease", "rapid heartbeat", tachycardia, "heart attack", "cardiac arrest", "Irregular heartbeat", "heart palpitations", "high blood pressure", hypertension, stroke, “brain attack”, “cerebrovascular accident”, “transient ischemic attack”.
[1] Quotes ("") ensure strings are searched as phrases, and not as individual words.	

Table A3. Study attributes and their contribution to assessment of quality

Study Attribute	**Quality criteria**
Study objectives	Clearly stated Relevant to research questions
Study methods	Adequately described Appropriate for objectives Minimize selection and information bias Reasonable statistical power
Outcome measurement	Well-defined, reasonably specific Accurate measurement or diagnosis Proper time frame for risk of outcome
Exposure measurement	Well-defined, specific Verified (e.g., with biomarkers) Accounts for changes over time
Control of confounding	Known risk factors considered and measured Reasonable analysis method(s) used (stratification, multivariate statistical models)

APPENDIX B
SEARCH STRATEGY

Search strategy for RAIS MRTPA systematic, critical literature review:

Literature Sources Searched: 10/06/2015
(with the exception of search strategy #3 where publications through 10/26/2015 were included)

PubMed	☑
HSDB	☐
ToxNet	☐
IRIS	☐
CICADs	☐
Bibliographies of relevant reviews	☑

I. Search of PubMed (standard site): All searches were limited to **Humans, English**.

II. The search term for the exposure, shown below, was used en bloc in each search:
((("Oral" AND "tobacco") OR ("chew" AND "tobacco") OR ("alternative" AND ("nicotine" OR "tobacco")) OR ("plug" AND "tobacco") OR "potential reduced exposure products" OR preps OR ("spit" AND "tobacco") OR "non-cigarette tobacco" OR ("chew" AND "plug") OR ("chewing" AND "tobacco") OR dip OR "dissolvable tobacco" OR dissolvable OR dissolvable OR "dry snuff" OR "non-combustible PREPs" OR ("smokeless tobacco") OR snuff OR snus OR ("spit" AND "tobacco") OR ("spitless" AND "tobacco" AND "lozenges") OR ("loose" AND "leaf" AND "chew") OR ("moist" AND "plug") OR ("personal" and "vaporizers") OR "non-cigarette tobacco" OR MRTP OR "modified risk tobacco product")

III. This term was paired with each outcome term, as shown in the table below. The exposure term was paired with every possible combination of the outcome terms, in order to capture all possible results. For the outcomes 'oral cancer' and 'lung cancer', all possible combinations of the synonyms for cancer and site were included.

IV. Each of these search results was downloaded in MEDLINE format and imported into ENDNOTE X5, with 'import options' set to 'Pubmed (NLM)'. Duplicates among the various search results were set to be eliminated during the import step.

V. In order to ensure that articles which were not yet classified in Pubmed were not missed due to filters set to capture studies in humans or published in the English language only, studies published in 2015 were specifically searched for in Pubmed, without these filters, and the search results were added to the final list of search results.

#	PubMed Search terms	Results (#)	Saved File	Notes
1.	**Main PubMed search**			
	Exposure **AND** (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields]) OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields])) **AND** ("oropharynx"[MeSH Terms] OR "oropharynx"[All Fields] OR "oropharyngeal"[All Fields]) **with filters 'human' and 'English'.**	269	medline_filters_oropharyngeal.txt	Oropharyngeal cancer
	Exposure **AND** (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields]) OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields])) **AND** ("buccal"[All Fields] OR "buccal cavity"[All Fields]) with filters **with filters 'human' and 'English'.**	157	medline_filters_buccal_cancer.txt	Buccal cancer
	Exposure **AND** (("mouth"[MeSH Terms] OR "mouth"[All Fields]) **AND** (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields]) OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]))) **with filters 'human' and 'English'.**	1,808	medline_filters_oral_mouth_cancer.txt	Mouth cancer
	Exposure **AND** (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields]) OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields])) **AND** (("larynx"[MeSH Terms] OR "larynx"[All Fields]) OR ("larynx"[MeSH Terms] OR "larynx"[All Fields] OR "laryngeal"[All Fields])) **with filters 'human' and 'English'.**	332	medline_filters_laryngeal_all terms.txt	Laryngeal cancer
	Exposure **AND** ("head and neck"[All Fields] AND (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields]) OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]))) **with filters 'human' and 'English'.**	597	medline_filters_h&n_all terms.txt	Head & neck cancer
6	Exposure **AND** ("oral cancer"[All Fields] OR "oral neoplasm"[All Fields] OR "oral carcinoma"[All Fields] OR "oropharyngeal cancer"[All Fields] OR "oropharyngeal neoplasm"[All Fields] OR "oropharyngeal carcinoma"[All Fields] OR "buccal cancer"[All Fields] OR (buccal[All Fields] AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields])) OR "buccal carcinoma"[All Fields] OR "buccal cavity cancer"[All Fields] OR (("mouth"[MeSH Terms] OR "mouth"[All Fields] OR ("buccal"[All Fields] AND "cavity"[All Fields]) OR "buccal cavity"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR	2,201	medline_filters_mouth_cancer-all terms.txt	Oral, oro-pharyngeal, buccal, laryngeal and head and neck cancer

#	PubMed Search terms	Results (#)	Saved File	Notes
	"neoplasm"[All Fields])) OR (("mouth"[MeSH Terms] OR "mouth"[All Fields] OR ("buccal"[All Fields] AND "cavity"[All Fields]) OR "buccal cavity"[All Fields]) AND ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields])) OR "cancer of the mouth"[All Fields] OR (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields])) OR (("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields])) OR "head and neck cancer"[All Fields] OR "head and neck neoplasms"[All Fields] OR "head and neck carcinoma"[All Fields] OR "laryngeal cancer"[All Fields] OR "laryngeal neoplasms"[All Fields] OR "laryngeal carcinoma"[All Fields]), **with filters 'human' and 'English'.**			
7	Exposure **AND** ("lung cancer"[All Fields] OR "lung carcinoma"[All Fields] OR "lung neoplasms"[All Fields] OR "pulmonary cancer"[All Fields] OR "pulmonary carcinoma"[All Fields] OR "pulmonary neoplasms"[All Fields] OR "respiratory cancer"[All Fields] OR "respiratory carcinoma"[All Fields] OR "respiratory neoplasms"[All Fields] OR "bronchial cancer"[All Fields] OR "bronchial neoplasms"[All Fields] OR "bronchial carcinoma"[All Fields] OR "bronchogenic carcinoma"[All Fields] OR "bronchogenic neoplasms"[All Fields] OR "bronchogenic cancer"[All Fields]) **with filters 'human' and 'English'.**	316	medline_filters_lung cancer_all terms.txt	Lung cancer
8	Exposure **AND** ("Cardiovascular disease"[All Fields] OR "angina pectoris"[All Fields] OR "fatal myocardial infarction"[All Fields] OR "nonfatal myocardial infarction"[All Fields] OR "acute myocardial infarction"[All Fields] OR "myocardial infarction"[All Fields] OR "cardiac arrhythmia"[All Fields] OR "peripheral vascular disease"[All Fields] OR "ischemic events"[All Fields] OR "heart disease"[All Fields] OR "rapid heartbeat"[All Fields] OR ("tachycardia"[MeSH Terms] OR "tachycardia"[All Fields]) OR "heart attack"[All Fields] OR "cardiac arrest"[All Fields] OR "Irregular heartbeat"[All Fields] OR "heart palpitations"[All Fields] OR "high blood pressure"[All Fields] OR ("hypertension"[MeSH Terms] OR "hypertension"[All Fields])) **with filters 'human' and 'English'.**	597	medline_cvd_filters.txt	Cardiovascular diseases
9	Exposure **AND** (("asthma"[MeSH Terms] OR "asthma"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR "COPD"[All Fields] OR ("bronchiectasis"[MeSH Terms] OR "bronchiectasis"[All Fields]) OR ("bronchitis"[MeSH Terms] OR "bronchitis"[All Fields]) OR ("pulmonary emphysema"[MeSH Terms] OR ("pulmonary"[All Fields] AND	251	medline_filters_ncrd.txt	Non-cancer respiratory outcomes

#	PubMed Search terms	Results (#)	Saved File	Notes
	"emphysema"[All Fields]) OR "pulmonary emphysema"[All Fields] OR "emphysema"[All Fields] OR "emphysema"[MeSH Terms])) **with filters 'human' and 'English'.**			
	Exposure AND ("brain attack"[All Fields] OR "cerebrovascular accident"[All Fields] OR "stroke"[All Fields] OR "TIA"[All Fields] OR "transient ischemic attack"[All Fields]) OR ("brain attack"[MeSH Terms] OR "cerebrovascular accident"[MeSH Terms] OR "stroke"[MeSH Terms] OR "TIA"[MeSH Terms] OR "transient ischemic attack"[MeSH Terms])	134	Search 1.txt	Stroke
	Total without duplicates (with duplicates)	**3,346 (6,662)**		
2.	**Searches without filters, published in 2015**			
	Exposure **AND** ("oropharynx"[MeSH Terms] OR "oropharynx"[All Fields] OR "oropharyngeal"[All Fields])	23	oropharyngeal since 2015.txt	Oropharyngeal cancer
	Exposure **AND** (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields]) OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields])) **AND** (buccal[All Fields] OR "buccal cavity"[All Fields])	9	buccal 2015.txt	Buccal cancer
	Exp and (("mouth"[MeSH Terms] OR "mouth"[All Fields]) **AND** (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields]) OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]))))	296	all combinations 2015.txt	Mouth cancer
	Exposure and (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields]) OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields])) **AND** (("larynx"[MeSH Terms] OR "larynx"[All Fields]) OR ("larynx"[MeSH Terms] OR "larynx"[All Fields] OR "laryngeal"[All Fields]))	19	larynx 2015.txt	Laryngeal cancer
	Exposure **AND** ("head and neck"[All Fields] AND (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields]) OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]))))	66	H&N 2015.txt	Head & neck cancer
	Exposure **AND** ("oral cancer"[All Fields] OR "oral neoplasm"[All Fields] OR "oral carcinoma"[All Fields] OR "oropharyngeal cancer"[All Fields] OR	296	all combos2015.txt	Oral, oro-pharyngeal,

#	PubMed Search terms	Results (#)	Saved File	Notes
	"oropharyngeal neoplasm"[All Fields] OR "oropharyngeal carcinoma"[All Fields] OR "buccal cancer"[All Fields] OR (buccal[All Fields] AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields])) OR "buccal carcinoma"[All Fields] OR "buccal cavity cancer"[All Fields] OR (("mouth"[MeSH Terms] OR "mouth"[All Fields] OR ("buccal"[All Fields] AND "cavity"[All Fields]) OR "buccal cavity"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields])) OR (("mouth"[MeSH Terms] OR "mouth"[All Fields] OR ("buccal"[All Fields] AND "cavity"[All Fields]) OR ("buccal cavity"[All Fields]) AND ("carcinoma"[MeSH Terms] OR ("carcinoma"[All Fields])) OR "cancer of the mouth"[All Fields] OR (("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields])) OR (("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields])) OR "head and neck cancer"[All Fields] OR "head and neck neoplasms"[All Fields] OR "head and neck carcinoma"[All Fields] OR "laryngeal cancer"[All Fields] OR "laryngeal neoplasms"[All Fields] OR "laryngeal carcinoma"[All Fields])			buccal laryngeal and head and neck cancer
	Exposure **AND** ("lung cancer"[All Fields] OR "lung carcinoma"[All Fields] OR "lung neoplasms"[All Fields] OR "pulmonary cancer"[All Fields] OR "pulmonary carcinoma"[All Fields] OR "pulmonary neoplasms"[All Fields] OR "respiratory cancer"[All Fields] OR "respiratory carcinoma"[All Fields] OR "respiratory neoplasms"[All Fields] OR "bronchial cancer"[All Fields] OR "bronchial neoplasms"[All Fields] OR "bronchial carcinoma"[All Fields] OR "bronchogenic carcinoma"[All Fields] OR "bronchogenic neoplasms"[All Fields] OR "bronchogenic cancer"[All Fields])	20	lung cancer 2015.txt	Lung cancer
	Exposure **AND** ("Cardiovascular disease"[All Fields] OR "angina pectoris"[All Fields] OR "fatal myocardial infarction"[All Fields] OR "nonfatal myocardial infarction"[All Fields] OR "acute myocardial infarction"[All Fields] OR "myocardial infarction"[All Fields] OR "cardiac arrhythmia"[All Fields] OR "peripheral vascular disease"[All Fields] OR "ischemic events"[All Fields] OR "heart disease"[All Fields] OR "rapid heartbeat"[All Fields] OR ("tachycardia"[MeSH Terms] OR "tachycardia"[All Fields]) OR "heart attack"[All Fields] OR "cardiac arrest"[All Fields] OR "Irregular heartbeat"[All Fields] OR "heart palpitations"[All Fields] OR "high blood pressure"[All Fields] OR ("hypertension"[MeSH Terms] OR "hypertension"[All Fields])).	52	CVD 2015.txt	Cardiovascular diseases

#	PubMed Search terms	Results (#)	Saved File	Notes
	Exposure **AND** (("asthma"[MeSH Terms] OR "asthma"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR "COPD"[All Fields] OR ("bronchiectasis"[MeSH Terms] OR "bronchiectasis"[All Fields]) OR ("bronchitis"[MeSH Terms] OR "bronchitis"[All Fields]) OR ("pulmonary emphysema"[MeSH Terms] OR ("pulmonary"[All Fields] AND "emphysema"[All Fields]) OR "pulmonary emphysema"[All Fields] OR "emphysema"[All Fields] OR "emphysema"[MeSH Terms])).	31	NCRD 2015.txt	Non-cancer respiratory disease
	Exposure AND ("brain attack"[All Fields] OR "cerebrovascular accident"[All Fields] OR "stroke"[All Fields] OR "TIA"[All Fields] OR "transient ischemic attack"[All Fields]) OR ("brain attack"[MeSH Terms] OR "cerebrovascular accident"[MeSH Terms] OR "stroke"[MeSH Terms] OR "TIA"[MeSH Terms] OR "transient ischemic attack"[MeSH Terms])	12	Search 2.txt	Stroke
	Total without duplicates in 2015 (with duplicates)	**331 (824)**		
3.	**Search results for Exposure and 'cancer', published between 1/1/2013 and 10/26/2015, without any additional filters**			
	(("Oral"[All Fields] AND "tobacco"[All Fields]) OR ("chew"[All Fields] AND "tobacco"[All Fields]) OR ("alternative"[All Fields] AND ("nicotine"[All Fields] OR "tobacco"[All Fields])) OR ("plug"[All Fields] AND "tobacco"[All Fields]) OR "potential reduced exposure products"[All Fields] OR preps[All Fields] OR ("spit"[All Fields] AND "tobacco"[All Fields]) OR "non-cigarette tobacco"[All Fields] OR ("chew"[All Fields] AND "plug"[All Fields]) OR ("chewing"[All Fields] AND "tobacco"[All Fields]) OR dip[All Fields] OR "dissolvable tobacco"[All Fields] OR dissolvable[All Fields] OR dissolvable[All Fields] OR "dry snuff"[All Fields] OR "non-combustible PREPs"[All Fields] OR "smokeless tobacco"[All Fields] OR ("tobacco, smokeless"[MeSH Terms] OR ("tobacco"[All Fields] AND "smokeless"[All Fields]) OR "smokeless tobacco"[All Fields] OR "snuff"[All Fields]) OR snus[All Fields] OR ("spit"[All Fields] AND "tobacco"[All Fields]) OR ("spitless"[All Fields] AND "tobacco"[All Fields] AND "lozenges"[All Fields]) OR ("loose"[All Fields] AND "leaf"[All Fields] AND "chew"[All Fields]) OR ("moist"[All Fields] AND "plug"[All Fields]) OR ("personal"[All Fields] AND "vaporizers"[All Fields]) OR "non-cigarette tobacco"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "carcinoma"[All Fields]) AND ("2013/01/01"[PDAT] : "2014/12/31"[PDAT])	487	exp and cancer 1.1.2013 to 12.31.2014 with filters.txt	Cancer

#	PubMed Search terms	Results (#)	Saved File	Notes
	(("Oral"[All Fields] AND "tobacco"[All Fields]) OR ("chew"[All Fields] AND "tobacco"[All Fields]) OR ("alternative"[All Fields] AND ("nicotine"[All Fields] OR "tobacco"[All Fields])) OR ("plug"[All Fields] AND "tobacco"[All Fields]) OR "potential reduced exposure products"[All Fields] OR preps[All Fields] OR ("spit"[All Fields] AND "tobacco"[All Fields]) OR "non-cigarette tobacco"[All Fields] OR ("chew"[All Fields] AND "plug"[All Fields]) OR ("chewing"[All Fields] AND "tobacco"[All Fields]) OR dip[All Fields] OR "dissolvable tobacco"[All Fields] OR dissolvable[All Fields] OR dissolvable[All Fields] OR "dry snuff"[All Fields] OR "non-combustible PREPs"[All Fields] OR "smokeless tobacco"[All Fields] OR ("tobacco, smokeless"[MeSH Terms] OR ("tobacco"[All Fields] AND "smokeless"[All Fields]) OR "smokeless tobacco"[All Fields] OR "snuff"[All Fields]) OR snus[All Fields] OR ("spit"[All Fields] AND "tobacco"[All Fields]) OR ("spitless"[All Fields] AND "tobacco"[All Fields] AND "lozenges"[All Fields]) OR ("loose"[All Fields] AND "leaf"[All Fields] AND "chew"[All Fields]) OR ("moist"[All Fields] AND "plug"[All Fields]) OR ("personal"[All Fields] AND "vaporizers"[All Fields]) OR "non-cigarette tobacco"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "carcinoma"[All Fields]) AND ("201/01/01"[PDAT] : "2014/10/26"[PDAT])	305	exp and cancer 1.1.2015 to 10.26.2015 no filters.txt	Cancer
	Total results without duplicates for Exposure and all cancers b/w 2013-2015 (with duplicates)	**201 (792)**		
4.	**Similar article searches using:**			
	Hansson J, Galanti MR, Hergens MP, Fredlund P, Ahlbom A, Alfredsson L, Bellocco R, Eriksson M, Hallqvist J, Hedblad B, Jansson JH, Nilsson P, Pedersen N, Trolle LY, Ostergren PO, Magnusson C. 2012. Use of snus and acute myocardial infarction: pooled analysis of eight prospective observational studies. *Eur J Epidemiol*. 27(10): 771-779.	110	Hansson - sim art search thru 12312015 filters.txt Hansson - sim art search 0101-10062015 no filters.txt	
	Luo J, Ye W, Zendehdel K, Adami J, Adami HO, Boffetta P, Nyren O. 2007. Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet* 369(9578):2015-2020.	103	Luo - sim art search thru 12312015 filters.txt	

#	PubMed Search terms	Results (#)	Saved File	Notes
			Luo - sim art search 0101-10062015 no filters.txt	
	Henley SJ, Thun MJ, Connell C, Calle EE. 2005. Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). Cancer Causes Control 16:347-358.	274	Henley - sim art search thru 12312015 filters.txt Henley - sim art search 0101-10062015 no filters.txt	
	Total without duplicates	**292 (487)**		**(158 not previously identified)**
5.	**Bibliographies of 97 review papers**			
	Articles identified without duplicates (with duplicates)	**158 (293)**		
6.	**UST report bibliography**	**0 not previously identified (34)**		
	TOTAL without duplicates	**4,328**		

APPENDIX C
ABSTRACTION TABLES

Contents

Acronynms

ABI = ankle brachial index

AMI = acute myocardial infarction

BMI = body mass index

BP = blood pressure

CIMT = carotid intima-media thickness

COPD = chronic obstructive pulmonary disease

CPS = Cancer Prevention Study

CVD = cardiovascular disease

DBP = diastolic blood pressure

ECO = expired carbon monoxide

FMD = flow-mediated dilation

HDL = high-density lipoprotein

HNSCC = head and neck squamous cell carcinoma

HR = hazard ratio

HRV = heart rate variability

IHD = ischemic heart disease

IRR = incidence rate ratio

LCL = lower confidence limit

MRR = mortality risk ratio

MSC = moist snuff consumers

NR = not reported

Ns = not significant

NTC = non-consumers of tobacco

OR = odds ratio

RE = risk estimate

RR = relative risk

SBP = systolic blood pressure

SD = standard deviation

SES = socioeconomic status

SIR = standardized incidence ratio

SMK = cigarette smokers

ST = smokeless tobacco

UCL = upper confidence limit

WBC = white blood cell

Description of the document

This document contains all studies determined to be of adequate or fair quality by Ramboll Environ. Study details and results are organized alphabetically by author. The first page for each study provides key study details including the specific exposure, study design, population, study period, endpoints examined, number of exposed and unexposed particpcants or number of cases and controls, any potential biases that were identified, the study quality ranking of adequate or fair, any limitations identified by the reviewers, and any remaining comments or details. Relevant results from each study are provided starting on the second page in table form. Each table includes the exposure, the health endpoint, any covariates included in the model, the comparison groups, a description of the risk estimate used, the risk estimate, and confidence intervals or p values, when provided.

Accortt 2002

Full citation: Accortt NA, Waterbor JW, Beall C, Howard G. 2002. Chronic disease mortality in a cohort of smokeless tobacco users. *Am J Epidemiol* 156:730-737.

Exposure: smokeless tobacco (ST)

Study Design: Cohort

Population (total): 13,861 noninstitutionalized US adults (NHANES I)

Study Period: Start: 1971-1975, End: 1992

Endpoints: Disease of respiratory system (non-malignant neoplasms), diseases of the circulatory system, lung cancer mortality, ischemic heart disease (IHD), stroke, and oral cancer mortality

Number of exposed/unexposed:

5,192 non-tobacco users
505 exclusive smokeless tobacco users
5,523 exclusive smokers

Apparent Biases: Non-differential misclassification of exposure (moderate)

Study Quality: Fair

Limitations (if not "Adequate"): Small number of observed disease cases

Comments: Exposure data collected 1982-1984 for majority of population and retroactively applied 1971-1974

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Accortt, 2002	ST	Diseases of respiratory system (non-malignant neoplasms)	Age, race, poverty index	Never tobacco, exclusive ST users - Males	aHR	0.9	0.2	2.5	
Accortt, 2002	ST	Diseases of respiratory system (non-malignant neoplasms)	Age, race, poverty index	Never tobacco, exclusive ST users - Females	aHR	0.6	0.1	2.3	
Accortt, 2002	ST	Diseases of the circulatory system	Age, race, poverty index	Never tobacco, exclusive ST users - Males	aHR	1.0	0.7	1.5	
Accortt, 2002	ST	Diseases of the circulatory system	Age, race, poverty index	Never tobacco, exclusive ST users - Females	aHR	1.2	0.7	1.9	
Accortt, 2002	ST	Lung cancer mortality	Age, race, poverty index, region of residence, alcohol, exercise, fruit/veg intake	Never tobacco, exclusive ST users - Males	aHR	9.1	1.1	75.4	
Accortt, 2002	ST	Lung cancer mortality	Age, race, poverty index, region of residence, alcohol, exercise, fruit/veg intake	Never tobacco, exclusive ST users - Females	aHR	0			
Accortt, 2002	ST	IHD	Age, race, poverty index, alcohol, exercise, fruit/veg intake, blood pressure, cholesterol, BMI	Never tobacco, exclusive ST users - Males	aHR	0.6	0.3	1.2	
Accortt, 2002	ST	IHD	Age, race, poverty index, alcohol,	Never tobacco, exclusive ST users	aHR	1.4	0.8	2.2	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			exercise, fruit/veg intake, blood pressure, cholesterol, BMI	- Females					
Accortt, 2002	ST	Stroke	Age, race, poverty index, exercise, fruit/veg intake, blood pressure	Never tobacco, exclusive ST users - Males	aHR	0.7	0.2	2.0	
Accortt, 2002	ST	Stroke	Age, race, poverty index, exercise, fruit/veg intake, blood pressure	Never tobacco, exclusive ST users - Females	aHR	1.0	0.3	2.9	
Accortt, 2002	ST	IHD	Age, race, poverty index, alcohol, exercise, fruit/veg intake, blood pressure, cholesterol, BMI	Never tobacco, ever exclusive current smokers - Males	aHR	1.5	1.1	2.1	
Accortt, 2002	ST	Lung cancer mortality	Age, race, poverty index, region of residence, alcohol, exercise, fruit/veg intake	Never tobacco, ever exclusive current smokers - Males	aHR	13.2	4.5	38.2	
Accortt, 2002	ST	IHD	Age, race, poverty index, alcohol, exercise, fruit/veg intake, blood pressure, cholesterol, BMI	Never tobacco, exclusive current smokers - Males	aHR	2.0	1.4	2.8	
Accortt, 2002	ST	Lung cancer mortality	Age, race, poverty index, region of residence, alcohol, exercise, fruit/veg intake	Never tobacco, exclusive current smokers - Males	aHR	24.7	8.3	73.5	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Accortt, 2002	ST	IHD	Age, race, poverty index, alcohol, exercise, fruit/veg intake, blood pressure, cholesterol, BMI	Never tobacco, exclusive former current smokers - Males	aHR	1.2	0.8	2.0	
Accortt, 2002	ST	Lung cancer mortality	Age, race, poverty index, region of residence, alcohol, exercise, fruit/veg intake	Never tobacco, exclusive former current smokers - Males	aHR	7.0	2.1	23.2	
Accortt, 2002	ST	Oral Cancer Mortality	Age	Never tobacco, exclusive smoker	SMR	2.88	1.42	4.8	
Accortt, 2002	ST	Oral Cancer Mortality	Age	Never tobacco, exclusive ST users	SMR	0	0	5.8	

Accortt 2005

Full citation: Accortt NA, Waterbor JW, Beall C, Howard G. 2005. Cancer incidence among a cohort of smokeless tobacco users (United States). *Cancer Causes Control* 16:1107-1115.

Exposure: smokeless tobacco (ST, snuff or chew)

Study Design: Cohort

Population (total): 6,779 white or black adults in US 45 years or older (NHANES I)

Study Period: Start: 1971-1975 End: 1992

Endpoints: Lung cancer incidence and oral cancer incidence

Number of exposed/unexposed:

2,979 non-tobacco users
414 exclusive ST users
2,733 exclusive smokers

Apparent Biases: Non-differential misclassification of exposure (moderate)

Study Quality: Fair

Limitations (if not "Adequate"): Small number of observed disease cases

Comments: Exposure data collected 1982-1984 for majority of population and retroactively applied 1971-1974.

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Accortt, 2005	ST (snuff or chew)	Lung cancer incidence	N/A	Never tobacco users, exclusive ST users - Males 45-64 years old	aHR	0			
Accortt, 2005	ST (snuff or chew)	Lung cancer incidence	N/A	Never tobacco users, exclusive ST users - Males >65 years old	aHR	0			
Accortt, 2005	ST (snuff or chew)	Lung cancer incidence	N/A	Never tobacco users, exclusive ST users - Males	aHR	0			
Accortt, 2005	ST (snuff or chew)	Lung cancer incidence	Age, race, poverty index, region of residence, exercise, fruit and veg intake, alcohol	Never tobacco users, exclusive smokers - Males	aHR	13.2	5.5	31.8	
Accortt, 2005	ST (snuff or chew)	Lung cancer incidence	Race, poverty index	Never tobacco users, exclusive ST users - Females 45-64 years old	aHR	1.2	0.1	17.2	
Accortt, 2005	ST (snuff or chew)	Lung cancer incidence	Race, poverty index	Never tobacco users, exclusive ST users - Females >65 years old	aHR	9.6	1.8	51.2	
Accortt, 2005	ST (snuff or chew)	Lung cancer incidence	Age, race, poverty index	Never tobacco users, exclusive ST users - Females	aHR	6.8	1.6	28.5	
Accortt, 2005	ST (snuff or chew)	Oral Cancer Incidence	N/A	Never tobacco users, exclusive ST users - Males	SIR	0			
Accortt, 2005	ST (snuff or chew)	Oral Cancer Incidence	N/A	Never tobacco users, exclusive ST users - Females	SIR	0			

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Accortt, 2005	ST (snuff or chew)	Oral Cancer Incidence	N/A	Never tobacco users, exclusive smokers	SIR	0			

Arefalk 2012

Full citation: Arefalk G, Hergens MP, Ingelsson E, Arnlov J, Michaelsson K, Lind L, Ye W, Nyren O, Lambe M, Sundstrom J. 2012. Smokeless tobacco (snus) and risk of heart failure: results from two Swedish cohorts. *Eur J Prev Cardiol* 19(5):1120-1127.

Exposure: Snus, smoking

Study Design: Prospective cohort (Swedish Construction Workers Cohort)

Population (total): 118,425 never-smoking male construction workers

Study Period: 1978-2004

Endpoints: Heart failure (as main reason for hospitalization)

Number of exposed/unexposed:

Among cases:

464 never tobacco users
75 current snus users
6 former users

Apparent Biases: Non-differential misclassification of exposure

Study Quality: Adequate

Limitations (if not "Adequate"): None

Comments: Another much smaller cohort is also analyzed, but the smaller cohort does not have an exclusive ST group.

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Arefalk, 2012	Snus, smoking	Heart failure (as main reason for hospitalization)	Age, BMI, region of residence, systolic and diastolic blood pressures, myocardial infarction during follow up	All current snus users vs. never tobacco users	HR	1.24	0.97	1.59	
Arefalk, 2012	Snus, smoking	Heart failure (as main reason for hospitalization)	Age, BMI, region of residence, systolic and diastolic blood pressures, myocardial infarction during follow up	<12.5 g/day snus use vs. never tobacco users	HR	1.15	0.78	1.68	
Arefalk, 2012	Snus, smoking	Heart failure (as main reason for hospitalization)	Age, BMI, region of residence, systolic and diastolic blood pressures, myocardial infarction during follow up	12.5–24.9 g/day snus vs. never tobacco users	HR	1.40	0.99	1.98	
Arefalk, 2012	Snus, smoking	Heart failure (as main reason for hospitalization)	Age, BMI, region of residence, systolic and diastolic blood pressures, myocardial infarction during follow up	25–49.9 g/day snus vs. never tobacco users	HR	1.02	0.50	2.06	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Arefalk, 2012	Snus, smoking	Heart failure (as main reason for hospitalization)	Age, BMI, region of residence, systolic and diastolic blood pressures, myocardial infarction during follow up	50 g/day snus vs. never tobacco users	HR	1.24	0.46	3.34	
Arefalk, 2012	Snus, smoking	Heart failure (as main reason for hospitalization)	Age, BMI, region of residence, systolic and diastolic blood pressures, myocardial infarction during follow up	Former snus users vs. never tobacco users	HR	0.99	0.44	2.22	

Asplund 2003

Full citation: Asplund K, Nasic S, Janlert U, Stegmayr B. 2003. Smokeless tobacco as a possible risk factor for stroke in men: a nested case-control study. *Stroke* 34(7):1754-1759.

Exposure: ST (snus)

Study Design: Nested case-control

Population (total): 73,880 individuals who participated in a Swedish health survey administered from 1985-1999 as part of the MONICA and Vasterbotten Intervention Program

Study Period: MONICA: 1986-1999; VIP: 1985-2000

Endpoints: Stroke (fatal and non-fatal)

Number of cases/controls:

276 cases
551 controls

Apparent Biases: Non-differential misclassification of exposure (low to moderate)

Study Quality: Fair

Limitations (if not "Adequate"): Small number of outcomes

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Asplund, 2003	ST (snus)	Stroke (fatal and nonfatal)	Matched on age, sex, geographic area, year of baseline exam, and cohort	Exclusive snus users vs. never tobacco users	OR	1.05	0.37	2.94	
Asplund, 2003	ST (snus)	Stroke (fatal and nonfatal)	Matched on age, sex, geographic area, year of baseline exam, and cohort	Exclusive smokers vs. never tobacco users	OR	2.21	1.29	3.79	

Blot 1988

Full citation: Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, Bernstein L, Schoenberg JB, Stemhagen A, Fraumeni JF. 1988. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* 48:3282-3287.

Exposure: smokeless tobacco (ST), cigarette smoking

Study Design: Case-control (population-based)

Population (total): Black and white patients ages 18-79 residing in Atlanta, Los Angeles, Santa Clara, and San Mateo counties south of San Francisco-Oakland, and New Jersey

Study Period: 1984-1985

Endpoints: Oral and pharyngeal cancer incidence

Number of cases/controls:

1,114 cases
1,268 controls

Apparent Biases: Potential information bias from proxy interviews in the cases, recall bias, selection bias (minor)

Study Quality: Fair

Limitations (if not "Adequate"): Small number of exposed cases and controls. ST estimates not adjusted for alcohol; direct comparison cannot be made between ST users and smokers in this cohort.

Comments: Cigarette smoking estimate may include smokeless tobacco users, but it is unlikely to have been substantially impacted due to low number of users.

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Blot, 1988	ST, cigarette smoking	Oral and pharyngeal cancer incidence	Age, race, study location, respondent status (self vs. next of kin)	Female exclusive ST users vs. never tobacco users	OR	6.2	1.9	19.8	
Blot, 1988	ST, cigarette smoking	Oral and pharyngeal cancer incidence	Alcohol consumption, age, race, study location, respondent status (self vs. next of kin)	Female exclusive smokers vs. never tobacco users	OR	3.0	2.0	4.5	

Boffetta 2005

Full citation: Boffetta P, Aagnes B, Weiderpass E, Andersen A. 2005. Smokeless tobacco use and risk of cancer of the pancreas and other organs. *Int J Cancer* 114(6):992-995.

Exposure: ST (snus)

Study Design: Cohort

Population (total): 10,136 Norwegian men

Study Period: 1966-2001

Endpoints: Lung cancer incidence

Number of exposed/unexposed:

6,921 never or occasional snus users
1,999 regular current snus users

Apparent Biases: Non-differential misclassification of exposure (moderate)

Study Quality: Fair

Limitations (if not "Adequate"): No RR estimate of smokers compared to non-smokers (for comparison to snus-users). Lack of descriptive data on cohort used.

Comments: None.

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Boffetta, 2005	ST (snus)	Lung Cancer Incidence	Age	Never tobacco users, exclusive ever snus users	aHR	0.96	0.26	3.56	

Bolinder 1992

Full citation: Bolinder GM, Ahlborg BO, Lindell JH. 1992. Use of smokeless tobacco: blood pressure elevation and other health hazards found in a large-scale population survey. *J Intern Med* 232(4):327-334.

Exposure: ST (snus)

Study Design: Cross sectional

Population (total): 97,586 Swedish construction workers

Study Period: 1971-1974

Endpoints: Cough in the morning, breathlessness on slight effort, more than 3 months' cough/year, cardiovascular diagnosis, hypertension, diastolic BP>90 mmHg, and systolic BP>160 mmHg

Number of exposed/unexposed:

23,885 never tobacco users
5,014 daily ST users
8,823 smokers of ≥ 15 cigarettes daily

Apparent Biases: Misclassification of exposure, recall bias, selection bias, possibly survivor bias

Study Quality: Fair

Limitations (if not "Adequate"): Temporality cannot be assessed, the exposure groups are defined arbitrarily. Each group has some low level of former mutual use.

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Bolinder, 1992	ST (snus)	Cough in the morning	Age, BMI	Never tobacco users, exclusive ever ST users	aOR	2.1	1.8	2.4	
Bolinder, 1992	ST (snus)	Breathlessness on slight effort	Age, BMI	Never tobacco users, exclusive ever ST users	aOR	1.4	1.3	1.6	
Bolinder, 1992	ST (snus)	More than 3 months' cough/year	Age, BMI	Never tobacco users, exclusive ever ST users	aOR	1.4	1.1	1.7	
Bolinder, 1992	ST (snus)	Cough in the morning	Age, BMI	Never tobacco users, exclusive smokers ≥15 cig/day	aOR	7.9	7.2	8.5	
Bolinder, 1992	ST (snus)	Breathlessness on slight effort	Age, BMI	Never tobacco users, exclusive smokers ≥15 cig/day	aOR	2.5	2.2	2.7	
Bolinder, 1992	ST (snus)	More than 3 months' cough/year	Age, BMI	Never tobacco users, exclusive smokers ≥15 cig/day	aOR	6.2	5.5	6.8	
Bolinder, 1992	ST (snus)	Cardiovascular diagnosis	Age, BMI	Never tobacco users, exclusive ever ST users	aOR	1.6	0.7	3.5	
Bolinder, 1992	ST (snus)	Cardiovascular diagnosis	Age, BMI	Never tobacco users, exclusive smokers ≥15 cig/day	aOR	2.2	1.3	3.9	
Bolinder, 1992	ST (snus)	Cardiovascular diagnosis	Age, BMI	Never tobacco users, exclusive ever ST users	aOR	1.5	1.1	1.9	
Bolinder, 1992	ST (snus)	Cardiovascular diagnosis	Age, BMI	Never tobacco users, exclusive smokers ≥15	aOR	1.3	0.9	1.9	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
				cig/day					
Bolinder, 1992	ST (snus)	Hypertension	Age, BMI	Never tobacco users, exclusive ever ST users	aOR	3.0	1.9	4.9	
Bolinder, 1992	ST (snus)	Hypertension	Age, BMI	Never tobacco users, exclusive smokers ≥15 cig/day	aOR	0.9	0.4	1.9	
Bolinder, 1992	ST (snus)	Diastolic bp >90 mmHg	None	Never tobacco users, exclusive ever ST users	aOR	1.3	1.0	1.7	
Bolinder, 1992	ST (snus)	Diastolic bp >90 mmHg	None	Never tobacco users, exclusive ever ST users	aOR	1.3	1.0	1.6	
Bolinder, 1992	ST (snus)	Diastolic bp >90 mmHg	None	Never tobacco users, exclusive ever ST users	aOR	1.8	1.5	2.1	
Bolinder, 1992	ST (snus)	Diastolic bp >90 mmHg	None	Never tobacco users, exclusive ever ST users	aOR	1.3	1.1	1.4	
Bolinder, 1992	ST (snus)	Diastolic bp >90 mmHg	None	Never tobacco users, exclusive smokers ≥15 cig/day	aOR	0.9	0.7	1.1	
Bolinder, 1992	ST (snus)	Diastolic bp >90 mmHg	None	Never tobacco users, exclusive smokers ≥15 cig/day	aOR	0.8	0.6	0.9	
Bolinder, 1992	ST (snus)	Diastolic bp >90 mmHg	None	Never tobacco users, exclusive smokers ≥15 cig/day	aOR	0.8	0.7	0.9	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Bolinder, 1992	ST (snus)	Diastolic bp >90 mm Hg	None	Never tobacco users, exclusive smokers ≥15 cig/day	aOR	0.7	0.5	0.8	
Bolinder, 1992	ST (snus)	Systolic BP >160 mm Hg	None	Never tobacco users, exclusive ever ST users	aOR	1.0	0.5	1.7	
Bolinder, 1992	ST (snus)	Systolic BP >160 mm Hg	None	Never tobacco users, exclusive ever ST users	aOR	1.3	0.8	2.1	
Bolinder, 1992	ST (snus)	Systolic BP >160 mm Hg	None	Never tobacco users, exclusive ever ST users	aOR	1.7	1.3	2.1	
Bolinder, 1992	ST (snus)	Systolic BP >160 mm Hg	None	Never tobacco users, exclusive ever ST users	aOR	1.2	1.1	1.4	
Bolinder, 1992	ST (snus)	Systolic BP >160 mm Hg	None	Never tobacco users, exclusive smokers ≥15 cig/day	aOR	0.7	0.4	1.1	
Bolinder, 1992	ST (snus)	Systolic BP >160 mm Hg	None	Never tobacco users, exclusive smokers ≥15 cig/day	aOR	0.8	0.6	1.1	
Bolinder, 1992	ST (snus)	Systolic BP >160 mm Hg	None	Never tobacco users, exclusive smokers ≥15 cig/day	aOR	0.9	0.7	1.1	
Bolinder, 1992	ST (snus)	Systolic BP >160 mm Hg	None	Never tobacco users, exclusive smokers ≥15 cig/day	aOR	0.7	0.6	0.8	

Bolinder 1994

Full citation: Bolinder G, Alfredsson L, Englund A, de Faire U. 1994. Smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers. *Am J Public Health* 84(3):399-404.

Exposure: ST

Study Design: Prospective cohort

Population (total): 84,781 male workers employed by the construction industry and received medical checkups in Sweden between 1971 and 1974

Study Period: 1974-1985

Endpoints: Ischemic heart disease mortality, all cardiovascular disease mortality, stroke and lung cancer mortality

Number of exposed/unexposed:

32,546 non-users
6,297 snus users
14,983 smokers <15/day
13,518 smokers ≥15/day

Apparent Biases: Possible selection bias - 25% of the eligible population did not respond to invitations to participate in the cohort, and their demographics are not reported.

Study Quality: Adequate

Limitations (if not "Adequate"): None

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Bolinder, 1994	ST	Ischemic heart disease mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	ST users vs non-tobacco users ages 35-54 at entry	Relative risk	2	1.4	2.9	NR
Bolinder, 1994	ST	Ischemic heart disease mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	<15/day Smokers vs non-tobacco users ages 35-54 at entry	Relative risk	2.6	2.1	3.4	NR
Bolinder, 1994	ST	Ischemic heart disease mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	≥15/day Smokers vs non-tobacco users ages 35-54 at entry	Relative risk	3.3	2.6	4.2	NR
Bolinder, 1994	ST	Ischemic heart disease mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	ST users vs non-tobacco users ages 55-65 at entry	Relative risk	1.2	1.0	1.5	NR
Bolinder, 1994	ST	Ischemic heart disease mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	<15/day Smokers vs non-tobacco users ages 55-65 at entry	Relative risk	1.7	1.4	1.9	NR
Bolinder, 1994	ST	Ischemic heart disease mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	≥15/day Smokers vs non-tobacco users ages 55-65 at entry	Relative risk	1.4	1.2	1.8	NR
Bolinder, 1994	ST	All cardiovascular disease mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous	ST users vs non-tobacco users ages 35-54 at entry	Relative risk	2.1	1.5	2.9	NR

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			CVD symptoms						
Bolinder, 1994	ST	All cardiovascular disease mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	<15/day Smokers vs non-tobacco users ages 35-54 at entry	Relative risk	2.7	2.2	3.4	NR
Bolinder, 1994	ST	All cardiovascular disease mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	≥15/day Smokers vs non-tobacco users ages 35-54 at entry	Relative risk	3.2	2.6	3.9	NR
Bolinder, 1994	ST	All cardiovascular disease mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	ST users vs non-tobacco users ages 55-65 at entry	Relative risk	1.1	1.0	1.4	NR
Bolinder, 1994	ST	All cardiovascular disease mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	<15/day Smokers vs non-tobacco users ages 55-65 at entry	Relative risk	1.5	1.3	1.7	NR
Bolinder, 1994	ST	All cardiovascular disease mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	≥15/day Smokers vs non-tobacco users ages 55-65 at entry	Relative risk	1.5	1.3	1.7	NR
Bolinder, 1994	ST	Stroke	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	ST users vs non-tobacco users ages 35-54 at entry	Relative risk	1.9	0.6	5.7	NR
Bolinder, 1994	ST	Stroke	Age, area of domicile, BP, BP medication, BMI,	<15/day Smokers vs non-tobacco users ages 35-54	Relative risk	2.7	1.4	5.4	NR

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			diabetes, previous CVD symptoms	at entry					
Bolinder, 1994	ST	Stroke	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	≥15/day Smokers vs non-tobacco users ages 35-54 at entry	Relative risk	3.0	1.5	5.7	NR
Bolinder, 1994	ST	Stroke	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	ST users vs non-tobacco users ages 55-65 at entry	Relative risk	1.2	0.7	1.8	NR
Bolinder, 1994	ST	Stroke	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	<15/day Smokers vs non-tobacco users ages 55-65 at entry	Relative risk	0.7	0.4	1.2	NR
Bolinder, 1994	ST	Stroke	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	≥15/day Smokers vs non-tobacco users ages 55-65 at entry	Relative risk	1.6	1.0	2.5	NR
Bolinder, 1994	ST	Lung cancer mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	ST users vs non-tobacco users ages 35-54 at entry	Relative risk	1.2	0.2	9.1	NR
Bolinder, 1994	ST	Lung cancer mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	<15/day Smokers vs non-tobacco users ages 35-54 at entry	Relative risk	8.1	3.2	20.4	NR
Bolinder, 1994	ST	Lung cancer mortality	Age, area of domicile, BP, BP	≥15/day Smokers vs non-tobacco	Relative risk	21.4	8.5	54.1	NR

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			medication, BMI, diabetes, previous CVD symptoms	users ages 35-54 at entry					
Bolinder, 1994	ST	Lung cancer mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	ST users vs non-tobacco users ages 55-65 at entry	Relative risk	0.8	0.1	3.9	NR
Bolinder, 1994	ST	Lung cancer mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	<15/day Smokers vs non-tobacco users ages 55-65 at entry	Relative risk	11.9	5.5	25.6	NR
Bolinder, 1994	ST	Lung cancer mortality	Age, area of domicile, BP, BP medication, BMI, diabetes, previous CVD symptoms	≥15/day Smokers vs non-tobacco users ages 55-65 at entry	Relative risk	30.6	14.6	64.1	NR

Bolinder 1997

Full citation: Bolinder G, Noren A, de Faire U, Wahren J. 1997. Smokeless tobacco use and atherosclerosis: an ultrasonographic investigation of carotid intima media thickness in healthy middle-aged men. *Atherosclerosis* 132(1): 95-103.

Exposure: ST

Study Design: Cross-sectional

Population (total): 135 healthy, male firefighters, between 35-60 years of age, from the Stockholm City Fire Brigade

Study Period: 1993

Endpoints: Wall thickness (mm), common carotid bulb, lumen diameter (mm)

Number of exposed/unexposed:

Nonusers: 40
ST users: 28

Apparent Biases: 1) Possible selection bias: No description given as to how this cohort was formed, the number and demographic of the respondents vs any non-respondents. 2) Lumen diameter is read manually and is a subjective measure, prone to inter-rater variation. A measurement bias might have been introduced due to using only one person interpret the lumen diameter reading.

Study Quality: Fair

Limitations (if not "Adequate"): 1) Small sample size - lack of adequate power to test the hypotheses. 2) lack of adequate adjustment for common confounders in atherosclerotic plaque formation (BMI, serum cholesterol, etc.)

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Bolinder, 1997	ST	Wall thickness (mm)	Age	ST users vs non-tobacco users	Comparison of mean right common carotid artery wall thickness	Mean for Nonusers / Users 0.68 / 0.67	NR	NR	NR
Bolinder, 1997	ST	Common carotid Carotid bulb	Age	ST users vs non-tobacco users	Comparison of wall thickness of right carotid bulb	Mean for Nonusers / Users 0.78 / 0.80	NR	NR	NR
Bolinder, 1997	ST	Lumen diameter (mm)	Age	ST users vs non-tobacco users	Lumen diameter	Mean for Nonusers / Users 5.79 / 5.83	NR	NR	NR

Bolinder 1998

Full citation: Bolinder G, de Faire U. 1998. Ambulatory 24-h blood pressure monitoring in healthy, middle-aged smokeless tobacco users, smokers, and nontobacco users. *Am J Hypertens* 11(10): 1153-63.

Exposure: ST

Study Design: Cross-sectional

Population (total): 135 healthy, male, firefighters, between 35-60 years of age, from the Stockholm City Fire Brigade

Study Period: 1993

Endpoints: SBP and DBP

Number of exposed/unexposed:

Nonusers: 59
ST users: 47

Apparent Biases: Possible non-differential misclassification of outcome in measurement of DBP - BP is measured using a sphygmomanometer and is inherently prone to misclassification, due to use of subjective criteria

Study Quality: Fair

Limitations (if not "Adequate"): Cross-sectional study; Small sample size - possible lack of adequate power to test the hypothesis.

Comments: Small sample size (total study population = 135)

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Bolinder, 1998	ST	SBP, casual	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	Mean for Nonusers / ST users 124 / 123	NR	NR	ns
Bolinder, 1998	ST	DBP, casual	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	78 / 78	NR	NR	ns
Bolinder, 1998	ST	Mean SBP, 24H	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	123 / 127	NR	NR	<0.05
Bolinder, 1998	ST	Mean DBP, 24H	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	77 / 79	NR	NR	ns
Bolinder, 1998	ST	Mean SBP, daytime	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	126 / 131	NR	NR	<0.05
Bolinder, 1998	ST	Mean DBP, daytime	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	79 / 81	NR	NR	ns
Bolinder, 1998	ST	Mean SBP, nighttime	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol	ST users vs non-tobacco users	Comparison of mean values by Student's t-	108 / 106	NR	NR	ns

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			consumption		test				
Bolinder, 1998	ST	Mean DBP, nighttime	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	66 / 67	NR	NR	ns
Bolinder, 1998	ST	SBP variability, 24H	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	13 / 14	NR	NR	ns
Bolinder, 1998	ST	DBP variability, 24H	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	11 / 11	NR	NR	ns
Bolinder, 1998	ST	SBP variability, daytime	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	11 / 10	NR	NR	ns
Bolinder, 1998	ST	DBP variability, daytime	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	10 / 10	NR	NR	ns
Bolinder, 1998	ST	SBP variability, nighttime	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	9 / 9	NR	NR	ns

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Bolinder, 1998	ST	DBP variability, nighttime	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	8 / 8	NR	NR	ns
Bolinder, 1998	ST	3H SBP and DBP recordings 6am - 9am: SBP	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	Mean for Nonusers / ST users 126 / 125	NR	NR	0.59
Bolinder, 1998	ST	6am - 9am: DBP	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	80 / 83	NR	NR	0.003
Bolinder, 1998	ST	9am-12noon: SBP	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	128 / 131	NR	NR	0.03
Bolinder, 1998	ST	9am-12noon: DBP	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	81 / 87	NR	NR	<0.001
Bolinder, 1998	ST	12noon-3pm: SBP	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	124 / 134	NR	NR	0.08
Bolinder, 1998	ST	12noon-3pm: DBP	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol	ST users vs non-tobacco users	Comparison of mean values by Student's t-	79 / 84	NR	NR	<0.001

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			consumption		test				
Bolinder, 1998	ST	3pm-6pm: SBP	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	126 / 128	NR	NR	0.34
Bolinder, 1998	ST	3pm-6pm: DBP	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	81 / 85	NR	NR	<0.001
Bolinder, 1998	ST	6pm-9pm: SBP	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	126 / 129	NR	NR	0.02
Bolinder, 1998	ST	6pm-9pm: DBP	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	79 / 83	NR	NR	<0.001
Bolinder, 1998	ST	9pm-12mn: SBP	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	120/ /122	NR	NR	0.1
Bolinder, 1998	ST	9pm-12mn: DBP	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	74 / 79	NR	NR	<0.001
Bolinder, 1998	ST	12mn-3am: SBP	Age, BMI waist-to-hip ratio, physical	ST users vs non-tobacco users	Comparison of mean	107 / 107	NR	NR	0.91

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			fitness levels, alcohol consumption		values by Student's t-test				
Bolinder, 1998	ST	12mn-3am: DBP	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	66 / 68	NR	NR	0.09
Bolinder, 1998	ST	3am-6am:SBP	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	107 / 106	NR	NR	0.60
Bolinder, 1998	ST	3am-6am: DBP	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	66 / 69	NR	NR	0.03
Bolinder, 1998	ST	Comparison of heart rate between ST Nonusers and Users: Casual (BPM)	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	Nonusers / Users 57 / 60	NR	NR	ns <0.05 <0.05 <0.05 <0.05 ns ns
Bolinder, 1998	ST	Mean HR, 24H	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	62 / 65	NR	NR	<0.05
Bolinder, 1998	ST	Mean HR, daytime	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol	ST users vs non-tobacco users	Comparison of mean values by Student's t-	63 / 69	NR	NR	<0.05

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			consumption		test				
Bolinder, 1998	ST	Mean HR, nighttime	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	54 / 56	NR	NR	<0.05
Bolinder, 1998	ST	Variability, 24H	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	9 / 11	NR	NR	<0.05
Bolinder, 1998	ST	Variability, daytime	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	9 / 11	NR	NR	ns
Bolinder, 1998	ST	Variability, nighttime	Age, BMI waist-to-hip ratio, physical fitness levels, alcohol consumption	ST users vs non-tobacco users	Comparison of mean values by Student's t-test	6 / 3	NR	NR	ns
Bolinder, 1998	ST	Wall thickness (mm)	Age	ST users vs non-tobacco users	Comparison of mean Right common carotid artery wall thickness	Mean for Nonusers / Users 0.68 / 0.67	NR	NR	NR
Bolinder, 1998	ST	common carotid carotid bulb	Age	ST users vs non-tobacco users	Comparison of wall thickness of right carotid bulb	Mean for Nonusers / Users 0.78 / 0.80	NR	NR	NR

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Bolinder, 1998	ST	Lumen diameter (mm)	Age	ST users vs non-tobacco users	Lumen diameter	Mean for Nonusers / Users 5.79 / 5.83	NR	NR	NR

Eliasson 1991

Full citation: Eliasson M, Lundblad D, Hagg E. 1991. Cardiovascular risk factors in young snuff-users and cigarette smokers. *J Intern Med* 230(1):17-22.

Exposure: Snuff, cigarettes

Study Design: Cross-sectional

Population (total): 58 male participants. "Male volunteers, who were snuff-users, smokers or non-tobacco-users, were recruited from populations of university students and teachers. Subjects with a BMl > 28 kg m-2, or who were aged > 31 years of age were excluded from the study."

Study Period: Not reported

Endpoints: DBP and pulse rate

Number of exposed/unexposed:

Non-tobacco users: 18
Snuff users: 21
Smokers: 19

Apparent Biases: 1) Apparent selection bias: Small number of smokers among students led to recruitment of smokers in the study by newspaper advertisement; if the outcomes varied between these two groups for any reason, it might have led to an erroneous attribution of the difference in mean diastolic blood pressures to this difference in tobacco usage. 2) Inadequate controlling for confounders. The details of which confounders/ covariates were controlled for in the statistical analysis in not clear.

Study Quality: Fair

Limitations (if not "Adequate"): 1) Apparent selection bias: Small number of smokers among students led to recruitment of smokers in the study by newspaper advertisement; if the outcomes varied between these two groups for any reason, that might have led to an erroneous attribution of the difference in mean diastolic blood pressures to this difference in tobacco usage. 2) Inadequate controlling for confounders. The details of which confounders/ covariates were controlled for in the statistical analysis in not clear. 3) Lack of pairwise comparisons between groups of relevant interest (Snuff users and non-tobacco users, Snuff users and smokers).

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Eliasson, 1991	Snuff, cigarettes	DBP	Not reported	Comparison of the group means for the three groups by Man-Whitney U-test; Pairwise comparison of group means between non-tobacco users and smokers	Group means for each of the three groups	Non-tobacco users: 72.8 mm Hg Snuff users: 71.9 mm Hg Smokers: 77.5 mm Hg	NR	NR	Report that no group differences were found; $p < 0.05$ for pairwise comparison between non-tobacco users and smokers.
Eliasson, 1991	Snuff, cigarettes	Pulse rate	Not reported	Comparison of the group means for the three groups by Man-Whitney U-test; Pairwise comparison of group means between non-tobacco users and smokers	Group means for each of the three groups	Not reported	NR	NR	Report that no group differences were found; $p < 0.05$ for pairwise comparison between non-tobacco users and smokers.

Ernster 1990

Full citation: Ernster VL, Grady DG, Greene JC, Walsh M, Robertson P, Daniels TE, Benowitz N, Siegel D, Gerbert B, Hauck WW. 1990. Smokeless tobacco use and health effects among baseball players. *JAMA* 264(2):218-224.

Exposure: smokeless tobacco (ST)

Study Design: Cross-sectional

Population (total): 282 healthy, male baseball players

Study Period: Feb-March 1988

Endpoints: systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate, resting

Number of exposed/unexposed:

Total study population 1,109; population used to conduct analysis for BP: 282. Numbers in individual groups not reported.

Apparent Biases: 1) Possible misclassification of exposure (self-reporting of all tobacco, coffee and alcohol use). 2) Only a subset of the population that did not come directly from the playing field was used for the analysis of blood pressure, leading to a possibility of selection bias

Study Quality: Fair

Limitations (if not "Adequate"): 1) Cross-sectional study. 2) Lack of reporting of the number of participants in each group. 3) Not a bias, but since the population consisted exclusively of active baseball players, limits the generalizability of the results, due to differences in physical activity levels, nutritional status, etc.

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Ernster, 1990	ST	SBP	Age, race, smoking, caffeine level	Non-tobacco users vs ST users	Comparison of mean SBP for non-users with a) users within the previous month b) users within the previous week	Mean for non-users: 118 Mean for current-month users: 114 Mean for current-week users: 116	NR	NR	NR
Ernster, 1990	ST	DBP	Age, race, smoking, caffeine level	Non-tobacco users vs ST users	Comparison of mean SBP for non-users with a) users within the previous month b) users within the previous week	Mean for non-users: 73 Mean for current-month users: 72 Mean for current-week users: 71	NR	NR	NR
Ernster, 1990	ST	Heart Rate, resting	Age, race, smoking, caffeine level	Non-tobacco users vs ST users	Comparison of mean resting HR for non-users with a) users within the previous month b) users within the previous week	Mean for non-users: 67 Mean for current-month users: 60 Mean for current-week users: 67	NR	NR	NR

Haglund 2007

Full citation: Haglund B, Eliasson M, Stenbeck M, Rosen M. 2007. Is moist snuff use associated with excess risk of IHD or stroke? A longitudinal follow-up of snuff users in Sweden. *Scand J Public Health* 35(6):618-622.

Exposure: ST (snus)

Study Design: Cohort

Population (total): 5,002 Swedish men aged 16-74 years old

Study Period: 1988-2003

Endpoints: Incident ischemic heart disease (IHD), stroke incidence, IHD mortality, and stroke mortality

Number of exposed/unexposed:

2,579 non-users
1,185 daily smokers
721 daily snuff users

Apparent Biases: Non-differential misclassification of exposure (moderate)

Study Quality: Fair

Limitations (if not "Adequate"): Exposure groups may have some low level of mutual use.

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Haglund, 2007	ST (snus)	Incident IHD	Age, SES, residential area, self-reported health, number of chronic illnesses, physical activity	Non-users, daily snus users	IRR	0.77	0.51	1.15	
Haglund, 2007	ST (snus)	Incident IHD	Age, SES, residential area, self-reported health, number of chronic illnesses, physical activity	Non-users, daily snus users	IRR	1.74	1.41	2.14	
Haglund, 2007	ST (snus)	Stroke incident	Age, SES, residential area, self-reported health, number of chronic illnesses, physical activity	Non-users, daily snus users	IRR	1.07	0.65	1.77	
Haglund, 2007	ST (snus)	Stroke incident	Age, SES, residential area, self-reported health, number of chronic illnesses, physical activity	Non-users, daily snus users	IRR	1.4	1.03	1.91	
Haglund, 2007	ST (snus)	IHD mortality	Age, SES, residential area, self-reported health, number of chronic illnesses, physical activity	Non-users, daily snus users	MRR	1.15	0.54	2.41	
Haglund, 2007	ST (snus)	IHD mortality	Age, SES, residential area, self-reported health, number of	Non-users, daily snus users	MRR	1.98	1.35	2.91	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			chronic illnesses, physical activity						
Haglund, 2007	ST (snus)	Stroke mortality	Age, SES, residential area, self-reported health, number of chronic illnesses, physical activity	Non-users, daily snus users	MRR	1.01	0.35	2.92	
Haglund, 2007	ST (snus)	Stroke mortality	Age, SES, residential area, self-reported health, number of chronic illnesses, physical activity	Non-users, daily smokers	MRR	1.02	0.50	2.05	

Hansson 2009

Full citation: Hansson J, Pedersen NL, Galanti MR, Andersson T, Ahlbom A, Hallqvist J, Magnusson C. 2009. Use of snus and risk for cardiovascular disease: results from the Swedish Twin Registry. *J Intern Med* 265(6):717-724.

Exposure: ST (snus)

Study Design: Cohort

Population (total): Male Swedish twins born 1926-1958

Study Period: 1998-2005

Endpoints: All cardiovascular disease (CVD) incidence, ischemic heart disease (IHD) incidence, and stroke

Number of exposed/unexposed:

12,525 never snus
1,456 former snus users
2,661 current users

Apparent Biases: Non-differential misclassification of exposure

Study Quality: Adequate

Limitations (if not "Adequate"): None

Comments: BMI, exercise, education, alcohol use assessed as covariates, but not included in the final analysis.

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hansson, 2009	ST (snus)	All CVD incidence	Age, diabetes, blood pressure, cholesterol, twin status.	Never tobacco users, exclusive current snus users	RR	1.00	0.69	1.46	
Hansson, 2009	ST (snus)	All CVD incidence	Age, diabetes, blood pressure, cholesterol, twin status.	Never tobacco users, former exclusive snus users	RR	1.21	0.75	1.97	
Hansson, 2009	ST (snus)	IHD incidence	Age, diabetes, blood pressure, cholesterol, twin status.	Never tobacco users, exclusive current snus users	RR	0.85	0.51	1.41	
Hansson, 2009	ST (snus)	IHD incidence	Age, diabetes, blood pressure, cholesterol, twin status.	Never tobacco userse, former exclusive snus users	RR	1.07	0.56	2.03	
Hansson, 2009	ST (snus)	Stroke	Age, diabetes, blood pressure, cholesterol, twin status.	Never tobacco users, exclusive current snus users	RR	1.18	0.67	2.08	
Hansson, 2009	ST (snus)	Stroke	Age, diabetes, blood pressure, cholesterol, twin status.	Never tobacco users, former exclusive snus users	RR	1.35	0.65	2.82	
Hansson, 2009	ST (snus)	All CVD incidence	Age, diabetes, blood pressure, cholesterol, twin status.	Never tobacco users, exclusive current smokers	RR	1.86	1.56	2.22	
Hansson, 2009	ST (snus)	All CVD incidence	Age, diabetes, blood pressure, cholesterol, twin status.	Never tobacco users, former exclusive smokers	RR	1.17	1.00	1.38	
Hansson, 2009	ST (snus)	IHD incidence	Age, diabetes, blood pressure,	Never tobacco users, exclusive	RR	1.99	1.59	2.50	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			cholesterol, twin status.	current smokers					
Hansson, 2009	ST (snus)	IHD incidence	Age, diabetes, blood pressure, cholesterol, twin status.	Never tobacco users, former exclusive smokers	RR	1.34	1.10	1.64	
Hansson, 2009	ST (snus)	Stroke	Age, diabetes, blood pressure, cholesterol, twin status.	Never tobacco users, exclusive current smokers	RR	1.61	1.22	2.13	
Hansson, 2009	ST (snus)	Stroke	Age, diabetes, blood pressure, cholesterol, twin status.	Never tobacco users, former exclusive smokers	RR	1.01	0.78	1.30	

Hansson 2012

Full citation: Hansson J, Galanti MR, Hergens MP, Fredlund P, Ahlbom A, Alfredsson L, Bellocco R, Eriksson M, Hallqvist J, Hedblad B, Jansson JH, Nilsson P, Pedersen N, Trolle LY, Ostergren PO, Magnusson C. 2012. Use of snus and acute myocardial infarction: pooled analysis of eight prospective observational studies. *Eur J Epidemiol* 27(10): 771-779.

Exposure: ST (snus)

Study Design: Pooled analyses

Population (total): 130,361 Swedish never smoking males

Study Period: N/A

Endpoints: acute myocardial infarction (AMI) incidence, one year AMI survival and 28 day AMI fatality

Number of exposed/unexposed:

32,560 current exclusive snus users
Unknown never tobacco users

Apparent Biases: Varied by study, but likely included non-differential misclassification of exposure and potential confounding

Study Quality: Adequate

Limitations (if not "Adequate"): None

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hansson, 2012	ST (snus)	AMI incidence	BMI, education	Never tobacco users, current snus users	HR	1.04	0.93	1.17	
Hansson, 2012	ST (snus)	AMI incidence	BMI, education	Never tobacco users, current snus users <4 cans/week	HR	1.02	0.90	1.16	
Hansson, 2012	ST (snus)	AMI incidence	BMI, education	Never tobacco users, current snus users 4-6 cans week	HR	0.94	0.64	1.38	
Hansson, 2012	ST (snus)	AMI incidence	BMI, education	Never tobacco users, current snus users >=7 cans/week	HR	1.17	0.79	1.72	
Hansson, 2012	ST (snus)	AMI incidence	BMI, education	Never tobacco users, snus users of <20 years	HR	0.96	0.80	1.14	
Hansson, 2012	ST (snus)	AMI incidence	BMI, education	Never tobacco users, snus users of ≥20 years	HR	1.1	0.95	1.27	
Hansson, 2012	ST (snus)	One year AMI survival	None	Never tobacco users, current snus users	K-M log rank test				<0.05
Hansson, 2012	ST (snus)	28 day AMI fatality	None	Never tobacco users, current snus users	HR	1.28	0.99	1.68	

Hansson 2014

Full citation: Hansson J, Galanti MR, Hergens MP, Fredlund P, Ahlbom A, Alfredsson L, Bellocco R, Engstrom G, Eriksson M, Hallqvist J, Hedblad B, Jansson JH, Pedersen NL, Trolle Lagerros Y, Ostergren PO, Magnusson C. 2014. Snus (Swedish smokeless tobacco) use and risk of stroke: pooled analyses of incidence and survival. *J Intern Med* 276(1): 87-95.

Exposure: ST (snus)

Study Design: Pooled analyses

Population (total): 130,485 never-smoking Swedish men

Study Period: N/A

Endpoints: All stroke, ischemic stroke, hemorrhagic stroke (incidence and survival); 28-day stroke fatality

Number of exposed/unexposed:

97,943 non-tobacco users
32,542 current snus users

Apparent Biases: Varied by study, but probably included non-differential misclassification of exposure and potential confounding

Study Quality: Adequate

Limitations (if not "Adequate"): None

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hansson, 2014	ST (snus)	All Stroke	None	Never tobacco users, current snus users	HR	1.04	0.92	1.17	
Hansson, 2014	ST (snus)	Ischemic Stroke	None	Never tobacco users, current snus users	HR	1.06	0.91	1.23	
Hansson, 2014	ST (snus)	Haemorrhagic Stroke	None	Never tobacco users, current snus users	HR	0.94	0.73	1.54	
Hansson, 2014	ST (snus)	All Stroke	Age, BMI, education	Never tobacco users, current snus users	HR	1.10	0.78	1.57	
Hansson, 2014	ST (snus)	All Stroke	None	Never tobacco users, current snus users <4 cans/week	HR	1.05	0.92	1.20	
Hansson, 2014	ST (snus)	All Stroke	None	Never tobacco users, current snus users 4-6 cans week	HR	1.00	0.67	1.47	
Hansson, 2014	ST (snus)	All Stroke	None	Never tobacco users, current snus users >=7 cans/week	HR	0.72	0.42	1.22	
Hansson, 2014	ST (snus)	All Stroke	None	Never tobacco users, snus users of <20 years	HR	0.98	0.81	1.18	
Hansson, 2014	ST (snus)	All Stroke	None	Never tobacco users, snus users of ≥20 years	HR	1.05	0.89	1.23	
Hansson, 2014	ST (snus)	Ischemic Stroke	None	Never tobacco users, current snus	HR	1.06	0.89	1.26	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
				users <4 cans/week					
Hansson, 2014	ST (snus)	Ischemic Stroke	None	Never tobacco users, current snus users 4-6 cans week	HR	1.02	0.62	1.68	
Hansson, 2014	ST (snus)	Ischemic Stroke	None	Never tobacco users, current snus users >=7 cans/week	HR	0.54	0.24	1.26	
Hansson, 2014	ST (snus)	Ischemic Stroke	None	Never tobacco users, snus users of <20 years	HR	1.01	0.79	1.29	
Hansson, 2014	ST (snus)	Ischemic Stroke	None	Never tobacco users, snus users of ≥20 years	HR	1.05	0.85	1.28	
Hansson, 2014	ST (snus)	Hemorrhagic Stroke	None	Never tobacco users, current snus users <4 cans/week	HR	0.95	0.71	1.27	
Hansson, 2014	ST (snus)	Hemorrhagic Stroke	None	Never tobacco users, current snus users 4-6 cans week	HR	1.02	0.51	2.07	
Hansson, 2014	ST (snus)	Hemorrhagic Stroke	None	Never tobacco users, current snus users >=7 cans/week	HR	0.78	0.32	1.90	
Hansson, 2014	ST (snus)	Hemorrhagic Stroke	None	Never tobacco users, snus users of <20 years	HR	0.99	0.71	1.38	
Hansson, 2014	ST (snus)	Hemorrhagic Stroke	None	Never tobacco users, snus users of ≥20 years	HR	0.89	0.59	1.35	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hansson, 2014	ST (snus)	Unspecified Stroke	None	Never tobacco users, current snus users <4 cans/week	HR	1.16	0.81	1.68	
Hansson, 2014	ST (snus)	Unspecified Stroke	None	Never tobacco users, current snus users 4-6 cans week	HR	0.75	0.19	3.01	
Hansson, 2014	ST (snus)	Unspecified Stroke	None	Never tobacco users, current snus users >=7 cans/week	HR	1.52	0.49	4.79	
Hansson, 2014	ST (snus)	Unspecified Stroke	None	Never tobacco users, snus users of <20 years	HR	0.79	0.41	1.51	
Hansson, 2014	ST (snus)	Unspecified Stroke	None	Never tobacco users, snus users of ≥20 years	HR	1.26	0.83	1.89	
Hansson, 2014	ST (snus)	Stroke Survival Rate	None	Current snus users, non-current snus users	KM (Log Rank test)				0.3
Hansson, 2014	ST (snus)	Death following stroke	Age, BMI, year of diagnosis	Never tobacco users, current snus users	HR	1.32	1.08	1.61	
Hansson, 2014	ST (snus)	Death following ischemic stroke	Age, BMI, year of diagnosis	Never tobacco users, current snus users	HR	1.29	1.00	1.67	
Hansson, 2014	ST (snus)	Death following hemorrhagic stroke	Age, BMI, year of diagnosis	Never tobacco users, current snus users	HR	1.76	1.16	2.67	
Hansson, 2014	ST (snus)	28 day stroke fatality	None	Never tobacco users, current snus	OR	1.42	0.99	2.04	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
				users					
Hansson, 2014	ST (snus)	28 day stroke fatality	Age, BMI, year of diagnosis	Never tobacco users, current snus users	OR	1.43	0.52	3.92	

Henley 2005

Full citation: Henley SJ, Thun MJ, Connell C, Calle EE. 2005. Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). *Cancer Causes Control* 16:347-358.

Exposure: ST (chew and snuff)

Study Design: Cohort

Population (total): White U.S. adult males ages 30+

Study Period: CPS I: 1959-1972, CPS II: 1982-2000

Endpoints: Oropharynx cancer mortality, lung cancer mortality, cardiovascular disease, coronary heart disease, cerebrovascular disease, other cardiovascular, respiratory system diseases, influenza/pneumonia and chronic obstructive pulmonary disease (COPD)

Number of exposed/unexposed:

7,745 current ST users,
69,662 never ST users,
2,488 current ST users,
111,482 never ST users,
839 former ST users

Apparent Biases: Non-differential misclassification of exposure, particularly in the longest exposed group

Study Quality: Fair

Limitations (if not "Adequate"): Small number of observed disease cases, large number of adjusted factors

Comments: CPS I did not assess former tobacco usage; likely includes some former users of ST cigarettes in all comparison groups

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Henley, 2005	ST (chew and snuff users)	Oropharynx Cancer Mortality	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin	Never tobacco users, current exclusive ST users	HR	2.02	0.53	7.74	
Henley, 2005	ST (chew and snuff users)	Lung cancer mortality	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin	Never tobacco users, current exclusive ST users	HR	1.08	0.64	1.83	
Henley, 2005	ST (chew and snuff users)	Cardiovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin	Never tobacco users, current exclusive ST users	HR	1.18	1.11	1.26	
Henley, 2005	ST (chew and snuff users)	Coronary heart disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin	Never tobacco users, current exclusive ST users	HR	1.12	1.03	1.21	
Henley, 2005	ST (chew and snuff users)	Cerebrovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin	Never tobacco users, current exclusive ST users	HR	1.12	1.03	1.21	
Henley, 2005	ST (chew and snuff users)	Other cardiovascular	Age, race, education, BMI, exercise, alcohol, fat, fruit,	Never tobacco users, current exclusive ST users	HR	1.05	0.91	1.22	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			vegetable intake, and aspirin						
Henley, 2005	ST (chew and snuff users)	Respiratory system diseases	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin	Never tobacco users, current exclusive ST users	HR	1.28	1.03	1.59	
Henley, 2005	ST (chew and snuff users)	Influenza and pneumonia	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin	Never tobacco users, current exclusive ST users	HR	1.16	0.88	1.51	
Henley, 2005	ST (chew and snuff users)	COPD	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin	Never tobacco users, current exclusive ST users	HR	1.86	1.12	3.06	
Henley, 2005	ST (chew and snuff users)	Oropharynx Cancer Mortality	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, current exclusive ST users	HR	0.90	0.12	6.71	
Henley, 2005	ST (chew and snuff users)	Lung cancer mortality	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, current exclusive ST users	HR	2.00	1.23	3.24	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Henley, 2005	ST (chew and snuff users)	Lung cancer mortality	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, current exclusive chew users	HR	1.97	1.10	3.54	
Henley, 2005	ST (chew and snuff users)	Lung cancer mortality	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, current exclusive snuff users	HR	2.08	0.51	8.46	
Henley, 2005	ST (chew and snuff users)	Lung cancer mortality	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, former exclusive ST users	HR	1.17	0.43	3.14	
Henley, 2005	ST (chew and snuff users)	Cardiovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, current exclusive ST users	HR	1.23	1.09	1.39	
Henley, 2005	ST (chew and snuff users)	Cardiovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin,	Never tobacco users, current exclusive chew users	HR	1.26	1.09	1.46	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			employment						
Henley, 2005	ST (chew and snuff users)	Cardiovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, current exclusive snuff users	HR	1.38	0.99	1.92	
Henley, 2005	ST (chew and snuff users)	Cardiovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, former exclusive ST users	HR	0.92	0.75	1.13	
Henley, 2005	ST (chew and snuff users)	Coronary heart disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, current exclusive ST users	HR	1.26	1.08	1.47	
Henley, 2005	ST (chew and snuff users)	Coronary heart disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, current exclusive chew users	HR	1.25	1.03	1.51	
Henley, 2005	ST (chew and snuff users)	Coronary heart disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake,	Never tobacco users, current exclusive snuff users	HR	1.59	1.06	2.39	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			and aspirin, employment						
Henley, 2005	ST (chew and snuff users)	Coronary heart disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, former exclusive ST users	HR	0.70	0.52	0.95	
Henley, 2005	ST (chew and snuff users)	Cerebrovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, current exclusive ST users	HR	1.40	1.10	1.79	
Henley, 2005	ST (chew and snuff users)	Cerebrovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, current exclusive chew users	HR	1.38	1.02	1.86	
Henley, 2005	ST (chew and snuff users)	Cerebrovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, current exclusive snuff users	HR	0.62	0.23	1.67	
Henley, 2005	ST (chew and snuff users)	Cerebrovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit,	Never tobacco users, former exclusive ST users	HR	1.21	0.83	1.76	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			vegetable intake, and aspirin, employment						
Henley, 2005	ST (chew and snuff users)	Influenza and pneumonia	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, current exclusive ST users	HR	0.85	0.56	1.29	
Henley, 2005	ST (chew and snuff users)	Influenza and pneumonia	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, former exclusive ST users	HR	1.18	0.73	1.92	
Henley, 2005	ST (chew and snuff users)	COPD	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, current exclusive ST users	HR	1.28	0.71	2.32	
Henley, 2005	ST (chew and snuff users)	COPD	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, former exclusive ST users	HR	1.88	0.54	3.84	
Henley, 2005	ST (chew and snuff users)	Cardiovascular Disease	Age, race, education, BMI, exercise, alcohol,	Never tobacco users, those who use ST < 7	HR	1.37	1.02	1.82	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			fat, fruit, vegetable intake, and aspirin, employment	times/week					
Henley, 2005	ST (chew and snuff users)	Cardiovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 7 times/week	HR	1.19	1.00	1.41	
Henley, 2005	ST (chew and snuff users)	Cardiovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST > 7 times/week	HR	1.10	0.79	1.53	
Henley, 2005	ST (chew and snuff users)	Cardiovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 1-10 years	HR	1.15	0.81	1.63	
Henley, 2005	ST (chew and snuff users)	Cardiovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 11-30 years	HR	1.24	0.91	1.70	
Henley, 2005	ST (chew and snuff	Cardiovascular Disease	Age, race, education, BMI,	Never tobacco users, those who	HR	1.24	1.05	1.45	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
	users)		exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	use ST 30+ years					
Henley, 2005	ST (chew and snuff users)	Lung cancer mortality	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST < 7 times/week	HR	1.95	0.62	6.09	
Henley, 2005	ST (chew and snuff users)	Lung cancer mortality	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 7 times/week	HR	2.01	1.03	3.93	
Henley, 2005	ST (chew and snuff users)	Lung cancer mortality	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST > 7 times/week	HR	2.00	0.64	6.27	
Henley, 2005	ST (chew and snuff users)	Lung cancer mortality	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 1-10 years	HR	1.39	0.34	5.6	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Henley, 2005	ST (chew and snuff users)	Lung cancer mortality	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 11-30 years	HR	1.64	0.53	5.15	
Henley, 2005	ST (chew and snuff users)	Lung cancer mortality	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 30+ years	HR	2.96	1.67	5.24	
Henley, 2005	ST (chew and snuff users)	Coronary heart disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST < 7 times/week	HR	1.34	0.92	1.95	
Henley, 2005	ST (chew and snuff users)	Coronary heart disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 7 times/week	HR	1.23	0.99	1.53	
Henley, 2005	ST (chew and snuff users)	Coronary heart disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin,	Never tobacco users, those who use ST > 7 times/week	HR	1.13	0.75	1.70	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			employment						
Henley, 2005	ST (chew and snuff users)	Coronary heart disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 1-10 years	HR	1.08	0.68	1.73	
Henley, 2005	ST (chew and snuff users)	Coronary heart disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 11-30 years	HR	1.36	0.93	1.99	
Henley, 2005	ST (chew and snuff users)	Coronary heart disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 30+ years	HR	1.20	0.97	1.48	
Henley, 2005	ST (chew and snuff users)	Cerebrovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST < 7 times/week	HR	1.75	1.03	2.97	
Henley, 2005	ST (chew and snuff users)	Cerebrovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit,	Never tobacco users, those who use ST 7 times/week	HR	1.51	1.09	2.07	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			vegetable intake, and aspirin, employment						
Henley, 2005	ST (chew and snuff users)	Cerebrovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST > 7 times/week	HR	1.31	0.70	2.44	
Henley, 2005	ST (chew and snuff users)	Cerebrovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 1-10 years	HR	1.20	0.57	2.53	
Henley, 2005	ST (chew and snuff users)	Cerebrovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 11-30 years	HR	1.04	0.49	2.18	
Henley, 2005	ST (chew and snuff users)	Cerebrovascular Disease	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 30+ years	HR	1.74	1.31	2.31	
Henley, 2005	ST (chew and snuff users)	COPD	Age, race, education, BMI, exercise, alcohol,	Never tobacco users, those who use ST < 7	HR	2.45	0.77	7.74	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			fat, fruit, vegetable intake, and aspirin, employment	times/week					
Henley, 2005	ST (chew and snuff users)	COPD	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 7 times/week	HR	1.02	0.41	2.49	
Henley, 2005	ST (chew and snuff users)	COPD	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST > 7 times/week	HR	1.41	0.35	5.74	
Henley, 2005	ST (chew and snuff users)	COPD	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 1-10 years	HR	1.10	0.15	7.88	
Henley, 2005	ST (chew and snuff users)	COPD	Age, race, education, BMI, exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	Never tobacco users, those who use ST 11-30 years	HR	1.81	0.45	7.34	
Henley, 2005	ST (chew and snuff	COPD	Age, race, education, BMI,	Never tobacco users, those who	HR	1.17	0.54	2.53	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
	users)		exercise, alcohol, fat, fruit, vegetable intake, and aspirin, employment	use ST 30+ years					

Hergens 2005

Full citation: Hergens MP, Ahlbom A, Andersson T, Pershagen G. 2005. Swedish moist snuff and myocardial infarction among men. *Epidemiology* 16(1):12-16.

Exposure: ST (snus)

Study Design: Case-control

Population (total): 3,242 men ages 45-70 in Stockholm Country or Vasternorrland county 1993-1994

Study Period: Stockholm - 1992-1993, Vasternorrland - 1993-1994

Endpoints: All first myocardial infarctions, non-fatal first myocardial infarctions, fatal first myocardial infarctions

Number of exposed/unexposed:

1,432 cases
1,810 controls

Apparent Biases: Recall bias, selection bias

Study Quality: Adequate

Limitations (if not "Adequate"): None

Comments: Diabetes, hyperlipidemia, hypertension, overweight, physical inactivity, and job strain had no influence on results as covariates.

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2005	ST (snus)	All First Myocardial Infarctions	Age, hospital catchment area	Never tobacco use, Former snus use	aOR	1.2	0.46	3.1	
Hergens, 2005	ST (snus)	All First Myocardial Infarctions	Age, hospital catchment area	Never tobacco use, Current snus use	aOR	0.73	0.35	1.5	
Hergens, 2005	ST (snus)	Non-Fatal, First Myocardial Infarctions	Age, hospital catchment area	Never tobacco use, Former snus use	aOR	1.2	0.43	3.2	
Hergens, 2005	ST (snus)	Non-Fatal, First Myocardial Infarctions	Age, hospital catchment area	Never tobacco use, Current snus use	aOR	0.59	0.25	1.4	
Hergens, 2005	ST (snus)	Fatal, First Myocardial Infarctions	Age, hospital catchment area	Never tobacco use, Former snus use	aOR	1.7	0.21	13.6	
Hergens, 2005	ST (snus)	Fatal, First Myocardial Infarctions	Age, hospital catchment area	Never tobacco use, Current snus use	aOR	1.7	0.48	5.5	
Hergens, 2005	ST (snus)	All First Myocardial Infarctions	Age, hospital catchment area	Never tobacco use, Former snus use	aOR	1.3	1.1	1.6	
Hergens, 2005	ST (snus)	All First Myocardial Infarctions	Age, hospital catchment area	Never tobacco use, Current snus use	aOR	2.8	2.3	3.4	
Hergens, 2005	ST (snus)	Non-Fatal, First Myocardial Infarctions	Age, hospital catchment area	Never tobacco use, Former snus use	aOR	1.2	0.98	1.5	
Hergens, 2005	ST (snus)	Non-Fatal, First Myocardial	Age, hospital catchment area	Never tobacco use, Current snus use	aOR	2.7	2.2	3.3	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
		Infarctions							
Hergens, 2005	ST (snus)	Fatal, First Myocardial Infarctions	Age, hospital catchment area	Never tobacco use, Former snus use	aOR	1.7	1.6	2.6	
Hergens, 2005	ST (snus)	Fatal, First Myocardial Infarctions	Age, hospital catchment area	Never tobacco use, Current snus use	aOR	3.6	2.4	5.2	

Hergens 2007

Full citation: Hergens MP, Alfredsson L, Bolinder G, Lambe M, Pershagen G, Ye W. 2007. Long-term use of Swedish moist snuff and the risk of myocardial infarction amongst men. *J Intern Med* 262(3):351-359.

Exposure: ST (snus)

Study Design: Cohort

Population (total): 118,395 nonsmoking male Swedish construction industry employees

Study Period: 1978-2004

Endpoints: All myocardial infarction (MI), non-fatal MI, fatal MI and cardiovascular deaths

Number of exposed/unexposed:

83,624 never snus users
34,841 ever snus users
32,358 current snus users
2,483 former snus users

Apparent Biases: Non-differential misclassification of exposure

Study Quality: Adequate

Limitations (if not "Adequate"): None

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, ever snus users	RR	0.99	0.9	1.1	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, former snus users	RR	0.76	0.55	1.05	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, current snus users	RR	1.02	0.92	1.14	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, those who use 12.5 g/day	RR	1.12	0.95	1.3	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, those who use 12.5-24.9 g/day	RR	0.93	0.79	1.09	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, those who use 25-49.9 g/day	RR	0.95	0.73	1.24	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, those who use 50+ g/day	RR	1.24	0.89	1.73	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, ever snus users	RR	0.91	0.81	1.02	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, former snus users	RR	0.7	0.48	1.02	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, current snus users	RR	0.94	0.83	1.06	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, those who use 12.5 g/day	RR	1.02	0.84	1.22	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, those who use 12.5-24.9 g/day	RR	0.85	0.7	1.03	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, those who use 25-49.9 g/day	RR	0.95	0.71	1.29	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, those who use 50+ g/day	RR	1.06	0.71	1.58	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, ever snus users	RR	1.28	1.06	1.55	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, former snus users	RR	1	0.54	1.88	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, current snus users	RR	1.32	1.08	1.61	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, those who use 12.5 g/day	RR	1.45	1.09	1.93	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, those who use 12.5-24.9 g/day	RR	1.22	0.9	1.65	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, those who use 25-49.9 g/day	RR	0.95	0.54	1.69	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, those who use 50+ g/day	RR	1.96	1.08	3.58	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, ever snus users ages 35-54 at baseline	RR	0.97	0.86	1.09	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, former snus users ages 35-54 at baseline	RR	0.76	0.53	1.1	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, current snus users ages 35-54 at baseline	RR	1	0.88	1.3	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, those who use 12.5 g/day ages 35-54 at baseline	RR	1.07	0.88	1.3	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, those who use 12.5-24.9 g/day ages 35-54 at baseline	RR	0.91	0.75	1.11	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, those who use 25-49.9 g/day ages 35-54 at baseline	RR	1	0.75	1.33	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, those who use 50+ g/day ages 35-54 at baseline	RR	1.12	0.76	1.64	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, ever snus users ages 35-54 at baseline	RR	0.9	0.79	1.04	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, former snus users ages 35-54 at baseline	RR	0.63	0.41	0.98	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, current snus users ages 35-54 at baseline	RR	0.94	0.82	1.09	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, those who use 12.5 g/day ages 35-54 at baseline	RR	0.97	0.77	1.22	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, those who use 12.5-24.9 g/day ages 35-54 at baseline	RR	0.88	0.71	1.09	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, those who use 25-49.9 g/day ages 35-54 at baseline	RR	0.98	0.71	1.35	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, those who use 50+ g/day ages 35-54 at baseline	RR	1.1	0.72	1.68	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, ever snus users ages 35-54 at baseline	RR	1.26	0.98	1.63	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, former snus users ages 35-54 at baseline	RR	1.44	0.74	2.95	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, current snus users ages 35-54 at baseline	RR	1.25	0.95	1.63	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, those who use 12.5 g/day ages 35-54 at baseline	RR	1.53	1.03	2.27	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, those who use 12.5-24.9 g/day ages 35-54 at baseline	RR	1.08	0.71	1.65	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, those who use 25-49.9 g/day ages 35-54 at baseline	RR	1.08	0.56	2.1	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, those who use 50+ g/day ages 35-54 at baseline	RR	1.22	0.5	2.96	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, ever snus users ages 55-65 at baseline	RR	1.04	0.9	1.2	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, former snus users ages 55-65 at baseline	RR	0.69	0.4	1.19	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, current snus users ages 55-65 at baseline	RR	1.08	0.93	1.26	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, those who use 12.5 g/day ages 55-65 at baseline	RR	1.27	1.03	1.55	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, those who use 12.5-24.9 g/day ages 55-65 at baseline	RR	0.95	0.75	1.2	
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, those who use 25-49.9 g/day ages 55-65 at baseline	RR	0.79	0.49	1.27	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2007	ST (snus)	All MI	Age, BMI, region of residence	Never snus users, those who use 50+ g/day ages 55-65 at baseline	RR	1.38	0.74	2.57	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, ever snus users ages 55-65 at baseline	RR	0.96	0.8	1.5	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, former snus users ages 55-65 at baseline	RR	0.62	0.31	1.23	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, current snus users ages 55-65 at baseline	RR	1	0.83	1.21	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, those who use 12.5 g/day ages 55-65 at baseline	RR	1.24	0.97	1.59	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, those who use 12.5-24.9 g/day ages 55-65 at baseline	RR	0.82	0.6	1.11	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, those who use 25-49.9 g/day ages 55-65 at baseline	RR	0.83	0.47	1.47	
Hergens, 2007	ST (snus)	Non-Fatal MI	Age, BMI, region of residence	Never snus users, those who use 50+ g/day ages 55-65 at baseline	RR	0.83	0.31	2.22	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, ever snus users ages 55-65 at baseline	RR	1.21	0.95	1.55	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, former snus users ages 55-65 at baseline	RR	0.87	0.36	2.09	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, current snus users ages 55-65 at baseline	RR	1.26	0.98	1.62	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, those who use 12.5 g/day ages 55-65 at baseline	RR	1.32	0.93	1.89	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, those who use 12.5-24.9 g/day ages 55-65 at baseline	RR	1.24	0.85	1.81	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, those who use 25-49.9 g/day ages 55-65 at baseline	RR	0.7	0.29	1.69	
Hergens, 2007	ST (snus)	Fatal MI	Age, BMI, region of residence	Never snus users, those who use 50+ g/day ages 55-65 at baseline	RR	2.46	1.09	5.55	
Hergens, 2007	ST (snus)	Cardiovascular deaths	None	Never snus users, ever snus users	K-M log rank test				<0.05

Hergens 2008a

Full citation: Hergens MP, Lambe M, Pershagen G, Terent A, Ye W. 2008a. Smokeless tobacco and the risk of stroke. *Epidemiology* 19(6):794-799.

Exposure: ST (snus)

Study Design: Cohort

Population (total): 118,465 never-smoking Swedish construction workers without history of stroke

Study Period: 1978-2003

Endpoints: Fatal and nonfatal stroke incidence, fatal and nonfatal ischemic stroke incidence, fatal and nonfatal hemorrhagic stroke incidence, fatal and nonfatal unspecified stroke incidence, stroke mortality

Number of exposed/unexposed:

84,110 never tobacco users
34,355 ever snus users
2,369 former snus users
31,986 current snus users

Apparent Biases: Non-differential misclassification of exposure
Study Quality: Adequate

Limitations (if not "Adequate"): None

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2008a	ST (Snus)	All stroke	Age	Never tobacco use, ever snus use	SIR	1.73			
Hergens, 2008a	ST (Snus)	All stroke	Age, BMI, region of residence	Never tobacco use, ever snus use	HR	1.02	0.92	1.13	
Hergens, 2008a	ST (Snus)	All stroke	Age	Never tobacco use, former snus use	SIR	1.04			
Hergens, 2008a	ST (Snus)	All stroke	Age, BMI, region of residence	Never tobacco use, former snus use	HR	0.72	0.50	1.02	
Hergens, 2008a	ST (Snus)	All stroke	Age	Never tobacco use, current snus use	SIR	1.82			
Hergens, 2008a	ST (Snus)	All stroke	Age, BMI, region of residence	Never tobacco use, current snus use	HR	1.05	0.95	1.17	
Hergens, 2008a	ST (Snus)	All non-fatal stroke	Age	Never tobacco use, ever snus use	SIR	1.54			
Hergens, 2008a	ST (Snus)	All non-fatal stroke	Age, BMI, region of residence	Never tobacco use, ever snus use	HR	1.00	0.89	1.11	
Hergens, 2008a	ST (Snus)	All non-fatal stroke	Age	Never tobacco use, former snus use	SIR	1.00			
Hergens, 2008a	ST (Snus)	All non-fatal stroke	Age, BMI, region of residence	Never tobacco use, former snus use	HR	0.75	0.53	1.08	
Hergens, 2008a	ST (Snus)	All non-fatal stroke	Age	Never tobacco use, current snus use	SIR	1.61			
Hergens, 2008a	ST (Snus)	All non-fatal stroke	Age, BMI, region of residence	Never tobacco use, current snus use	HR	1.02	0.91	1.14	
Hergens,	ST (Snus)	All fatal	Age	Never tobacco use,	SIR	0.19			

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
2008a		stroke		ever snus use					
Hergens, 2008a	ST (Snus)	All fatal stroke	Age, BMI, region of residence	Never tobacco use, ever snus use	HR	1.27	0.92	1.76	
Hergens, 2008a	ST (Snus)	All fatal stroke	Age	Never tobacco use, former snus use	SIR	0.05			
Hergens, 2008a	ST (Snus)	All fatal stroke	Age, BMI, region of residence	Never tobacco use, former snus use	HR	0.30	0.04	2.11	
Hergens, 2008a	ST (Snus)	All fatal stroke	Age	Never tobacco use, current snus use	SIR	0.21			
Hergens, 2008a	ST (Snus)	All fatal stroke	Age, BMI, region of residence	Never tobacco use, current snus use	HR	1.38	0.99	1.91	
Hergens, 2008a	ST (Snus)	All Ischemic stroke	Age	Never tobacco use, ever snus use	SIR	1.22			
Hergens, 2008a	ST (Snus)	All Ischemic stroke	Age, BMI, region of residence	Never tobacco use, ever snus use	HR	1.03	0.91	1.16	
Hergens, 2008a	ST (Snus)	All Ischemic stroke	Age	Never tobacco use, former snus use	SIR	0.72			
Hergens, 2008a	ST (Snus)	All Ischemic stroke	Age, BMI, region of residence	Never tobacco use, former snus use	HR	0.68	0.44	1.06	
Hergens, 2008a	ST (Snus)	All Ischemic stroke	Age	Never tobacco use, current snus use	SIR	1.29			
Hergens, 2008a	ST (Snus)	All Ischemic stroke	Age, BMI, region of residence	Never tobacco use, current snus use	HR	1.07	0.94	1.22	
Hergens, 2008a	ST (Snus)	Nonfatal Ischemic stroke	Age	Never tobacco use, ever snus use	SIR	1.12			

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2008a	ST (Snus)	Nonfatal Ischemic stroke	Age, BMI, region of residence	Never tobacco use, ever snus use	HR	1.00	0.88	1.13	
Hergens, 2008a	ST (Snus)	Nonfatal Ischemic stroke	Age	Never tobacco use, former snus use	SIR	0.67			
Hergens, 2008a	ST (Snus)	Nonfatal Ischemic stroke	Age, BMI, region of residence	Never tobacco use, former snus use	HR	0.67	0.43	1.06	
Hergens, 2008a	ST (Snus)	Nonfatal Ischemic stroke	Age	Never tobacco use, current snus use	SIR	1.18			
Hergens, 2008a	ST (Snus)	Nonfatal Ischemic stroke	Age, BMI, region of residence	Never tobacco use, current snus use	HR	1.04	0.91	1.18	
Hergens, 2008a	ST (Snus)	Fatal Ischemic Stroke	Age	Never tobacco use, ever snus use	SIR	0.10			
Hergens, 2008a	ST (Snus)	Fatal Ischemic Stroke	Age, BMI, region of residence	Never tobacco use, ever snus use	HR	1.63	1.02	2.62	
Hergens, 2008a	ST (Snus)	Fatal Ischemic Stroke	Age	Never tobacco use, former snus use	SIR	0.05			
Hergens, 2008a	ST (Snus)	Fatal Ischemic Stroke	Age, BMI, region of residence	Never tobacco use, former snus use	HR	0.82	0.12	5.93	
Hergens, 2008a	ST (Snus)	Fatal Ischemic	Age	Never tobacco use, current snus use	SIR	0.11			

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
		Stroke							
Hergens, 2008a	ST (Snus)	Fatal Ischemic Stroke	Age, BMI, region of residence	Never tobacco use, current snus use	HR	1.72	1.06	2.78	
Hergens, 2008a	ST (Snus)	All Hemorrhagic Stroke	Age	Never tobacco use, ever snus use	SIR	0.25			
Hergens, 2008a	ST (Snus)	All Hemorrhagic Stroke	Age, BMI, region of residence	Never tobacco use, ever snus use	HR	0.86	0.67	1.10	
Hergens, 2008a	ST (Snus)	All Hemorrhagic Stroke	Age	Never tobacco use, former snus use	SIR	0.21			
Hergens, 2008a	ST (Snus)	All Hemorrhagic Stroke	Age, BMI, region of residence	Never tobacco use, former snus use	HR	0.90	0.45	1.82	
Hergens, 2008a	ST (Snus)	All Hemorrhagic Stroke	Age	Never tobacco use, current snus use	SIR	0.26			
Hergens, 2008a	ST (Snus)	All Hemorrhagic Stroke	Age, BMI, region of residence	Never tobacco use, current snus use	HR	0.85	0.65	1.10	
Hergens, 2008a	ST (Snus)	Nonfatal Hemorrhagic Stroke	Age	Never tobacco use, ever snus use	SIR	0.19			
Hergens, 2008a	ST (Snus)	Nonfatal Hemorrhagic Stroke	Age, BMI, region of residence	Never tobacco use, ever snus use	HR	0.82	0.62	1.08	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2008a	ST (Snus)	Nonfatal Hemorrhagic Stroke	Age	Never tobacco use, former snus use	SIR	0.21			
Hergens, 2008a	ST (Snus)	Nonfatal Hemorrhagic Stroke	Age, BMI, region of residence	Never tobacco use, former snus use	HR	1.10	0.54	2.21	
Hergens, 2008a	ST (Snus)	Nonfatal Hemorrhagic Stroke	Age	Never tobacco use, current snus use	SIR	0.19			
Hergens, 2008a	ST (Snus)	Nonfatal Hemorrhagic Stroke	Age, BMI, region of residence	Never tobacco use, current snus use	HR	0.77	0.57	1.04	
Hergens, 2008a	ST (Snus)	Fatal Hemorrhagic Stroke	Age	Never tobacco use, ever snus use	SIR	0.06			
Hergens, 2008a	ST (Snus)	Fatal Hemorrhagic Stroke	Age, BMI, region of residence	Never tobacco use, ever snus use	HR	1.05	0.61	1.80	
Hergens, 2008a	ST (Snus)	Fatal Hemorrhagic Stroke	Age	Never tobacco use, former snus use	SIR	no estimate			
Hergens, 2008a	ST (Snus)	Fatal Hemorrhagic Stroke	Age, BMI, region of residence	Never tobacco use, former snus use	HR	no estimate			
Hergens, 2008a	ST (Snus)	Fatal Hemorrhagic Stroke	Age	Never tobacco use, current snus use	SIR	0.07			
Hergens, 2008a	ST (Snus)	Fatal Hemorrhagic	Age, BMI, region of residence	Never tobacco use, current snus use	HR	1.17	0.68	2.01	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
		Stroke							
Hergens, 2008a	ST (Snus)	All Unspecified Stroke	Age	Never tobacco use, ever snus use	SIR	0.26			
Hergens, 2008a	ST (Snus)	All Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, ever snus use	HR	1.22	0.93	1.61	
Hergens, 2008a	ST (Snus)	All Unspecified Stroke	Age	Never tobacco use, former snus use	SIR	0.11			
Hergens, 2008a	ST (Snus)	All Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, former snus use	HR	0.66	0.21	2.06	
Hergens, 2008a	ST (Snus)	All Unspecified Stroke	Age	Never tobacco use, current snus use	SIR	0.28			
Hergens, 2008a	ST (Snus)	All Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, current snus use	HR	1.35	1.02	1.80	
Hergens, 2008a	ST (Snus)	Nonfatal Unspecified Stroke	Age	Never tobacco use, ever snus use	SIR	0.22			
Hergens, 2008a	ST (Snus)	Nonfatal Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, ever snus use	HR	1.25	0.93	1.67	
Hergens, 2008a	ST (Snus)	Nonfatal Unspecified Stroke	Age	Never tobacco use, former snus use	SIR	0.11			

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2008a	ST (Snus)	Nonfatal Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, former snus use	HR	0.69	0.22	2.14	
Hergens, 2008a	ST (Snus)	Nonfatal Unspecified Stroke	Age	Never tobacco use, current snus use	SIR	0.24			
Hergens, 2008a	ST (Snus)	Nonfatal Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, current snus use	HR	1.31	0.98	1.77	
Hergens, 2008a	ST (Snus)	Fatal Unspecified Stroke	Age	Never tobacco use, ever snus use	SIR	0.03			
Hergens, 2008a	ST (Snus)	Fatal Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, ever snus use	HR	1.03	0.47	2.31	
Hergens, 2008a	ST (Snus)	Fatal Unspecified Stroke	Age	Never tobacco use, former snus use	SIR	no estimate			
Hergens, 2008a	ST (Snus)	Fatal Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, former snus use	HR	no estimate			
Hergens, 2008a	ST (Snus)	Fatal Unspecified Stroke	Age	Never tobacco use, current snus use	SIR	0.04			
Hergens, 2008a	ST (Snus)	Fatal Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, current snus use	HR	1.14	0.51	2.54	
Hergens, 2008a	ST (Snus)	All stroke	Age	Never tobacco use, current snus use	SIR	1.82			

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
				<12.5 g/day					
Hergens, 2008a	ST (Snus)	All stroke	Age, BMI, region of residence	Never tobacco use, current snus use <12.5 g/day	HR	1.08	0.92	1.27	
Hergens, 2008a	ST (Snus)	All stroke	Age	Never tobacco use, current snus use 12.5-29.9 g/day	SIR	1.85			
Hergens, 2008a	ST (Snus)	All stroke	Age, BMI, region of residence	Never tobacco use, current snus use 12.5-29.9 g/day	HR	1.11	0.95	1.29	
Hergens, 2008a	ST (Snus)	All stroke	Age	Never tobacco use, current snus use 25-49.9 g/day	SIR	1.64			
Hergens, 2008a	ST (Snus)	All stroke	Age, BMI, region of residence	Never tobacco use, current snus use 25-49.9 g/day	HR	1.06	0.82	1.38	
Hergens, 2008a	ST (Snus)	All stroke	Age	Never tobacco use, current snus use 50+ g/day	SIR	1.74			
Hergens, 2008a	ST (Snus)	All stroke	Age, BMI, region of residence	Never tobacco use, current snus use 50+ g/day	HR	1.13	0.78	1.64	
Hergens, 2008a	ST (Snus)	All non-fatal stroke	Age	Never tobacco use, current snus use <12.5 g/day	SIR	1.61			
Hergens, 2008a	ST (Snus)	All non-fatal stroke	Age, BMI, region of residence	Never tobacco use, current snus use <12.5 g/day	HR	1.05	0.88	1.25	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2008a	ST (Snus)	All non-fatal stroke	Age	Never tobacco use, current snus use 12.5-29.9 g/day	SIR	1.62			
Hergens, 2008a	ST (Snus)	All non-fatal stroke	Age, BMI, region of residence	Never tobacco use, current snus use 12.5-29.9 g/day	HR	1.07	0.91	1.26	
Hergens, 2008a	ST (Snus)	All non-fatal stroke	Age	Never tobacco use, current snus use 25-49.9 g/day	SIR	1.50			
Hergens, 2008a	ST (Snus)	All non-fatal stroke	Age, BMI, region of residence	Never tobacco use, current snus use 25-49.9 g/day	HR	1.05	0.80	1.38	
Hergens, 2008a	ST (Snus)	All non-fatal stroke	Age	Never tobacco use, current snus use 50+ g/day	SIR	1.61			
Hergens, 2008a	ST (Snus)	All non-fatal stroke	Age, BMI, region of residence	Never tobacco use, current snus use 50+ g/day	HR	1.13	0.77	1.66	
Hergens, 2008a	ST (Snus)	All Fatal Stroke	Age	Never tobacco use, current snus use <12.5 g/day	SIR	0.21			
Hergens, 2008a	ST (Snus)	All Fatal Stroke	Age, BMI, region of residence	Never tobacco use, current snus use <12.5 g/day	HR	1.42	0.86	2.32	
Hergens, 2008a	ST (Snus)	All Fatal Stroke	Age	Never tobacco use, current snus use 12.5-29.9 g/day	SIR	0.24			
Hergens, 2008a	ST (Snus)	All Fatal Stroke	Age, BMI, region of residence	Never tobacco use, current snus use	HR	1.57	0.99	2.49	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
				12.5-29.9 g/day					
Hergens, 2008a	ST (Snus)	All Fatal Stroke	Age	Never tobacco use, current snus use 25-49.9 g/day	SIR	0.14			
Hergens, 2008a	ST (Snus)	All Fatal Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 25-49.9 g/day	HR	1.24	0.51	3.03	
Hergens, 2008a	ST (Snus)	All Fatal Stroke	Age	Never tobacco use, current snus use 50+ g/day	SIR	0.12			
Hergens, 2008a	ST (Snus)	All Fatal Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 50+ g/day	HR	1.16	0.29	4.69	
Hergens, 2008a	ST (Snus)	All Ischemic stroke	Age	Never tobacco use, current snus use <12.5 g/day	SIR	1.29			
Hergens, 2008a	ST (Snus)	All Ischemic stroke	Age, BMI, region of residence	Never tobacco use, current snus use <12.5 g/day	HR	2.11	1.10	4.07	
Hergens, 2008a	ST (Snus)	All Ischemic stroke	Age	Never tobacco use, current snus use 12.5-29.9 g/day	SIR	1.28			
Hergens, 2008a	ST (Snus)	All Ischemic stroke	Age, BMI, region of residence	Never tobacco use, current snus use 12.5-29.9 g/day	HR	1.66	0.80	3.44	
Hergens, 2008a	ST (Snus)	All Ischemic stroke	Age	Never tobacco use, current snus use 25-49.9 g/day	SIR	1.20			

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2008a	ST (Snus)	All Ischemic stroke	Age, BMI, region of residence	Never tobacco use, current snus use 25-49.9 g/day	HR	0.66	0.09	4.76	
Hergens, 2008a	ST (Snus)	All Ischemic stroke	Age	Never tobacco use, current snus use 50+ g/day	SIR	1.30			
Hergens, 2008a	ST (Snus)	All Ischemic stroke	Age, BMI, region of residence	Never tobacco use, current snus use 50+ g/day	HR	3.28	0.79	13.6	
Hergens, 2008a	ST (Snus)	Nonfatal Ischemic stroke	Age	Never tobacco use, current snus use <12.5 g/day	SIR	1.17			
Hergens, 2008a	ST (Snus)	Nonfatal Ischemic stroke	Age, BMI, region of residence	Never tobacco use, current snus use <12.5 g/day	HR	1.05	0.85	1.28	
Hergens, 2008a	ST (Snus)	Nonfatal Ischemic stroke	Age	Never tobacco use, current snus use 12.5-29.9 g/day	SIR	1.18			
Hergens, 2008a	ST (Snus)	Nonfatal Ischemic stroke	Age, BMI, region of residence	Never tobacco use, current snus use 12.5-29.9 g/day	HR	1.08	0.89	1.31	
Hergens, 2008a	ST (Snus)	Nonfatal Ischemic stroke	Age	Never tobacco use, current snus use 25-49.9 g/day	SIR	1.16			
Hergens, 2008a	ST (Snus)	Nonfatal Ischemic stroke	Age, BMI, region of residence	Never tobacco use, current snus use 25-49.9 g/day	HR	1.15	0.84	1.58	
Hergens, 2008a	ST (Snus)	Nonfatal Ischemic	Age	Never tobacco use, current snus use	SIR	1.18			

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
		stroke		50+ g/day					
Hergens, 2008a	ST (Snus)	Nonfatal Ischemic stroke	Age, BMI, region of residence	Never tobacco use, current snus use 50+ g/day	HR	1.19	0.76	1.88	
Hergens, 2008a	ST (Snus)	Fatal Ischemic Stroke	Age	Never tobacco use, current snus use <12.5 g/day	SIR	0.13			
Hergens, 2008a	ST (Snus)	Fatal Ischemic Stroke	Age, BMI, region of residence	Never tobacco use, current snus use <12.5 g/day	HR	2.11	1.10	4.07	
Hergens, 2008a	ST (Snus)	Fatal Ischemic Stroke	Age	Never tobacco use, current snus use 12.5-29.9 g/day	SIR	0.10			
Hergens, 2008a	ST (Snus)	Fatal Ischemic Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 12.5-29.9 g/day	HR	1.99	0.80	3.44	
Hergens, 2008a	ST (Snus)	Fatal Ischemic Stroke	Age	Never tobacco use, current snus use 25-49.9 g/day	SIR	0.05			
Hergens, 2008a	ST (Snus)	Fatal Ischemic Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 25-49.9 g/day	HR	0.66	0.09	4.76	
Hergens, 2008a	ST (Snus)	Fatal Ischemic Stroke	Age	Never tobacco use, current snus use 50+ g/day	SIR	0.12			
Hergens, 2008a	ST (Snus)	Fatal Ischemic Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 50+ g/day	HR	3.28	0.79	13.6	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2008a	ST (Snus)	All Hemorrhagic Stroke	Age	Never tobacco use, current snus use <12.5 g/day	SIR	0.23			
Hergens, 2008a	ST (Snus)	All Hemorrhagic Stroke	Age, BMI, region of residence	Never tobacco use, current snus use <12.5 g/day	HR	0.79	0.51	1.24	
Hergens, 2008a	ST (Snus)	All Hemorrhagic Stroke	Age	Never tobacco use, current snus use 12.5-29.9 g/day	SIR	0.26			
Hergens, 2008a	ST (Snus)	All Hemorrhagic Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 12.5-29.9 g/day	HR	0.92	0.64	1.33	
Hergens, 2008a	ST (Snus)	All Hemorrhagic Stroke	Age	Never tobacco use, current snus use 25-49.9 g/day	SIR	0.22			
Hergens, 2008a	ST (Snus)	All Hemorrhagic Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 25-49.9 g/day	HR	0.83	0.45	1.52	
Hergens, 2008a	ST (Snus)	All Hemorrhagic Stroke	Age	Never tobacco use, current snus use 50+ g/day	SIR	0.24			
Hergens, 2008a	ST (Snus)	All Hemorrhagic Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 50+ g/day	HR	0.91	0.40	2.05	
Hergens, 2008a	ST (Snus)	Nonfatal Hemorrhagic stroke	Age	Never tobacco use, current snus use <12.5 g/day	SIR	0.17			
Hergens, 2008a	ST (Snus)	Nonfatal Hemorrhagic	Age, BMI, region of residence	Never tobacco use, current snus use	HR	0.73	0.44	1.23	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
		stroke		<12.5 g/day					
Hergens, 2008a	ST (Snus)	Nonfatal Hemorrhagic stroke	Age	Never tobacco use, current snus use 12.5-29.9 g/day	SIR	0.18			
Hergens, 2008a	ST (Snus)	Nonfatal Hemorrhagic stroke	Age, BMI, region of residence	Never tobacco use, current snus use 12.5-29.9 g/day	HR	0.82	0.53	1.25	
Hergens, 2008a	ST (Snus)	Nonfatal Hemorrhagic stroke	Age	Never tobacco use, current snus use 25-49.9 g/day	SIR	0.17			
Hergens, 2008a	ST (Snus)	Nonfatal Hemorrhagic stroke	Age, BMI, region of residence	Never tobacco use, current snus use 25-49.9 g/day	HR	0.70	0.35	1.42	
Hergens, 2008a	ST (Snus)	Nonfatal Hemorrhagic stroke	Age	Never tobacco use, current snus use 50+ g/day	SIR	0.24			
Hergens, 2008a	ST (Snus)	Nonfatal Hemorrhagic stroke	Age, BMI, region of residence	Never tobacco use, current snus use 50+ g/day	HR	1.05	0.47	2.37	
Hergens, 2008a	ST (Snus)	Fatal Hemorrhagic Stroke	Age	Never tobacco use, current snus use <12.5 g/day	SIR	0.06			
Hergens, 2008a	ST (Snus)	Fatal Hemorrhagic Stroke	Age, BMI, region of residence	Never tobacco use, current snus use <12.5 g/day	HR	1.05	0.43	2.59	
Hergens, 2008a	ST (Snus)	Fatal Hemorrhagic Stroke	Age	Never tobacco use, current snus use 12.5-29.9 g/day	SIR	0.08			

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2008a	ST (Snus)	Fatal Hemorrhagic Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 12.5-29.9 g/day	HR	1.43	0.69	2.96	
Hergens, 2008a	ST (Snus)	Fatal Hemorrhagic Stroke	Age	Never tobacco use, current snus use 25-49.9 g/day	SIR	0.05			
Hergens, 2008a	ST (Snus)	Fatal Hemorrhagic Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 25-49.9 g/day	HR	1.56	0.46	4.99	
Hergens, 2008a	ST (Snus)	Fatal Hemorrhagic Stroke	Age	Never tobacco use, current snus use 50+ g/day	SIR	no estimate			
Hergens, 2008a	ST (Snus)	Fatal Hemorrhagic Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 50+ g/day	HR	no estimate			
Hergens, 2008a	ST (Snus)	All Unspecified Stroke	Age	Never tobacco use, current snus use <12.5 g/day	SIR	0.30			
Hergens, 2008a	ST (Snus)	All Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, current snus use <12.5 g/day	HR	1.39	0.92	2.10	
Hergens, 2008a	ST (Snus)	All Unspecified Stroke	Age	Never tobacco use, current snus use 12.5-29.9 g/day	SIR	0.30			
Hergens, 2008a	ST (Snus)	All Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 12.5-29.9 g/day	HR	1.46	0.98	2.17	
Hergens, 2008a	ST (Snus)	All Unspecified	Age	Never tobacco use, current snus use	SIR	0.21			

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
		Stroke		25-49.9 g/day					
Hergens, 2008a	ST (Snus)	All Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 25-49.9 g/day	HR	1.16	0.55	2.47	
Hergens, 2008a	ST (Snus)	All Unspecified Stroke	Age	Never tobacco use, current snus use 50+ g/day	SIR	0.20			
Hergens, 2008a	ST (Snus)	All Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 50+ g/day	HR	0.75	0.19	3.03	
Hergens, 2008a	ST (Snus)	Nonfatal Unspecified Stroke	Age	Never tobacco use, current snus use <12.5 g/day	SIR	0.27			
Hergens, 2008a	ST (Snus)	Nonfatal Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, current snus use <12.5 g/day	HR	1.49	0.97	2.30	
Hergens, 2008a	ST (Snus)	Nonfatal Unspecified Stroke	Age	Never tobacco use, current snus use 12.5-29.9 g/day	SIR	0.25			
Hergens, 2008a	ST (Snus)	Nonfatal Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 12.5-29.9 g/day	HR	1.42	0.93	2.18	
Hergens, 2008a	ST (Snus)	Nonfatal Unspecified Stroke	Age	Never tobacco use, current snus use 25-49.9 g/day	SIR	0.17			
Hergens, 2008a	ST (Snus)	Nonfatal Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 25-49.9 g/day	HR	1.11	0.49	2.50	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2008a	ST (Snus)	Nonfatal Unspecified Stroke	Age	Never tobacco use, current snus use 50+ g/day	SIR	0.20			
Hergens, 2008a	ST (Snus)	Nonfatal Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 50+ g/day	HR	0.81	0.20	3.27	
Hergens, 2008a	ST (Snus)	Fatal Unspecified Stroke	Age	Never tobacco use, current snus use <12.5 g/day	SIR	0.03			
Hergens, 2008a	ST (Snus)	Fatal Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, current snus use <12.5 g/day	HR	0.78	0.18	3.21	
Hergens, 2008a	ST (Snus)	Fatal Unspecified Stroke	Age	Never tobacco use, current snus use 12.5-29.9 g/day	SIR	0.05			
Hergens, 2008a	ST (Snus)	Fatal Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 12.5-29.9 g/day	HR	1.71	0.62	4.76	
Hergens, 2008a	ST (Snus)	Fatal Unspecified Stroke	Age	Never tobacco use, current snus use 25-49.9 g/day	SIR	0.05			
Hergens, 2008a	ST (Snus)	Fatal Unspecified Stroke	Age, BMI, region of residence	Never tobacco use, current snus use 25-49.9 g/day	HR	1.65	0.22	12.06	
Hergens, 2008a	ST (Snus)	Fatal Unspecified Stroke	Age	Never tobacco use, current snus use 50+ g/day	SIR	no estimate			
Hergens, 2008a	ST (Snus)	Fatal Unspecified	Age, BMI, region of residence	Never tobacco use, current snus use	HR	no estim			

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
		Stroke		50+ g/day		ate			
Hergens, 2008a	ST (Snus)	Stroke Mortality	Age, BMI, region of residence	Never tobacco users, ever snus users	HR	1.52	1.01	2.29	
Hergens, 2008a	ST (Snus)	Stroke Mortality	Age, BMI, region of residence	Never tobacco users, ever snus users	Log-Rank test (KM Curve)				0.02

Hergens 2008b

Full citation: Hergens MP, Lambe M, Pershagen G, Ye W. 2008b. Risk of hypertension amongst Swedish male snuff users: a prospective study. *J Intern Med* 264(2):187-194.

Exposure: ST (snus)

Study Design: Cross-sectional, cohort

Population (total): Cross-sectional: 120,930 non-smoking Swedish male construction workers. Cohort: 77,469 non-smoking Swedish male construction workers with normal blood pressure (BP)

Study Period: 1978-1993

Endpoints: High BP prevalence, high BP and hypertension

Number of exposed/unexposed:

Cross-sectional:
85,413 never snus users
35,517 ever snus users
32,973 current snus users
2,487 former snus users

Cohort:
29,892 never snus users
12,093 ever snus users
11,235 current snus users
858 former snus users

Apparent Biases: Non-differential misclassification of exposure

Study Quality: Adequate

Limitations (if not "Adequate"): None

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, ever snus users	OR	1.23	1.15	1.33	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, former snus users	OR	1.04	0.83	1.31	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, current snus users	OR	1.25	1.16	1.35	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, ever snus users <45 years old at baseline	OR	1.18	1.06	1.32	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, former snus users <45 years old at baseline	OR	0.98	0.72	1.35	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, current snus users <45 years old at baseline	OR	1.2	1.08	1.34	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, ever snus users 45-49 years old at baseline	OR	1.37	1.1	1.72	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, former snus users 45-49 years old at baseline	OR	1.42	0.8	2.51	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, current snus users 45-49 years old at baseline	OR	1.35	1.07	1.72	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, ever snus users 50-54 years old at	OR	1.37	1.1	1.71	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
				baseline					
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, former snus users 50-54 years old at baseline	OR	1.12	0.52	2.39	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, current snus users 50-54 years old at baseline	OR	1.39	1.1	1.75	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, ever snus users 55-59 years old at baseline	OR	1.35	1.11	1.63	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, former snus users 55-59 years old at baseline	OR	0.73	0.38	1.43	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, current snus users 55-59 years old at baseline	OR	1.43	1.17	1.75	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, ever snus users 60-64 years old at baseline	OR	1.2	0.98	1.45	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, former snus users 60-64 years old at baseline	OR	1.3	0.7	2.4	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, current snus users 60-64 years old at baseline	OR	1.19	0.97	1.46	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, ever snus users 65+ years old at baseline	OR	2.2	0.7	6.95	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, current snus users 65+ years old at baseline	OR	2.2	0.7	6.95	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 12.5 g/day	OR	1.12	0.98	1.28	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 12.5-24.9 g/da ages 55-65 at baseline	OR	1.31	1.17	1.46	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 25-49.9 g/day	OR	1.25	1.07	1.47	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 50+ g/day	OR	1.45	1.18	1.78	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 12.5 g/day <45 years old at baseline	OR	1.18	0.96	1.44	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 12.5-24.9 g/da <45 years old at baseline	OR	1.12	0.96	1.31	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 25-	OR	1.3	1.07	1.58	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
				49.9 g/day <45 years old at baseline					
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 50+ g/day <45 years old at baseline	OR	1.36	1.06	1.75	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 12.5 g/day 45-49 years old at baseline	OR	1.24	0.8	1.9	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 12.5-24.9 g/da 45-49 years old at baseline	OR	1.62	1.17	2.26	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 25-49.9 g/day 45-49 years old at baseline	OR	1.01	0.57	1.83	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 50+ g/day 45-49 years old at baseline	OR	1.22	0.62	2.42	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 12.5 g/day 50-54 years old at baseline	OR	1.11	0.74	1.65	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 12.5-24.9 g/day	OR	1.37	0.97	1.96	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
				50-54 years old at baseline					
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 25-49.9 g/day 50-54 years old at baseline	OR	1.68	1.01	2.8	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 50+ g/day 50-54 years old at baseline	OR	2.18	1.11	4.3	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 12.5 g/day 55-59 years old at baseline	OR	1.15	0.83	1.6	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 12.5-24.9 g/da 55-59 years old at baseline	OR	1.73	1.29	2.31	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 25-49.9 g/day 55-59 years old at baseline	OR	1.31	0.76	2.25	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 50+ g/day 55-59 years old at baseline	OR	1.61	0.75	3.46	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 12.5 g/day 60-64 years old at	OR	0.96	0.72	1.29	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
				baseline					
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 12.5-24.9 g/da 60-64 years old at baseline	OR	1.65	1.22	2.23	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 25-49.9 g/day 60-64 years old at baseline	OR	0.61	0.29	1.29	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 50+ g/day 60-64 years old at baseline	OR	1.83	0.7	4.8	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 12.5 g/day 65+ years old at baseline	OR	1.78	0.38	8.36	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 12.5-24.9 g/da 65+ years old at baseline	OR	4.57	0.33	47.6	
Hergens, 2008b	ST (snus)	High BP prevalence	Age, BMI, region of residence	Never snus users, those who use 25-49.9 g/day 65+ years old at baseline	OR	1.36	0.08	24	
Hergens, 2008b	ST (snus)	High BP	Age, BMI, region of residence	Never snus users, ever snus users	RR	1.39	1.08	1.79	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2008b	ST (snus)	High BP	Age, BMI, region of residence	Never snus users, former snus users	RR	1.49	0.76	2.9	
Hergens, 2008b	ST (snus)	High BP	Age, BMI, region of residence	Never snus users, current snus users	RR	1.34	1.03	1.74	
Hergens, 2008b	ST (snus)	High BP	Age, BMI, region of residence	Never snus users, those who currently use <12.5 g/day	RR	1.49	0.97	2.27	
Hergens, 2008b	ST (snus)	High BP	Age, BMI, region of residence	Never snus users, those who currently use 12.5-24.9 g/day	RR	1.24	0.86	1.8	
Hergens, 2008b	ST (snus)	High BP	Age, BMI, region of residence	Never snus users, those who currently use 25-49.9 g/day	RR	1.19	0.69	2.05	
Hergens, 2008b	ST (snus)	High BP	Age, BMI, region of residence	Never snus users, those who currently use 50+ g/day	RR	1.67	0.86	3.28	
Hergens, 2008b	ST (snus)	Hypertension	Age, BMI, region of residence	Never snus users, ever snus users	RR	1.36	1.07	1.72	
Hergens, 2008b	ST (snus)	Hypertension	Age, BMI, region of residence	Never snus users, former snus users	RR	0.85	0.4	1.79	
Hergens, 2008b	ST (snus)	Hypertension	Age, BMI, region of residence	Never snus users, current snus users	RR	1.43	1.12	1.83	
Hergens, 2008b	ST (snus)	Hypertension	Age, BMI, region of residence	Never snus users, those who currently use <12.5 g/day	RR	1.18	0.77	1.82	
Hergens, 2008b	ST (snus)	Hypertension	Age, BMI, region of residence	Never snus users, those who currently use 12.5-	RR	1.43	1.01	2.02	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
				24.9 g/day					
Hergens, 2008b	ST (snus)	Hypertension	Age, BMI, region of residence	Never snus users, those who currently use 25-49.9 g/day	RR	1.77	1.08	2.90	
Hergens, 2008b	ST (snus)	Hypertension	Age, BMI, region of residence	Never snus users, those who currently use 50+ g/day	RR	1.76	0.90	3.42	

Hergens 2014

Full citation: Hergens MP, Galanti R, Hansson J, Fredlund P, Ahlbom A, Alfredsson L, Bellocco R, Eriksson M, Fransson EI, Hallqvist J, Jansson JH, Knutsson A, Pedersen N, Lagerros YT, Ostergren PO, Magnusson C. 2014. Use of Scandinavian moist smokeless tobacco (snus) and the risk of atrial fibrillation. *Epidemiology* 25(6):872-6.

Exposure: ST (snus)

Study Design: Cohort, pooled analysis of 7 prospective Swedish studies

Population (total): 274,882 men and identified from the Swedish National Patient Register

Study Period: 1978-2004

Endpoints: first hospitalization for atrial fibrillation

Number of exposed/unexposed:

127,907 male never-smokers, 25% of whom were current snus users

Apparent Biases: Restricted to men; not a primary study in and of itself (pooled analysis); some subcohort-related effects might be masked

Study Quality: Adequate

Limitations (if not "Adequate"): None

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Hergens, 2014	ST (snus)	First hospitalization for atrial fibrillation	Age, BMI, education	425 current snus/never smokers vs. 3,069 noncurrent snus/never smokers	HR	0.97	0.71	1.33	
Hergens, 2014	ST (snus)	First hospitalization for atrial fibrillation	Age, BMI, education	3,009 current smokers/noncurrent snus users vs. 3,069 noncurrent snus/never smokers	HR	1.16	1.01	1.33	
Hergens, 2014	ST (snus)	First hospitalization for atrial fibrillation	Age, BMI, education	564 current smokers/current snus users vs. 3,069 noncurrent snus/never smokers	HR	1.13	0.82	1.56	
Hergens, 2014	ST (snus)	First hospitalization for atrial fibrillation	Age, BMI, education	2,865 former smokers/noncurrent snus users vs. 3,069 noncurrent snus/never smokers	HR	1.11	1.01	1.21	
Hergens, 2014	ST (snus)	First hospitalization for atrial fibrillation	Age, BMI, education	661 former smokers/current snus users vs. 3,069 noncurrent snus/never smokers	HR	1.05	0.87	1.28	

Huhtasaari 1992

Full citation: Huhtasaari F, Asplund K, Lundberg V, Stegmayr B, Wester PO. 1992. Tobacco and myocardial infarction: is snuff less dangerous than cigarettes? *BMJ* 305(6864):1252-1256.

Exposure: ST (snus)

Study Design: Case-control

Population (total): 35-64 year old Swedish males from the Norrbotten and Vasterbotten provinces

Study Period: 1989-1991

Endpoints: First myocardial infarction (MI)

Number of exposed/unexposed:

585 cases (males with first MI)
589 controls without history of MI

Apparent Biases: Potential differential misclassification of exposure, non-differential misclassification of exposure, recall bias, selection bias

Study Quality: Fair

Limitations (if not "Adequate"): Exposure groups (including non-tobacco users) included occasional (<1 / day) users of different tobacco forms and former users. The numbers in the exposed groups do not add up, and there is ambiguity in the language used. Therefore, it is uncertain if the groups used for most of the analyses were exclusive groups (even on a daily level).

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Huhtasaari, 1992	ST (snus)	First MI	Age	Cigarette smoking (ref) vs snus	OR	2.09	1.39	3.15	
Huhtasaari, 1992	ST (snus)	First MI	Age	Cigarette smoking (ref) vs snus -> 35-54 year olds	OR	3.22	1.82	5.7	
Huhtasaari, 1992	ST (snus)	First MI	Age	Cigarette smoking (ref) vs snus -> 55-64 year olds	OR	1.09	0.55	2.16	
Huhtasaari, 1992	ST (snus)	First MI	Age	Non tobacco users vs current smokers	OR	1.87	1.4	2.48	
Huhtasaari, 1992	ST (snus)	First MI	Age	Non tobacco users vs current smokers -> 35-54 year olds	OR	3.11	2.09	4.63	
Huhtasaari, 1992	ST (snus)	First MI	Age	Non tobacco users vs current smokers -> 55-64 year olds	OR	1.35	0.87	2.1	
Huhtasaari, 1992	ST (snus)	First MI	Age	Non tobacco users vs current snus users	OR	0.89	0.62	1.29	
Huhtasaari, 1992	ST (snus)	First MI	Age	Non tobacco users vs current snus users -> 35-54 year olds	OR	0.96	0.56	1.67	
Huhtasaari, 1992	ST (snus)	First MI	Age	Non tobacco users vs current snus users -> 55-64 year olds	OR	1.24	0.67	2.3	
Huhtasaari, 1992	ST (snus)	First MI	ns	Non tobacco users vs current snus users < 2 can/week	OR	0.63	0.41	0.98	
Huhtasaari, 1992	ST (snus)	First MI	ns	Non tobacco users vs current snus	OR	0.93	0.61	1.41	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
				users ≥ 2 can/week					
Huhtasaari, 1992	ST (snus)	First MI	ns	Non tobacco users vs current smokers ≤ 10/day	OR	0.98	0.68	1.42	
Huhtasaari, 1992	ST (snus)	First MI	ns	Non tobacco users vs current smokers > 10/day	OR	1.77	1.31	2.39	
Huhtasaari, 1992	ST (snus)	First MI	Age	Non tobacco users vs current daily snus users (never regular users) (ref)	OR	1.8	1.04	3.11	
Huhtasaari, 1992	ST (snus)	First MI	Age	Non tobacco users vs former daily snus users (never regular users) (ref)	OR	4.5	2.72	7.47	

Huhtasaari 1999

Full citation: Huhtasaari F, Lundberg V, Eliasson M, Janlert U, Asplund K. 1999. Smokeless tobacco as a possible risk factor for myocardial infarction: a population-based study in middle-aged men. *J Am Coll Cardiol* 34(6):1784-1790.

Exposure: ST (snus)

Study Design: Case-control

Population (total): 25-64 year old Swedish Males from the Norrbotten and Vasterbotten provinces

Study Period: 1991-1993

Endpoints: First myocardial infarction (MI)

Number of exposed/unexposed:

687 cases with first MI
687 population based geographic and age matched controls

Apparent Biases: Recall bias, selection bias, non-differential misclassification of exposure

Study Quality: Fair

Limitations (if not "Adequate"): Moderate amount of mixed exposure as all of the study's exposure groups (including non-tobacco users) included occasional (<1 / day) users of different tobacco forms.

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Huhtasaari, 1999	ST (snus)	First MI	None	Non-tobacco users, current daily snus use	OR	0.96	0.65	1.41	
Huhtasaari, 1999	ST (snus)	First MI	None	Non-tobacco users, current smoker	OR	3.65	2.67	4.99	
Huhtasaari, 1999	ST (snus)	First MI	None	Non-tobacco users, former daily snus use	OR	1.23	0.54	2.82	
Huhtasaari, 1999	ST (snus)	First MI	None	Non-tobacco users, former smoker	OR	1.05	0.77	1.43	
Huhtasaari, 1999	ST (snus)	First MI	Hypertension, education, marital status, diabetes, cholesterol, heredity	Non-tobacco users, daily snus use	OR	0.58	0.35	0.94	
Huhtasaari, 1999	ST (snus)	First MI	Hypertension, education, marital status, diabetes, cholesterol, heredity	Non-tobacco users, daily smoking	OR	3.53	2.48	5.03	
Huhtasaari, 1999	ST (snus)	First MI, fatal	Hypertension, education, marital status, diabetes, cholesterol, heredity	Non-tobacco users, daily snus use	OR	1.5	0.45	5.03	
Huhtasaari, 1999	ST (snus)	First MI	Hypertension, education, marital status, diabetes, cholesterol, heredity	Non-tobacco users, daily smoking	OR	8.57	2.48	30.3	

Janzon 2009

Full citation: Janzon E, Hedblad B. 2009. Swedish snuff and incidence of cardiovascular disease. A population-based cohort study. *BMC Cardiovasc Disord* 9(1):21.

Exposure: ST (snus)

Study Design: Cohort

Population (total):

10,473 45-73 year old Swedish males
16,754 45-73 year old Swedish females

Study Period: 1991-2004

Endpoints: First incident myocardial infarction (MI), stroke

Number of exposed/unexposed:

2,946 non-tobacco users
67 exclusive current snus users
2,776 exclusive current smokers

Apparent Biases: Non-differential misclassification of exposure

Study Quality: Fair

Limitations (if not "Adequate"): Small number of observed disease cases, large number of adjusted factors

Comments: No analyses undertaken for women

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Janzon, 2009	ST (snus)	First incident MI	Age, BMI, diabetes, hypertension, physical activity, marital status, occupation	Non-tobacco users, exclusive snus users	RR	0.75	0.3	1.8	0.532
Janzon, 2009	ST (snus)	Stroke	Age, BMI, diabetes, hypertension, physical activity, marital status, occupation	Non-tobacco users, exclusive snus users	RR	0.59	0.2	1.5	0.311

Johansson 2005

Full citation: Johansson SE, Sundquist K, Qvist J, Sundquist J. 2005. Smokeless tobacco and coronary heart disease: a 12-year follow-up study. *Eur J Cardiovasc Prev Rehabil* 12(4):387-392.

Exposure: ST (snus)

Study Design: Cohort

Population (total): 3,120 30-74 year old Swedish males

Study Period: 1988-2000

Endpoints: Coronary heart disease

Number of exposed/unexposed:

1,036 non tobacco users
245 exclusive daily snus user
793 daily smokers

Apparent Biases: Non-differential misclassification of exposure

Study Quality: Fair

Limitations (if not "Adequate"): Moderate amount of mixed exposure as all of the study's exposure groups (including non-tobacco users) included occasional (<1 / day) users of different tobacco forms. Large number of adjustments for a relatively small sample size. Large number of adjustments for a relatively small sample size.

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Johansson, 2005	ST (snus)	Coronary heart disease	BMI, physical activity, diabetes, hypertension	Non-tobacco users, daily snus users	HR	1.41	0.61	3.28	
Johansson, 2005	ST (snus)	Coronary heart disease	BMI, physical activity, diabetes, hypertension	Non-tobacco users, daily smoker	HR	2.3	1.66	3.19	
Johansson, 2005	ST (snus)	Coronary heart disease	BMI, physical activity, diabetes, hypertension	Non-tobacco users, former daily smoker	HR	1.47	1.07	2.03	

Keller 1970

Full citation: Keller AZ. 1970. Cellular types, survival, race, nativity, occupations, habits and associated diseases in the pathogenesis of lip cancers. *Am J Epidemiol* 91(5):486-499.

Exposure: smokeless tobacco (ST), cigarettes

Study Design: Case-control (matched)

Population (total): 20% systematic sample of all the patients admitted to the VA hospital system 1958-1962

Study Period: 1958-1962

Endpoints: Cancer of a) the gum, mucosa and b) pharynx and other parts of the mouth

Number of cases/controls:

304 cases of cancer of the extra-oral labial mucosal membrane, 304 general controls and 304 cancer controls (with cancer of the mouth, mesopharynx or hypopharynx)

Apparent Biases: 1) Confounding - inadequate matching for other potentially confounding variables (level of education, smoking status, etc.). 2) Lack of comparable accuracy - the method of exposure measurement was not reported, leading to a possibility of information bias, whose direction is not determinable.

Study Quality: Fair

Limitations (if not "Adequate"): Case-control study, with design issues: did not adhere to deconfounding principle and comparable accuracy principle - inaccurate measurement of exposure in the study.

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Keller, 1970	ST, cigarettes	Cancer of a) the gum, mucosa and b)pharynx and other parts of the mouth	Matched for age (±5 years), race and hospital admitted to.	1) Cases vs general controls 2) Cases vs. cancer controls 3) Combined cancer cases vs controls	Odds ratio for snuff use among cases or cancer controls compared to general control	2.4	NR	NR	NR

Ksir 1986

Full citation: Ksir C, Shank M, Kraemer W, Noble B. 1986. Effects of chewing tobacco on heart rate and blood pressure during exercise. *J Sports Med Phys Fitness* 26(4):384-389.

Exposure: ST (chewing tobacco)

Study Design: Experimental

Population (total): 5 male college students recruited from the University of Wisconsin baseball team using Copenhagen moist snuff; average use 1.5- cans per week

Study Period: 2 separate evaluations (1 tobacco day, 1 non-tobacco day)

Endpoints: Heart rate, systolic blood pressure, and diastolic blood pressure

Number of exposed/unexposed: Results from tobacco use days of 5 individuals vs. results from tobacco non-use days in 5 individuals

Apparent Biases: Extremely small and non-generalizable sample (5 college-aged, athletic men), although the snuff was weighed before use, unsure how consistent the snuff use was between individuals or across days, no assessment of other behaviors (incl. smoking)

Study Quality: Fair

Limitations (if not "Adequate"): Small, non-generalizable population

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Ksir, 1986	ST (chewing tobacco)	Heart rate	General time of day of study, chewing tobacco, weight, position prior to monitoring	Test condition (tobacco use) vs. non-test condition (tobacco non-use) in the same 5 men	Difference in heart rate prior to exercise (at rest)	10 beats/minute higher on the tobacco day compared to non-tobacco day			p<0.01
Ksir, 1986	ST (chewing tobacco)	Heart rate	General time of day of study, chewing tobacco, weight, position prior to monitoring	Test condition (tobacco use) vs. non-test condition (tobacco non-use) in the same 5 men	Difference in heart rate during low level exercise period (4 min exercise at 300 kgm/min)	Significantly higher heart rate on tobacco use days; F=12.2			p<0.025
Ksir, 1986	ST (chewing tobacco)	Heart rate	General time of day of study, chewing tobacco, weight, position prior to monitoring	Test condition (tobacco use) vs. non-test condition (tobacco non-use) in the same 5 men	Difference in heart rate during intermediate level exercise period (4 min exercise at 600 kgm/min)	Significantly higher heart rate on tobacco use days; F=8.04			p<0.05
Ksir, 1986	ST (chewing tobacco)	Heart rate	General time of day of study, chewing tobacco, weight, position prior to monitoring	Test condition (tobacco use) vs. non-test condition (tobacco non-use) in the same 5 men	Difference in heart rate during high level exercise period (4 min exercise at 900	Difference of 6 beats/min between tobacco, non-tobacco days			NS

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
					kgm/min)				
Ksir, 1986	ST (chewing tobacco)	Heart rate	General time of day of study, chewing tobacco, weight, position prior to monitoring	Test condition (tobacco use) vs. non-test condition (tobacco non-use) in the same 5 men	Difference in heart rate during a 15-minute recovery period following 4 min exercise (exercise at various intensities: 300, 600, and 900 kgm/min)	Overall difference between tobacco and non-tobacco days, F=45.6			p<0.005
Ksir, 1986	ST (chewing tobacco)	Systolic blood pressure	General time of day of study, chewing tobacco, weight, position prior to monitoring	Test condition (tobacco use) vs. non-test condition (tobacco non-use) in the same 5 men	Difference in systolic blood pressure prior to exercise (at rest)	4 mmHg higher on tobacco day			p<0.05
Ksir, 1986	ST (chewing tobacco)	Systolic blood pressure	General time of day of study, chewing tobacco, weight, position prior to monitoring	Test condition (tobacco use) vs. non-test condition (tobacco non-use) in the same 5 men	Difference in systolic blood pressure during three different exercise periods (4 min exercise at various intensities:	Sigifnicantly higher systolic blood pressure on tobacco days across all exercise periods			p<0.025

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
					300, 600, and 900 kgm/min)				
Ksir, 1986	ST (chewing tobacco)	Systolic blood pressure	General time of day of study, chewing tobacco, weight, position prior to monitoring	Test condition (tobacco use) vs. non-test condition (tobacco non-use) in the same 5 men	Difference in systolic blood pressure during a 15-minute recovery period following 4 min exercise (exercise at various intensities: 300, 600, and 900 kgm/min)	No difference between tobacco and non-tobacco days			NS
Ksir, 1986	ST (chewing tobacco)	Diastolic blood pressure	General time of day of study, chewing tobacco, weight, position prior to monitoring	Test condition (tobacco use) vs. non-test condition (tobacco non-use) in the same 5 men	Difference in diastolic blood pressure prior to exercise (at rest)	No difference between tobacco and non-tobacco days			NS
Ksir, 1986	ST (chewing tobacco)	Diastolic blood pressure	General time of day of study, chewing tobacco, weight, position prior to monitoring	Test condition (tobacco use) vs. non-test condition (tobacco non-use) in the same 5 men	Difference in diastolic blood pressure during three different exercise periods (4	No difference between tobacco and non-tobacco days			NS

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
					min exercise at various 300, 600, and 900 kgm/min)				

Lewin 1998

Full citation: Lewin F, Norell SE, Johansson H, Gustavsson P, Wennerberg J, Biorklund A, Rutqvist LE. 1998. Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck: a population-based case-referent study in Sweden. *Cancer* 82(7):1367-1375.

Exposure: Smoking (cigarette, pipe, cigar), ST (snus)

Study Design: Case-control

Population (total): 1,361 Swedish men between the ages of 40-79 and residing in Stockholm or southern healthcare region

Study Period: 1988-1991

Endpoints: Head and neck cancer (squamous cell carcinoma of oral cavity, oro- and hypopharynx, larynx, and esophagus)

Number of cases/controls: 605 cases, 756 controls matched for region and age

Apparent Biases: Recall bias

Study Quality: Fair

Limitations (if not "Adequate"): Low numbers - 9 cases and 10 controls used ST but never smoked. Classification is broad and includes non-oral cancers. Case-control design.

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Lewin, 1998	Smoking (cigarette, pipe, cigar), ST (snus)	Head and neck cancer (SCC of oral cavity, oro- and hypopharynx, larynx, and esophagus)	Design	Never tobacco users, ever snus users	RR	4.7	1.6	13.8	
Lewin, 1998	Smoking (cigarette, pipe, cigar), ST (snus)	Head and neck cancer (SCC of oral cavity, oro- and hypopharynx, larynx, and esophagus)	Design	Never tobacco users, current snus users	RR	3.3	0.8	12	
Lewin, 1998	Smoking (cigarette, pipe, cigar), ST (snus)	Head and neck cancer (SCC of oral cavity, oro- and hypopharynx, larynx, and esophagus)	Design	Never tobacco users, former snus users	RR	10.5	1.4	117.8	
Lewin, 1998	Smoking (cigarette, pipe, cigar), ST (snus)	Head and neck cancer (SCC of oral cavity, oro- and hypopharynx, larynx, and esophagus)	Design	Current smokers (ref), ever snus users	RR	0.8	0.5	1.2	
Lewin, 1998	Smoking (cigarette, pipe, cigar), ST (snus)	Head and neck cancer (SCC of oral cavity, oro- and hypopharynx, larynx, and	Design	Current smokers (ref), current snus users	RR	0.6	0.3	1.1	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
		esophagus)							
Lewin, 1998	Smoking (cigarette, pipe, cigar), ST (snus)	Head and neck cancer (SCC of oral cavity, oro- and hypopharynx, larynx, and esophagus)	Design	Current smokers (ref), former snus users	RR	1	0.5	2	

Luo 2007

Full citation: Luo J, Ye W, Zendehdel K, Adami J, Adami HO, Boffetta P, Nyren O. 2007. Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet* 369(9578):2015-2020.

Exposure: ST (snus)

Study Design: Cohort

Population (total): 279,897 Male Swedish construction workers

Study Period: 1971-2004

Endpoints: Oral cancer (OC) and lung cancer (LC)

Number of exposed/unexposed:

87,821 never tobacco users,
37,755 ever snus users,
34,818 current snus users,
154,321 ever smokers,
103,309 current smokers

Apparent Biases: Non-differential misclassification of exposure

Study Quality: Adequate

Limitations (if not "Adequate"): None

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Luo, 2007	ST (snus)	OC	Age, BMI	Never tobacco users, ever snus users	RR	0.8	0.4	1.7	
Luo, 2007	ST (snus)	OC	Age, BMI	Never tobacco users, former snus users	RR	0.7	0.1	5	
Luo, 2007	ST (snus)	OC	Age, BMI	Never tobacco users, current snus users	RR	0.9	0.4	1.8	
Luo, 2007	ST (snus)	OC	Age, BMI	Never tobacco users, snus use 1-9 g/day	RR	0.7	0.2	2.8	
Luo, 2007	ST (snus)	OC	Age, BMI	Never tobacco users, snus use10+ g/day	RR	0.9	0.4	2	
Luo, 2007	ST (snus)	LC	Age, BMI	Never tobacco users, ever snus users	RR	0.8	0.5	1.3	
Luo, 2007	ST (snus)	LC	Age, BMI	Never tobacco users, former snus users	RR	0.9	0.3	3	
Luo, 2007	ST (snus)	LC	Age, BMI	Never tobacco users, current snus users	RR	0.9	0.4	1.3	
Luo, 2007	ST (snus)	LC	Age, BMI	Never tobacco users, snus use 1-9 g/day	RR	1	0.5	2.1	
Luo, 2007	ST (snus)	LC	Age, BMI	Never tobacco users, snus use10+ g/day	RR	0.7	0.4	1.3	

Morente-Sanchez 2015

Full citation: Morente-Sanchez J, Zandonai T, Mateo-March M, Sanabria D, Sanchez-Munoz C, Chiamulera C, Zabala Diaz M. 2015. Acute effect of Snus on physical performance and perceived cognitive load on amateur footballers. *Scand J Med Sci Sports* 25(4):e423-431.

Exposure: Snus

Study Design: Clinical Trial (double-blind randomly assigned crossover)

Population (total): 18 non-smoking, nun-snus-using male football players, mean age 22.5 years. All participants were recruited from the Faculty of Sport Sciences at the University of Granada in Spain.

Study Period: Two 90-minute laboratory sessions with 5 days recovery/washout between sessions

Endpoints: Heart rate variability (HRV)

Number of exposed/unexposed:

18; crossover design, each subject exposed to both snus and placebo

Apparent Biases: 4 subjects could not complete all physical tests due to side effects of snus

Study Quality: Fair

Limitations (if not "Adequate"): Small sample size (n=18), of whom 4 did not complete all tests due to side effects.

Comments: Subjects were non-snus users; acute effects may be different in habituated users

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Morente-Sanchez, 2015	Snus	Heart rate variability (HRV)	Sleep hours; exhaled CO concentration	Snus use vs. placebo	R-R interval, substance (snus, placebo)	F(1,15) = 5.79, η partial^2 = 0.27			p=0.02
Morente-Sanchez, 2015	Snus	Heart rate variability (HRV)	Sleep hours; exhaled CO concentration	Snus use vs. placebo	Root mean square of successive differences, substance (snus, placebo)	F(1,15) = 3.86			p=0.06
Morente-Sanchez, 2015	Snus	Heart rate variability (HRV)	Sleep hours; exhaled CO concentration	Snus use vs. placebo	Instantaneous beat-to-beat variability of the data, substance (snus, placebo)	F(1,15) = 4.04			p=0.06
Morente-Sanchez, 2015	Snus	Heart rate variability (HRV)	Sleep hours; exhaled CO concentration	Snus use vs. placebo	R-R interval, measurement (first, second)	F(1,15) = 47.32, η partial^2 =0.76			p<.001
Morente-Sanchez, 2015	Snus	Heart rate variability (HRV)	Sleep hours; exhaled CO concentration	Snus use vs. placebo	Root mean square of successive differences, measurement (first, second)	F < 1			
Morente-Sanchez, 2015	Snus	Heart rate variability (HRV)	Sleep hours; exhaled CO concentration	Snus use vs. placebo	Instantaneous beat-to-beat variability of the data, measurement (first, second)	F < 1			
Morente-Sanchez, 2015	Snus	Heart rate variability (HRV)	Sleep hours; exhaled CO concentration	Snus use vs. placebo	R-R interval, substance measurement	F(1,15) = 33.06, η partial^2 = 0.68			p<0.001
Morente-Sanchez, 2015	Snus	Heart rate variability (HRV)	Sleep hours; exhaled CO concentration	Snus use vs. placebo	Root mean square of successive differences, substance measurement	F(1,15) = 7.13, η partial^2 = 0.32			p=0.01
Morente-Sanchez, 2015	Snus	Heart rate variability (HRV)	Sleep hours; exhaled CO concentration	Snus use vs. placebo	Instantaneous beat-to-beat variability of the data, substance measurement	F(1,15) = 7.69, η partial^2 = 0.34			p=0.01

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Morente-Sanchez, 2015	Snus	Heart rate variability (HRV)	Sleep hours; exhaled CO concentration	Snus use vs. placebo	Mean R-R interval, snus basal effect	948.85, SD 119.72 665.19, SD 97.70			p<0.001
Morente-Sanchez, 2015	Snus	Heart rate variability (HRV)	Sleep hours; exhaled CO concentration	Snus use vs. placebo	Mean R-R interval, placebo basal effect	895.42, SD 131.75 887.29, SD 137.55			p=0.81
Morente-Sanchez, 2015	Snus	Heart rate variability (HRV)	Sleep hours; exhaled CO concentration	Snus use vs. placebo	Mean root mean square of successive differences, snus basal effect	62.09, SD 28.30 50.11, SD 28.29			p=0.05
Morente-Sanchez, 2015	Snus	Heart rate variability (HRV)	Sleep hours; exhaled CO concentration	Snus use vs. placebo	Mean root mean square of successive differences, placebo basal effect	63.59, SD 22.88 71.73, SD 29.69			p=0.10
Morente-Sanchez, 2015	Snus	Heart rate variability (HRV)	Sleep hours; exhaled CO concentration	Snus use vs. placebo	Mean instantaneous beat-to-beat variability, snus basal effect	43.99, SD 20.06 35.22, SD 19.45			p=0.04
Morente-Sanchez, 2015	Snus	Heart rate variability (HRV)	Sleep hours; exhaled CO concentration	Snus use vs. placebo	Mean instantaneous beat-to-beat variability, placebo basal effect	44.94, SD 16.26 50.81, SD 21.04			p=0.11

Nordenvall 2013

Full citation: Nordenvall C, Nilsson PJ, Ye W, Andersson TM, Nyren O. 2013. Tobacco use and cancer survival: a cohort study of 40,230 Swedish male construction workers with incident cancer. *Int J Cancer* 132(1):155-161.

Exposure: Snus, smoking

Study Design: Retrospective cohort

Population (total): 40,230 incident cancer cases identified among 336,381 male workers from the Swedish construction workers cohort who had provided tobacco use information between 1971 and 1992.

Study Period: 1971-2007

Endpoints: Lung cancer mortality

Number of exposed/unexposed:

9,578 never tobacco users
1,946 snus users
22,321 smokers

Apparent Biases: Misclassification of exposure, likely biasing towards null

Study Quality: Fair

Limitations (if not "Adequate"):

Number of lung cancer cases is unclear.
Unclear, but seems likely that lung cancer results were adjusted.

Comments: "Modeling of hazard ratios (HRs) for single cancer sites was hampered by imprecision because of insufficient numbers of observed events."

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Nordenvall, 2013	Snus, smoking	Lung cancer mortality	Age at cancer diagnosis, calendar period of diagnosis, cancer site, BMI (not entirely if used for LC results).	Pure snus user v. never users of any tobacco	HR	1.21	0.71	2.08	n/a

Nordskog 2015

Full citation: Nordskog BK, Brown BG, Marano KM, Campell LR, Jones BA, Borgerding MF. 2015. Study of cardiovascular disease biomarkers among tobacco consumers, part 2: biomarkers of biological effect. *Inhal Toxicol* 27(3):157-166.

Exposure: Cigarettes, moist snuff

Study Design: Single site, age-stratified, intervention study. On Day 1, participants abstained from tobacco use for 45 minutes and then used a single tobacco product. Shortly thereafter, urine and blood were collected, and expired carbon monoxide (ECO), ankle brachial index (ABI), and flow-mediated dilation (FMD) were measured. On Day 2, after fasting and abstaining from tobacco use overnight, blood and spot urine samples were collected, and ECO, ABI, FMD and carotid intima-media thickness (CIMT) were measured.

Population (total): 168 healthy US males, aged 26–49 years, recruited into one of three exclusive use groups (cigarette smokers, moist snuff consumers, non-consumers of tobacco).

Study Period: September 2008-February 2009

Endpoints: Flow-mediated dilation, ankle-brachial index, and carotid intima-media thickness by age group

Number of exposed/unexposed:
Cigarette smokers: 60
Moist snuff consumers: 48
Non-consumers of tobacco: 60

Apparent Biases: The similarity of CIMT for non-tobacco users compared to smokers suggests the possibility of selection bias influencing the results: study subjects were recruited voluntarily through advertisements, and may have volunteered due to personal or family health concerns related to stroke risk..

Study Quality: Fair

Limitations (if not "Adequate"):
1) Small study sample - limits study power; 2) Lack of adjustment for other covariates besides age.

Comments: None.

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Nordskog, 2015	Cigarette, moist snuff	Flow-mediated dilation, Day 1	Age	MSC vs SMK MSC vs NTC	Comparison of least squares means of smokers and moist snuff users, and non-tobacco users and moist snuff users (% change in dilation in response to stimulus)	SMK: 8.59 MSC: 6.57 NTC: 8.64	NR	NR	SMK vs MSC: 0.4134 MSC vs NTC: 0.3895
Nordskog, 2015	Cigarette, moist snuff	Flow-mediated dilation, Day 2	Age	MSC vs SMK	Comparison of least squares means of smokers and moist snuff users, and non-tobacco users and moist snuff users (% change in dilation in response to stimulus)	SMK: 10.19 MSC: 9.97 NTC: 8.26	NR	NR	1
Nordskog, 2015	Cigarette, moist snuff	Flow-mediated dilation, Day 2	Age	MSC vs NTC	Comparison of least squares means of smokers and moist snuff users, and non-tobacco users and moist snuff users (% change in dilation in response to stimulus)	SMK: 10.19 MSC: 9.97 NTC: 8.26	NR	NR	0.8773

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Nordskog, 2015	Cigarette, moist snuff	Ankle-Brachial index, Day 1	Age	MSC vs SMK	Comparison of least squares means of smokers and moist snuff users, and non-tobacco users and moist snuff users (ratio of systolic BP at ankle to brachial region)	SMK: 1.12 MSC: 1.14 NTC: 1.15	NR	NR	0.3252
Nordskog, 2015	Cigarette, moist snuff	Ankle-Brachial index, Day 1	Age	MSC vs NTC	Comparison of least squares means of smokers and moist snuff users, and non-tobacco users and moist snuff users (ratio of systolic BP at ankle to brachial region)	SMK: 1.12 MSC: 1.14 NTC: 1.15	NR	NR	0.583
Nordskog, 2015	Cigarette, moist snuff	Ankle-Brachial index, Day 2	Age	MSC vs SMK	Comparison of least squares means of smokers and moist snuff users, and non-tobacco users and moist snuff users (ratio of systolic BP at ankle to brachial region)	SMK: 1.16 MSC: 1.15 NTC: 1.17	NR	NR	1
Nordskog, 2015	Cigarette, moist snuff	Ankle-Brachial index, Day 2	Age	MSC vs NTC	Comparison of least squares means of smokers and moist snuff	SMK: 1.16 MSC: 1.15	NR	NR	0.5853

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
					users, and non-tobacco users and moist snuff users (ratio of systolic BP at ankle to brachial region)	NTC: 1.17			
Nordskog, 2015	Cigarette, moist snuff	Carotid intima media thickness by age group, on Day 2	Age	MSC vs SMK	Comparison of least squares means of smokers and moist snuff users, and non-tobacco users and moist snuff users (in mm)	All ages SMK: 0.64 MSC: 0.63	NR	NR	1
Nordskog, 2015	Cigarette, moist snuff	Carotid intima media thickness by age group, on Day 2	Age	MSC vs SMK	Comparison of least squares means of smokers and moist snuff users, and non-tobacco users and moist snuff users (in mm)	26-31 SMK: 0.56 MSC: 0.58	NR	NR	1
Nordskog, 2015	Cigarette, moist snuff	Carotid intima media thickness by age group, on Day 2	Age	MSC vs SMK	Comparison of least squares means of smokers and moist snuff users, and non-tobacco users and moist snuff users (in mm)	32-37 SMK: 0.61 MSC: 0.63	NR	NR	1
Nordskog, 2015	Cigarette, moist snuff	Carotid intima media thickness by age group, on	Age	MSC vs SMK	Comparison of least squares means of smokers and moist snuff	38-43 SMK: 0.65	NR	NR	1

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
		Day 2			users, and non-tobacco users and moist snuff users (in mm)	MSC: 0.66			
Nordskog, 2015	Cigarette, moist snuff	Carotid intima media thickness by age group, on Day 2	Age	MSC vs SMK	Comparison of least squares means of smokers and moist snuff users, and non-tobacco users and moist snuff users (in mm)	44-49 SMK: 0.73 MSC: 0.63	NR	NR	0.0173
Nordskog, 2015	Cigarette, moist snuff	Carotid intima media thickness by age group, on Day 2	Age	MSC vs NTC	Comparison of least squares means of smokers and moist snuff users, and non-tobacco users and moist snuff users (in mm)	All ages SMK: 0.64 NTC: 0.62	NR	NR	1
Nordskog, 2015	Cigarette, moist snuff	Carotid intima media thickness by age group, on Day 2	Age	MSC vs NTC	Comparison of least squares means of smokers and moist snuff users, and non-tobacco users and moist snuff users (in mm)	26-31 SMK: 0.56 NTC: 0.56	NR	NR	1
Nordskog, 2015	Cigarette, moist snuff	Carotid intima media thickness by age group, on Day 2	Age	MSC vs NTC	Comparison of least squares means of smokers and moist snuff users, and non-tobacco users and	32-37 SMK: 0.61 NTC: 0.61	NR	NR	1

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
					moist snuff users (in mm)				
Nordskog, 2015	Cigarette, moist snuff	Carotid intima media thickness by age group, on Day 2	Age	MSC vs NTC	Comparison of least squares means of smokers and moist snuff users, and non-tobacco users and moist snuff users (in mm)	38-43 SMK: 0.65 NTC: 0.63	NR	NR	0.6399
Nordskog, 2015	Cigarette, moist snuff	Carotid intima media thickness by age group, on Day 2	Age	MSC vs NTC	Comparison of least squares means of smokers and moist snuff users, and non-tobacco users and moist snuff users (in mm)	44-49 SMK: 0.73 NTC: 0.69	NR	NR	0.3501

Rohani 2004

Full citation: Rohani M, Agewall S. 2004. Oral snuff impairs endothelial function in healthy snuff users. *J Intern Med* 255(3):379-383.

Exposure: ST (snuff)

Study Design: Experimental; case-crossover

Population (total): 20 middle-aged health snuff users, who did not use any other drugs

Study Period: Not stated; not applicable

Endpoints: Baseline brachial artery diameter (mm), peak hyperaemic, blood flow increase (%), flow-mediated dilation of brachial artery (FMD) (%)

Number of exposed/unexposed:

20 snuff users; 10 placebo users (10/20 subjects were studied once with snuff; other 10/20 subjects were randomized to placebo or snuff and studied twice by cross-over procedure)

Apparent Biases: Small number of subjects, even smaller number of controls. No information regarding cigarette use in snuff users.

Study Quality: Fair

Limitations (if not "Adequate"): Small number of subjects, no information regarding cigarette use in snuff users.

Comments: All values unchanged relative to baseline following placebo administration.

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Rohani, 2004	ST (snuff)	Baseline brachial artery diameter (mm)	Not stated	Baseline vs. 20 mins after administration of moist snuff	mm (continuous variable, mean ± SD)	Baseline: 3.80 ± 0.34 20 min: 3.78 ± 0.35			
Rohani, 2004	ST (snuff)	Baseline brachial artery diameter (mm)	Not stated	Baseline vs. 35 mins after administration of moist snuff	mm (continuous variable, mean ± SD)	Baseline: 3.80 ± 0.34 35 min: 3.81 ± 0.30			
Rohani, 2004	ST (snuff)	Peak hyperaemic blood flow	Not stated	Baseline vs. 20 mins after administration of moist snuff	Blood flow (continuous variable, mean ± SD)	Baseline: 438 ± 140 20 min: 465 ± 125			
Rohani, 2004	ST (snuff)	Peak hyperaemic blood flow	Not stated	Baseline vs. 35 mins after administration of moist snuff	Blood flow (continuous variable, mean ± SD)	Baseline: 438 ± 140 35 min: 419 ± 105			
Rohani, 2004	ST (snuff)	Blood flow increase (%)	Not stated	Baseline vs. 20 mins after administration of moist snuff	%, (continuous variable, mean ± SD)	Baseline: 338 ± 138 20 min: 365 ± 125			
Rohani, 2004	ST (snuff)	Blood flow increase (%)	Not stated	Baseline vs. 35 mins after administration of moist snuff	%, (continuous variable, mean ± SD)	Baseline: 338 ± 138 35 min: 319 ± 105			
Rohani, 2004	ST (snuff)	FMD (%)	Not stated	Baseline vs. 20 mins after administration of moist snuff	%, (continuous variable, mean ± SD)	Baseline: 3.4 ± 2.0 20 min: 3.1 ± 2.4			
Rohani, 2004	ST (snuff)	FMD (%)	Not stated	Baseline vs. 35 mins after administration of moist snuff	%, (continuous variable, mean ± SD)	Baseline: 3.4 ± 2.0 35 min: 2.3 ± 1.3			<0.05
Rohani, 2004	ST (snuff)	SBP	Not stated	Baseline vs. 20 mins after administration	continuous variable,	Baseline: 109 20 min: 111			<0.05

				of moist snuff	mean ± SD)				
Rohani, 2004	ST (snuff)	SBP	Not stated	Baseline vs. 35 mins after administration of moist snuff	continuous variable, mean ± SD	Baseline: 109 35 min: 110			
Rohani, 2004	ST (snuff)	DBP	Not stated	Baseline vs. 20 mins after administration of moist snuff	continuous variable, mean ± SD	Baseline: 74 20 min: 78			<0.05
Rohani, 2004	ST (snuff)	DBP	Not stated	Baseline vs. 35 mins after administration of moist snuff	continuous variable, mean ± SD	Baseline:74 35 min: 76			

Roosaar 2008

Full citation: Roosaar A, Johansson AL, Sandborgh-Englund G, Axell T, Nyren O. 2008. Cancer and mortality among users and nonusers of snus. *Int J Cancer* 123(1):168-173.

Exposure: Snus, smoking

Study Design: Prospective Cohort

Population (total): 9,976 male Swedish residents of Uppsala County aged 15+ at baseline

Study Period: 1976-2002

Endpoints: Oral and pharyngeal cancer combined, cardiovascular death, and respiratory death

Number of exposed/unexposed:

867 exclusive daily snus users
5,309 exclusive daily smokers
692 both

Apparent Biases: Nondifferential misclassification of exposure. However, results will bias towards null.

Study Quality: Adequate

Limitations (if not "Adequate"): None

Comments: Smokers may include other users. Results for ever smoking are compared to never smokers. Smoking-related cancers are defined as oral and pharyngeal cancer, esophageal and gastric cancer, pancreatic cancer, laryngeal and pulmonary cancer, and cancer of the kidney, bladder and other urinary organs.

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Roosaar, 2008	Snus, smoking	Oral and pharyngeal cancer, combined	Smoking, alcohol, area of residence, calendar period, age	Never vs. ever daily snus use, among never smokers.	HR	2.3	0.7	8.3	N/A
Roosaar, 2008	Snus, smoking	Cardiovascular death	Smoking, alcohol, area of residence, calendar period, age	Never vs. ever daily snus use, among never smokers.	HR	1.15	0.97	1.37	N/A
Roosaar, 2008	Snus, smoking	Respiratory death	Alcohol, area of residence, calendar period, age	Never vs. ever daily snus use, among never smokers <80 years attained age	HR	0.8	0.2	3.0	N/A
Roosaar, 2008	Snus, smoking	Respiratory death	Alcohol, area of residence, calendar period, age	Never vs. ever daily snus use, among never smokers 80+ years attained age	HR	2.0	1.2	3.4	N/A

Schildt 1998

Full citation: Schildt EB, Eriksson M, Hardell L, Magnuson A. 1998. Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. *Int J Cancer* 77(3):341-346.

Exposure: Smoking, ST (Swedish moist snuff)

Study Design: Case-control study (matched)

Population (total): Cases were residents living in the 4 most northern counties of Sweden who were diagnosed with squamous oral cell cancer between 1980 and 1989. Controls for living cases were identified using the National Population Registry and controls for deceased cases were drawn from the National Registry for Causes of Death. Cases and controls were matched on age, sex, county of residence, and, if deceased, year of death.

Study Period: 1980-1989

Endpoints: Oral squamous cell carcinomas

Number of cases/controls:

410 cases, 410 controls

(354 cases, 354 controls in analysis)

Apparent Biases: Recall bias, information bias from proxy interview

Study Quality: Fair

Limitations (if not "Adequate"): Smaller number of ST users

Comments: Controls matched on age, sex, county of residence, and year of death (if deceased). Used proxy interviews for the deceased. The authors did try to use a one year lag time, but may be less helpful on the large number of deceased. Good response rates. Elevated risks among former snuff users vs. never smokers suggests some quitting may have been due to diagnoses or symptoms related to oral cancer.

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Schildt, 1998	Smoking, ST (Swedish moist snuff)	Oral squamous cell carcinomas	Design - cases and controls matched on age, sex, county	Never snuff user, never smoker	OR	1.0 (ref)			
Schildt, 1998	Smoking, ST (Swedish moist snuff)	Oral squamous cell carcinomas	Design - cases and controls matched on age, sex, county	Never snuff user, Ex-smoker	OR	0.9	0.6	1.4	
Schildt, 1998	Smoking, ST (Swedish moist snuff)	Oral squamous cell carcinomas	Design - cases and controls matched on age, sex, county	Never snuff user, Active smoker	OR	1.7	1.1	2.6	
Schildt, 1998	Smoking, ST (Swedish moist snuff)	Oral squamous cell carcinomas	Design - cases and controls matched on age, sex, county	Ex-user of snuff, never smoker	OR	1.8	0.9	3.5	
Schildt, 1998	Smoking, ST (Swedish moist snuff)	Oral squamous cell carcinomas	Design - cases and controls matched on age, sex, county	Active snuff user, Never smoker	OR	0.7	0.4	1.2	
Schildt, 1998	Smoking, ST (Swedish moist snuff)	Oral squamous cell carcinomas	Design - cases and controls matched on age, sex, county. Smoking, light beer, beer, wine, liquor included in model.	Never smoker, never snuff	OR	1.0 (ref)			
Schildt, 1998	Smoking, ST (Swedish moist snuff)	Oral squamous cell carcinomas	Design - cases and controls matched on age, sex, county. Smoking, light beer, beer, wine, liquor included in model.	Low smoking consumption, never snuff	OR	1.2	0.7	1.9	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Schildt, 1998	Smoking, ST (Swedish moist snuff)	Oral squamous cell carcinomas	Design - cases and controls matched on age, sex, county. Smoking, light beer, beer, wine, liquor included in model.	High smoking consumption,, never snuff	OR	1.8	1.1	2.9	
Schildt, 1998	Smoking, ST (Swedish moist snuff)	Oral squamous cell carcinomas	Design - cases and controls matched on age, sex, county. Smoking, light beer, beer, wine, liquor included in model.	Never smoking, low snuff consumption	OR	0.8	0.4	1.6	
Schildt, 1998	Smoking, ST (Swedish moist snuff)	Oral squamous cell carcinomas	Design - cases and controls matched on age, sex, county. Smoking, light beer, beer, wine, liquor included in model.	Never smoking, high snuff consumption	OR	1.3	0.6	2.6	

Siegel 1992

Full citation: Siegel D, Benowitz N, Ernster VL, Grady DG, Hauck WW. 1992. Smokeless tobacco, cardiovascular risk factors, and nicotine and cotinine levels in professional baseball players. *Am J Public Health* 82(3):417-421.

Exposure: ST (snuff, chewing tobacco)

Study Design: Cross-sectional

Population (total): Major league professional baseball teams in spring training in Phoenix or Tucson

Study Period: 1988 and 1989

Endpoints: Systolic BP (mm Hg), Diastolic BP (mm Hg), Pulse (beats/min), Total cholesterol, HDL cholesterol, white blood cell count (WBCs x 10^9/L)

Number of exposed/unexposed:

176 v. 127 (nonuser v. user)
175 v. 126 (nonuser v. user)
489 v. 396 (nonuser v. user)
485 v. 395 (nonuser v. user)
419 v. 332 (nonuser v. user)
69 v. 26 (snuff v. chewing tobacco)
180 v. 48 (snuff v. chewing tobacco)
179 v. 48 (snuff v. chewing tobacco)
154 v. 33 (snuff v. chewing tobacco)

Apparent Biases: Possible misclassification of exposure from self-assessment of exposure.

Study Quality: Fair

Limitations (if not "Adequate"): No tobacco comparison group, lack of selection information.

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Siegel, 1992	ST (snuff, chewing tobacco)	Systolic BP (mm Hg)	Age, race, alcohol use, and serum caffeine level	Non-user v. user of ST	Mean	117.1 v. 117.1	-2.48	2.53	
Siegel, 1992	ST (snuff, chewing tobacco)	Diastolic BP (mm Hg)	Age, race, alcohol use, and serum caffeine level	Non-user v. user of ST	Mean	72.1 v. 71.5	-1.62	2.79	
Siegel, 1992	ST (snuff, chewing tobacco)	Pulse (beats/min)	Age, race, alcohol use, and serum caffeine level	Non-user v. user of ST	Mean	65.6 v. 65.4	-2.67	3.13	
Siegel, 1992	ST (snuff, chewing tobacco)	Total cholesterol	Age, race, alcohol use, and serum caffeine level	Non-user v. user of ST	Mean	4.42 v 4.39	-0.09	0.15	
Siegel, 1992	ST (snuff, chewing tobacco)	HDL cholesterol	Age, race, alcohol use, and serum caffeine level	Non-user v. user of ST	Mean	1.30 v. 1.31	-0.05	0.04	
Siegel, 1992	ST (snuff, chewing tobacco)	WBCs x 10^9/L	Age, race, alcohol use, and serum caffeine level	Non-user v. user of ST	Mean	6.6 v. 6.2	0.12	0.64	P<0.01
Siegel, 1992	ST (snuff, chewing tobacco)	Systolic BP (mm Hg)	Age, race, alcohol use, serum caffeine level, hours of smokeless tobacco use per day, time since last ST use, years of ST use	Mean of snuff user v. chewing tobacco user	Mean	115.3 v. 119.3	-9.1	1.07	
Siegel, 1992	ST (snuff, chewing tobacco)	Diastolic BP (mm Hg)	Age, race, alcohol use, serum caffeine level, hours of smokeless tobacco use per day, time since last ST use, years of ST use	Mean of snuff user v. chewing tobacco user	Mean	71.9 v. 70.9	-2.19	5.14	
Siegel, 1992	ST (snuff, chewing	Pulse (beats/min)	Age, race, alcohol use, serum caffeine	Mean of snuff user v.	Mean	64.5 v. 65.4	-4.22	6.05	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
	tobacco)		level, hours of smokeless tobacco use per day, time since last ST use, years of ST use	chewing tobacco user					
Siegel, 1992	ST (snuff, chewing tobacco)	Total cholesterol	Age, race, alcohol use, serum caffeine level, hours of smokeless tobacco use per day, time since last ST use, years of ST use	Mean of snuff user v. chewing tobacco user	Mean	4.34 v. 4.39	-0.33	0.21	
Siegel, 1992	ST (snuff, chewing tobacco)	HDL cholesterol	Age, race, alcohol use, serum caffeine level, hours of smokeless tobacco use per day, time since last ST use, years of ST use	Mean of snuff user v. chewing tobacco user	Mean	1.33 v. 1.33	-0.11	0.09	
Siegel, 1992	ST (snuff, chewing tobacco)	WBCs x 10^9/L	Age, race, alcohol use, serum caffeine level, hours of smokeless tobacco use per day, time since last ST use, years of ST use	Mean of snuff user v. chewing tobacco user	Mean	6.1 v. 6.2	-0.66	0.49	

Squires 1984

Full citation: Squires WG, Jr., Brandon TA, Zinkgraf S, Bonds D, Hartung GH, Murray T, Jackson AS, Miller RR. 1984. Hemodynamic effects of oral smokeless tobacco in dogs and young adults. *Prev Med* 13(2):195-206.

Exposure: Moist snuff (2.5-g dose of commercially available oral smokeless tobacco (moistened snuff), having been previously analyzed for nicotine content by the method of Cundiff and Markunas)

Study Design: Experimental with repeated measures

Population (total): 20 healthy males with a mean age of 20 years.

Study Period: Not given

Endpoints: Heart rate, systolic BP (mm Hg), diastolic BP (mm Hg)

Number of exposed/unexposed:

10 ST users, 10 non-tobacco users (all non-smokers, all abstained from ST prior to test)

Apparent Biases: None.

Study Quality: Fair

Limitations (if not "Adequate"): Small sample size.

Comments: All 20 years old, none treated for hypertension, all male, no resting BP >130/90, height and weight not statistically different in results table.

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Squires, 1984	Moist snuff	Heart rate	None	Pretest baseline v. experimental period (given ST) v. post-test baseline	Means	69 v. 89.3 v. 84.6			P <0.05 for pretest baseline v. experimental P <0.05 for pretest baseline v. post-test baseline The group (user vs nonuser) x time interaction, was not statistically significant (P > 0.05)
Squires, 1984	Moist snuff	Systolic BP (mm Hg)	None	Pretest baseline v. experimental period (given ST) v. post-test baseline	Means	118 v. 129 v. 126			P <0.05 for pretest baseline v. experimental P <0.05 for pretest baseline v. post-test baseline The group (user vs nonuser) x

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
									time interaction, was not statistically significant (P > 0.05)
Squires, 1984	Moist snuff	Diastolic BP (mm Hg)	None	Pretest baseline v. experimental period (given ST) v. post-test baseline	Means	72 v. 79 v. 76			P <0.05 for pretest baseline v. experimental The group (user vs nonuser) x time interaction, was not statistically significant (P > 0.05)

Wennberg 2007

Full citation: Wennberg P, Eliasson M, Hallmans G, Johansson L, Boman K, Jansson JH. 2007. The risk of myocardial infarction and sudden cardiac death amongst snuff users with or without a previous history of smoking. *J Intern Med* 262(3):360-367.

Exposure: ST (snus)

Study Design: Nested case-control

Population (total): 73,880 individuals who participated in a Swedish health survey administered from 1985-1999 as part of the MONICA and Vasterbotten Intervention Program

Study Period: 1985-1999

Endpoints: Myocardial infarction, myocardial infarction fatal within 28 days, sudden cardiac death (mortality), with survival time <24 hours, sudden cardiac death (mortality), with survival time <1 hour

Number of cases/controls: 525 cases/1,798 controls (men only)

Apparent Biases: Restricted to men; small sample and lack of precision in some of the more detailed subcategories; did not capture changes in tobacco use behaviors.

Study Quality: Adequate

Limitations (if not "Adequate"): None

Comments: The authors used a change-in-estimate method to determine if diabetes, hypertension, cholesterol, nitrate use, or heart medicine use were mediators of the effect of snuff use on myocardial infarction.

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Wennberg, 2007	ST (snus)	Myocardial infarction	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	21 never smoker, current snuff users vs. 130 never users of tobacco (referent)	OR	0.82	0.46	1.43	
Wennberg, 2007	ST (snus)	Myocardial infarction	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	37 former smokers, current snuff users vs. 130 never users of tobacco (referent)	OR	1.25	0.8	1.96	
Wennberg, 2007	ST (snus)	Myocardial infarction	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	136 current smoker, noncurrent snuff users vs. 130 never users of tobacco (referent)	OR	2.6	1.91	3.54	
Wennberg, 2007	ST (snus)	Myocardial infarction	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey,	30 current smoker, current snuff users vs. 130 never users of tobacco (referent)	OR	2.14	1.28	3.6	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			geographical region.						
Wennberg, 2007	ST (snus)	Myocardial infarction	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	11 never smoker, former snuff users vs. 130 never users of tobacco (referent)	OR	0.66	0.32	1.34	
Wennberg, 2007	ST (snus)	Myocardial infarction	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	58 former smoker, never snuff users vs. 130 never users of tobacco (referent)	OR	1.18	0.82	1.7	
Wennberg, 2007	ST (snus)	Myocardial infarction	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	33 former smoker, former snuff users vs. 130 never users of tobacco (referent)	OR	1.34	0.84	2.12	
Wennberg, 2007	ST (snus)	Myocardial infarction, fatal within 28 days	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex,	7 never smoker, current snuff users vs. 30 never users of tobacco (referent)	OR	1.12	0.38	3.29	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			age, date of health survey, geographical region.						
Wennberg, 2007	ST (snus)	Myocardial infarction, fatal within 28 days	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	7 former smokers, current snuff users vs. 30 never users of tobacco (referent)	OR	1.24	0.44	3.53	
Wennberg, 2007	ST (snus)	Myocardial infarction, fatal within 28 days	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	37 current smoker, noncurrent snuff users vs. 30 never users of tobacco (referent)	OR	3.53	1.83	6.84	
Wennberg, 2007	ST (snus)	Myocardial infarction, fatal within 28 days	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	5 current smoker, current snuff users vs. 30 never users of tobacco (referent)	OR	1.11	0.34	3.69	
Wennberg, 2007	ST (snus)	Myocardial infarction, fatal within	BMI, leisure time physical activity, educational level,	2 never smoker, former snuff users vs. 30 never users	OR	0.64	0.13	3.18	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
		28 days	cholesterol level. Matched on sex, age, date of health survey, geographical region.	of tobacco (referent)					
Wennberg, 2007	ST (snus)	Myocardial infarction, fatal within 28 days	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	11 former smoker, never snuff users vs. 30 never users of tobacco (referent)	OR	1.02	0.45	2.31	
Wennberg, 2007	ST (snus)	Myocardial infarction, fatal within 28 days	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	4 former smoker, former snuff users vs. 30 never users of tobacco (referent)	OR	0.60	0.18	2.02	
Wennberg, 2007	ST (snus)	Sudden cardiac death (mortality), with survival time < 24 hours	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	7 never smoker, current snuff users vs. 24 never users of tobacco (referent)	OR	1.18	0.38	3.70	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Wennberg, 2007	ST (snus)	Sudden cardiac death (mortality), with survival time < 24 hours	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	6 former smokers, current snuff users vs. 24 never users of tobacco (referent)	OR	1.39	0.44	4.42	
Wennberg, 2007	ST (snus)	Sudden cardiac death (mortality), with survival time < 24 hours	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	31 current smoker, noncurrent snuff users vs. 24 never users of tobacco (referent)	OR	3.12	1.53	6.33	
Wennberg, 2007	ST (snus)	Sudden cardiac death (mortality), with survival time < 24 hours	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	3 current smoker, current snuff users vs. 24 never users of tobacco (referent)	OR	0.75	0.17	3.28	
Wennberg, 2007	ST (snus)	Sudden cardiac death (mortality), with survival time < 24 hours	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey,	2 never smoker, former snuff users vs. 24 never users of tobacco (referent)	OR	0.70	0.14	3.64	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			geographical region.						
Wennberg, 2007	ST (snus)	Sudden cardiac death (mortality), with survival time < 24 hours	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	7 former smoker, never snuff users vs. 24 never users of tobacco (referent)	OR	0.74	0.28	1.97	
Wennberg, 2007	ST (snus)	Sudden cardiac death (mortality), with survival time < 24 hours	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	3 former smoker, former snuff users vs. 24 never users of tobacco (referent)	OR	0.50	0.12	2.03	
Wennberg, 2007	ST (snus)	Sudden cardiac death (mortality), with survival time < 1 hour	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	4 never smoker, current snuff users vs. 13 never users of tobacco (referent)	OR	0.38	0.08	1.89	
Wennberg, 2007	ST (snus)	Sudden cardiac death (mortality), with survival	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex,	5 former smokers, current snuff users vs. 13 never users of tobacco (referent)	OR	2.67	0.52	13.8	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
		time < 1 hour	age, date of health survey, geographical region.						
Wennberg, 2007	ST (snus)	Sudden cardiac death (mortality), with survival time < 1 hour	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	21 current smoker, noncurrent snuff users vs. 13 never users of tobacco (referent)	OR	4.54	1.55	13.25	
Wennberg, 2007	ST (snus)	Sudden cardiac death (mortality), with survival time < 1 hour	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	1 current smoker, current snuff users vs. 13 never users of tobacco (referent)	OR	0.13	0.01	2.1	
Wennberg, 2007	ST (snus)	Sudden cardiac death (mortality), with survival time < 1 hour	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	1 never smoker, former snuff users vs. 13 never users of tobacco (referent)	OR	0.35	0.03	4.56	
Wennberg, 2007	ST (snus)	Sudden cardiac death	BMI, leisure time physical activity, educational level,	4 former smoker, never snuff users vs. 13 never users	OR	0.35	0.07	1.78	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
		(mortality), with survival time < 1 hour	cholesterol level. Matched on sex, age, date of health survey, geographical region.	of tobacco (referent)					
Wennberg, 2007	ST (snus)	Sudden cardiac death (mortality), with survival time < 1 hour	BMI, leisure time physical activity, educational level, cholesterol level. Matched on sex, age, date of health survey, geographical region.	0 former smoker, former snuff users vs. 13 never users of tobacco (referent)	OR	N/A	N/A	N/A	

Winn 1981

Full citation: Winn DM, Blot WJ, Shy CM, Pickle LW, Toledo A, Fraumeni JF, Jr. 1981. Snuff dipping and oral cancer among women in the southern United States. *N Engl J Med* 304(13):745-749.

Exposure: Snuff

Study Design: Case-control (matched)

Population (total): Females residing in 67 counties in North Carolina

Study Period: Discharge records from 09/01/1975-12/31/1978, and death certificate diagnoses from 01/01/1976-12/31/1978

Endpoints: Oral and pharyngeal cancer, cancer of the gum and mucosa, and cancer of the pharynx and other parts of the mouth

Number of cases/controls:

232 cases (91% response rate)
410 controls (82% response rate)

Apparent Biases: Possible misclassification of exposure via next-of kin interviews (51% in cases, 21% controls). Possible recall error.

Study Quality: Fair

Limitations (if not "Adequate"): Small sample sizes, possible misclassification of exposure and possible recall error.

Comments: Large ORs and 95% CIs for risk of cancer by duration of use of snuff, due to small cell numbers.

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Winn, 1981	Snuff	Oral and pharyngeal cancer	Matched according to age, race, source of ascertainment, county of residence	Non-smokers, non-snuff users: Whites: 36 cases, 153 controls	OR	Whites: 4.2	2.6	6.7	NR
Winn, 1981	Snuff	Oral and pharyngeal cancer	Matched according to age, race, source of ascertainment, county of residence	5 cases, 16 controls	OR	1.5	0.5	4.8	NR
Winn, 1981	Snuff	Cancer of the Gum and Mucosa	Matched according to age, race, source of ascertainment, county of residence	Non-smokers, non-snuff users: Whites: 36 cases, 153 controls; Blacks: 5 cases, 16 controls	OR	13.8	1.9	98	NR
Winn, 1981	Snuff	Cancer of the Gum and Mucosa	Matched according to age, race, source of ascertainment, county of residence	Non-smokers, non-snuff users: Whites: 36 cases, 153 controls; Blacks: 5 cases, 16 controls	OR	12.6	2.7	58.3	NR
Winn, 1981	Snuff	Cancer of the Gum and Mucosa	Matched according to age, race, source of ascertainment, county of residence	Non-smokers, non-snuff users: Whites: 36 cases, 153 controls; Blacks: 5 cases, 16 controls	OR	47.5	9.1	249.5	NR

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Winn, 1981	Snuff	Cancer of the pharynx and other parts of the mouth	Matched according to age, race, source of ascertainment, county of residence	Non-smokers, non-snuff users: Whites: 36 cases, 153 controls; Blacks: 5 cases, 16 controls	OR	1.7	0.4	7.2	NR
Winn, 1981	Snuff	Cancer of the pharynx and other parts of the mouth	Matched according to age, race, source of ascertainment, county of residence	Non-smokers, non-snuff users: Whites: 36 cases, 153 controls; Blacks: 5 cases, 16 controls	OR	3.8	1.5	9.6	NR
Winn, 1981	Snuff	Cancer of the pharynx and other parts of the mouth	Matched according to age, race, source of ascertainment, county of residence	Non-smokers, non-snuff users: Whites: 36 cases, 153 controls; Blacks: 5 cases, 16 controls	OR	1.3	0.5	3.2	NR

Winn 1984

Full citation: Winn DM, Ziegler RG, Pickle LW, Gridley G, Blot WJ, Hoover RN. 1984. Diet in the etiology of oral and pharyngeal cancer among women from the southern United States. *Cancer Res* 44(3): 1216-22.

Exposure: Snuff use, cigarette smoking

Study Design: Case-control, hospital-based and population-based

Population (total): 632 women in North Carolina - 227 cases of oral and pharyngeal cancer, 405 controls. Cases selected from 5 hospitals in NC and from population-based registries; ~ 2 controls per case selected from the same source as case.

Study Period: 1975-1978

Endpoints: All cancer of the tongue, gums, buccal mucosa, floor of mouth, palate, tonsils, or pharynx and hypopharynx

Number of cases/controls: 227 cases, 405 controls

Apparent Biases: Lack of adjustment for other confounders (BMI, alcohol intake, etc.)

Study Quality: Fair

Limitations (if not "Adequate"): Relatively small sample size; lack of adjustment for common confounders

Comments: BMI was measured as weight/(height)^1.5, possibly overestimating the BMI of a few participants.

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Winn, 1984	Snuff use, cigarette smoking	All cancer of the tongue, gums, buccal mucosa, floor of mouth, palate, tonsils, or pharynx and hypopharynx	None	Exclusive, ever snuff users, never tobacco users	OR	3.8	2.3	6.8	NR
Winn, 1984	Snuff use, cigarette smoking	All cancer of the tongue, gums, buccal mucosa, floor of mouth, palate, tonsils, or pharynx and hypopharynx	None	Exclusive, ever smoker, never tobacco users	OR	1.5	0.7	2.9	NR
Winn, 1984	Snuff use, cigarette smoking	All cancer of the tongue, gums, buccal mucosa, floor of mouth, palate, tonsils, or pharynx and hypopharynx	In estimating odds ratio for snuff users: only fruit intake	Ever snuff users, low fruit and veg. intake vs. low fruit intake, never tobacco users	OR	3.8	1.4	10.7	NR
Winn, 1984	Snuff use, cigarette smoking	All cancer of the tongue, gums, buccal mucosa, floor of mouth, palate, tonsils, or pharynx and hypopharynx	In estimating odds ratio for snuff users: only fruit intake	Ever snuff users, medium fruit and veg. intake vs. low fruit intake, never tobacco users	OR	2.8	1.1	7.2	NR

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Winn, 1984	Snuff use, cigarette smoking	All cancer of the tongue, gums, buccal mucosa, floor of mouth, palate, tonsils, or pharynx and hypopharynx	In estimating odds ratio for snuff users: only fruit intake	Ever snuff users, high fruit and veg. intake vs. low fruit intake, never tobacco users	OR	3.8	1.4	10.7	NR
Winn, 1984	Snuff use, cigarette smoking	All cancer of the tongue, gums, buccal mucosa, floor of mouth, palate, tonsils, or pharynx and hypopharynx	In estimating odds ratio for snuff users: only fruit intake	Ever smokers, low fruit and veg. intake vs. low fruit intake, never tobacco users	OR	4.4	1.6	12.3	NR
Winn, 1984	Snuff use, cigarette smoking	All cancer of the tongue, gums, buccal mucosa, floor of mouth, palate, tonsils, or pharynx and hypopharynx	In estimating odds ratio for snuff users: only fruit intake	Ever smokers, medium fruit and veg. intake vs. low fruit intake, never tobacco users	OR	2.5	1.0	6.4	NR
Winn, 1984	Snuff use, cigarette smoking	All cancer of the tongue, gums, buccal mucosa, floor of mouth, palate, tonsils, or pharynx and hypopharynx	In estimating odds ratio for snuff users: only fruit intake	Ever smokers, high fruit and veg. intake vs. low fruit intake, never tobacco users	OR	1.6	0.6	4.4	NR

Yatsuya 2010

Full citation: Yatsuya H, Folsom AR, for the ARIC Investigators. 2010. Risk of incident cardiovascular disease among users of smokeless tobacco in the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Epidemiol* 172(5):600-605.

Exposure: Smokeless tobacco use (Chewing tobacco and Snuff)

Study Design: Prospective cohort

Population (total): 14498 participants in the ARIC study between the ages of 45 and 64 years at recruitment; exclusion criteria: 1) missing values on cigarette smoking status and use of other tobacco products (snuff, chewing tobacco, pipes, and cigars) at baseline; 2) missing values on educational level, cigarette smoking status, usual ethanol consumption, or physical activity; and 3) a self-reported history of coronary heart disease or stroke at visit 1.

Study Period: 1987-2005

Endpoints: Incident Coronary heart disease or stroke (a validated definite or probable hospitalized myocardial infarction, a definite coronary heart disease death, an unrecognized myocardial infarction defined by ARIC electrocardiography reading, or coronary revascularization; a validated definite or probable hospitalized ischemic or hemorrhagic stroke confirmed by imaging).

Number of exposed/unexposed:

Never: 1,510/ 9,906; Past: 112/494
Never: 1,510/ 9,906; Current: 102/354

Apparent Biases: None

Study Quality: Adequate

Limitations (if not "Adequate"): None

Comments: Never and past smokers included in the final analysis. "...Separately calculated associations for never and past cigarette smokers were virtually identical..." "...Analysis excluding current cigar or pipe users at visit 1 or visit 2, as well as any current cigarette smoking reported at visits 1–4, yielded similar results (for current smokeless tobacco use in model 2, HR = 1.32, 95% CI: 1.04, 1.67)..."

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Yatsuya, 2010	Smokeless tobacco use (Chewing tobacco and Snuff)	Incident coronary heart disease or stroke	Age, Sex, race-center, education level, total annual household income, usual alcohol consumption, physical activity, never or past cigarette smoking, past and current use of pipes and cigars, secondhand smoke exposure	Never used ST, never smoked or smoked in the past: N = 9906	Hazard Ratio	Past users: 0.90	Past users: 0.73	Past users: 1.11	NR
Yatsuya, 2010	Smokeless tobacco use (Chewing tobacco and Snuff)	Incident coronary heart disease or stroke	Age, Sex, race-center, education level, total annual household income, usual alcohol consumption, physical activity, never or past cigarette smoking, past and current use of pipes and cigars, secondhand smoke exposure	Never used ST, never smoked or smoked in the past: N = 9906	Hazard Ratio	Current users: 1.31	Current users: 1.06	Current users: 1.61	NR

Zahm 1992

Full citation: Zahm SH, Heineman EF, Vaught JB. 1992. Soft tissue sarcoma and tobacco use: data from a prospective cohort study of United States veterans. *Cancer Causes Control* 3(4):371-376.

Exposure: ST (Chewing tobacco and snuff)

Study Design: Prospective cohort study

Population (total): 248,046 US military veterans, aged 31-84, who held active US government life insurance policies in 1953

Study Period: January 1, 1954 (or January 1, 1957 for respondents to the second mailing) to September 30, 1980

Endpoints: Mortalities of soft tissue sarcomas of head, face, and neck, trunk, upper and lower limbs, and multiple, unspecified, and unknown sites.

Number of exposed/unexposed: 2,308 exclusive ST users / 52,741 non-users of any tobacco products

Apparent Biases: 1) Non-differential misclassification of exposure - self reported current or past use of any tobacco products 2) The statistical procedures applied while analyzing the results were not described in detail, and the covariates used to adjust for confounders for the other groups were not mentioned in the report, lending less weight to the final conclusion.

Study Quality: Fair

Limitations (if not "Adequate"): The cohort identified exclusive ST users (current and past), exclusive smokers (current and past) and non-users of any form of tobacco, but there were no cases in the ST-exclusive group.

Comments: No outcomes observed in exclusive ST users; estimation of risk of soft tissue sarcoma according to duration of ST use included groups who also either concurrently or intermittently smoked cigarettes.

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Zahm, 1992	ST (Chewing tobacco and Snuff)	Mortalities of soft tissue sarcomas of head, face, and neck, trunk, upper and lower limbs, and multiple, unspecified, and unknown sites.	Not specified	Exclusive ST users vs non-users of any tobacco products	Relative risk of mortality	0 (No deaths reported in the exclusive ST users group)	N/A	N/A	N/A

Zhou 2013

Full citation: Zhou J, Michaud DS, Langevin SM, McClean MD, Eliot M, Kelsey KT. 2013. Smokeless tobacco and risk of head and neck cancer: evidence from a case-control study in New England. *Int J Cancer* 132(8):1911-1917.

Exposure: smokeless tobacco (ST) (types not specified)

Study Design: Case-control study

Population (total): Cases were 18+ years of age and residents of the greater Boston area who were recruited from 9 medical facilities in the greater Boston area. Controls were residents of Massachusetts identified through town books which list all residents 17+ years of age.

Study Period: Not provided

Endpoints: Head and neck squamous cell carcinoma (HNSCC)

Number of cases/controls: 1,239 controls and 1,046 cases were available for analysis. Frequency matched on age, gender, town of residence. When restricted to non-smokers, 250 cases (or fewer) and 496 controls.

Apparent Biases: Lower participation rate for controls compared to cases (47% v 78%). Recall bias.

Study Quality: Fair

Limitations (if not "Adequate"): Small numbers. Does not specify type of ST examined. Does not specify study period. Restricted to never smokers so table 4 footnote is confusing because it suggests controlling for smoking variables.

Comments: None

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
Zhou, 2013	ST (types not specified)	Head and neck squamous cell carcinoma (HNSCC)	Frequency-matching variables of age and gender; additionally controlled for race, education level, smoking, ever smoker, alcohol drinking.	Smokeless tobacco use : ≥ 20 times v. never (limited to never smokers)	OR	4.21	1.01	17.57	
Zhou, 2013	ST (types not specified)	Head and neck squamous cell carcinoma (HNSCC)	Frequency-matching variables of age and gender; additionally controlled for race, education level, smoking, ever smoker, alcohol drinking.	Duration of smokeless tobacco use in lifetime: >0-<10 years v. never (limited to never smokers)	OR	0.78	0.15	4.13	
Zhou, 2013	ST (types not specified)	Head and neck squamous cell carcinoma (HNSCC)	Frequency-matching variables of age and gender; additionally controlled for race, education level, smoking, ever smoker, alcohol drinking.	Duration of smokeless tobacco use in lifetime: ≥10 years v. never (limited to never smokers)	OR	13.21	1.53	114.46	p for trend: 0.018
Zhou, 2013	ST (types not specified)	Head and neck squamous cell carcinoma (HNSCC)	Frequency-matching variables of age and gender; additionally controlled for race, education level, smoking, ever	Average frequency of smokeless tobacco use per week: >0-<7 times per week v. never	OR	1.94	0.54	7.03	

Author, year	Exposure	Endpoint	Covariates	Comparison Groups	RE Description	RE	LCL	UCL	P value
			smoker, alcohol drinking.	(limited to never smokers)					
Zhou, 2013	ST (types not specified)	Head and neck squamous cell carcinoma (HNSCC)	Frequency-matching variables of age and gender; additionally controlled for race, education level, smoking, ever smoker, alcohol drinking.	Average frequency of smokeless tobacco use per week: ≥7 times per week v. never (limited to never smokers)	OR	5.11	0.47	55.94	p for trend: 0.142
Zhou, 2013	ST (types not specified)	Head and neck squamous cell carcinoma (HNSCC)	Frequency-matching variables of age and gender; additionally controlled for race, education level, smoking, ever smoker, alcohol drinking.	Lifetime numbers of smokeless tobacco use (times/week x yrs): >0 to <20 times/wk x years (limited to never smokers)	OR	1.22	0.29	5.26	
Zhou, 2013	ST (types not specified)	Head and neck squamous cell carcinoma (HNSCC)	Frequency-matching variables of age and gender; additionally controlled for race, education level, smoking, ever smoker, alcohol drinking.	Lifetime numbers of smokeless tobacco use (times/week x yrs): ≥20 times/wk x years (limited to never smokers)	OR	9.15	0.97	86.59	p for trend: 0.053