Intended for
Swedish Match

Prepared by
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SYSTEMATIC REVIEW AND UPDATE OF THE LITERATURE ON THE HEALTH EFFECTS OF SWEDISH SNUS

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EXECUTIVE SUMMARY

Ramboll (formerly ENVIRON) was asked by Swedish Match to conduct a systematic review of the literature relating to the health effects of Swedish snus as part of an update to the 2013 ENVIRON report. The 2013 report included literature published through at least December 31, 2012, and this update includes articles published through July 28, 2017 (i.e., an additional four and a half years). In the first section of the report, Ramboll defines the study protocol, the individual assessment of study quality, and the weight of the evidence approach for synthesis. In the following three content sections of this report, Ramboll evaluated: the human health effects of snus (section 2), health risks in dual users and switchers compared to smokers (section 3), and non-clinical toxicological studies of snus (section 4). A summary of the results for each section are presented below.

Section 2 – Systematic Review of The Human Health Effects of Snus

Over 100 distinct endpoints have been investigated in the scientific literature, including new endpoints identified from 47 newly identified studies, and those identified from literature reviewed in the 2013 ENVIRON report. The results for each endpoint were synthesized and one of six conclusions were reached based on the table below:

Table E-1: Total Evidence Integration Guidelines

Adapted from the IOM *Gulf War and Health, Volume II* review.

Conclusion	Guidelines
Sufficient Evidence of an Association	• Evidence from available studies is sufficient to conclude that there is a positive association (i.e., exposure leads to outcome) • Consistent positive association from human studies in which chance and bias, including confounding, could be ruled out with reasonable confidence • For example, several well-conducted studies report consistent positive associations. This may include 2 studies providing "strong" evidence of an association, or a mix of a single study providing "strong" evidence, and 2 or more studies providing "moderate" evidence of an association • Epidemiological data suggests a dose-response relationship between exposure and health endpoint
Limited/Suggestive Evidence of an Association	• Evidence from available human studies suggests an association, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence • This may include at least one study providing "strong" evidence, and/or at least two studies providing "moderate" evidence of an association between the exposure and the outcome • Alternatively, several studies providing weak evidence (e.g., cross-sectional), but a consistent positive association, and results are probably not due to bias, including confounding (studies may be methodologically flawed in different ways)
Limited/Suggestive Evidence of No Association	• Evidence from well-conducted studies is consistent in not showing a positive association after exposure of any magnitude • Conclusion is limited to the conditions, magnitudes of exposure, and length of observation in available studies

	• This may include at least one study providing "strong" evidence of a null association, or at least two studies providing "moderate" evidence of a null association that is reliably measured within reason (i.e., reasonably narrow confidence intervals) • Alternatively, several studies providing weak evidence (e.g., cross-sectional), but a consistent null association, and results are probably not due to bias, including confounding • Possibility of a very small increase in risk from exposure studied cannot be excluded
Balanced/Mixed	• Approximately equal amounts of evidence suggesting an association and providing null results that are reliably measured within reason (i.e., reasonably narrow confidence intervals) • Not necessarily based on quantity of studies suggesting particular association(s) • At least some "moderate" or "strong" evidence from available studies
Inadequate/Insufficient Evidence to Determine Whether an Association Exists	• Evidence from available studies is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association

The following table presents the conclusions for each endpoint in this report.

Table E-2: Conclusions Regarding the Absolute Risk among Users of Swedish Snus		
Sufficient Evidence of an Association		
Oral Mucosal Effects Snuff Dipper's Lesion		
Limited/Suggestive Evidence of an Association		
Risk factors for CVD Acute increases in heart rate Acute increases in blood pressure	**Pregnancy outcomes and reproductive effects** Stillbirth Preterm birth Lower birthweight Neonatal apnea Small for gestational age	**Other Health Effects** All-cause mortality
Limited/Suggestive Evidence of an Inverse Association		
Skin Cancer & Melanoma CSCC, all melanoma, and CMM	**Other Health Effects** Parkinson's disease	
Limited/Suggestive Evidence of No Association		
Dental Effects and Periodontal Disease Dental Caries and Caries-associated Factors	**Head and Neck Cancers** Oral Cancer Oral and Pharyngeal Cancer	**Metabolic Effects** Insulin resistance or impaired glucose tolerance Metabolic syndrome

- Tooth Loss
- Gingivitis
- Periodontal Disease

Risk Factors for CVD

- Lipid Levels
- Biochemical or Physical Measures of clotting
- Measures of Fitness including oxygen uptake, work capacity, and cardiac output

Heart Disease

- Incident ischemic heart disease, myocardial infarction, and heart failure
- Incident overall cardiovascular disease
- Atrial Fibrillation

Stroke

- Incident stroke
- Esophageal Adenocarcinoma

Pancreatic Cancer

Stomach Cancer

- Overall stomach cancer
- Cardia stomach cancer

Colorectal and Anal Cancer

- Colon and rectal cancer

Lung Cancer

Skin Cancer & Melanoma

- Melanoma in situ

Hematopoietic Cancer

- Multiple myeloma
- Leukemia (ALL, AML, CLL)
- Non-Hodgkin's Lymphoma

All Cancers

- BMI

Gastro Intestinal Effects

- Crohn's disease and ulcerative colitis
- Celiac disease

Pregnancy outcomes and reproductive effects

- Early neonatal mortality
- Maternal antenatal bleeding
- Maternal preeclampsia
- Maternal gestational hypertension

Other Health Effects

- Complications after hernia surgery
- Multiple sclerosis
- Respiratory performance during exercise
- Rheumatoid arthritis
- Sarcoidosis
- Skin conditions

Balanced/Mixed

Risk Factors for CVD

- Non-acute effects on heart rate and blood pressure
- High blood pressure or hypertension

Heart Disease

- Fatal ischemic heart disease, myocardial infarction, and/or sudden cardiac death
- Fatal overall cardiovascular disease

Stroke

- Fatal stroke

Head and Neck Cancers

- Esophageal Cancer
- Esophageal Squamous Cell Carcinoma

Metabolic Effects

- Diabetes
- Overweight/Obese
- Waist circumference or waist-to-hip ratio

Inadequate/Insufficient Evidence

Dental Effects and Periodontal Disease

- Tooth Wear
- Gingival Recession

Oral Mucosal Effects

- Dysplasia
- Leukoplakia
- Oral melanin pigmentation
- p-53 expression

Risk Factors for CVD

Head and Neck Cancers

- Cancer at other sites in the head and neck

Stomach Cancer

- Non-cardia stomach cancer

Colorectal and Anal Cancer

- Anal cancer

Other Health Effects

- Acoustic neuroma
- Acute adverse symptoms
- Amyotrophic lateral sclerosis
- Chronic pain intensity
- Delayed bone healing
- Gallstone disease
- General health
- Groin hernias

- Acute ventricular heart function and heart-rate variability
- White blood cell count
- Cardiovascular/circulatory symptoms
- Allostatic load

Gastro Intestinal Effects

- Heart burn or gastroesophageal reflux symptoms, and peptic ulcer
- Irritable bowel syndrome
- Other gastrointestinal symptoms and effects including dyspepsia, epigastric pain, abdominal pain, H. pylori infection, and esophagitis

Kidney and Bladder Cancer

Skin Cancer & Melanoma

- Intraocular malignant melanoma

Hematopoietic Cancer

- Hodgkin's Lymphoma

Smoke-related Cancer

Pregnancy outcomes and reproductive effects

- Infant heartrate variability
- Infant oral clefts
- Male fertility

Metabolic Effects

- Becoming underweight
- Incident weight gain
- Musculoskeletal disorders
- Pain and post-operative nausea
- Non-affective psychosis and schizophrenia
- Nervous problems and psychosocial distress
- Major depression and depressive symptoms
- Asthma and other respiratory issues
- Respiratory death
- Sleeping problems
- Survival following a cancer diagnosis
- Survival following an MI diagnosis
- Tongue abnormalities
- Vitamin D levels

Section 3 – Health Risks of Dual Users and Switchers Compared to Smokers

This section reviewed the subset of studies identified in sections 1 and 2 that reported health effect estimates for snus users who concurrently smoke referred to as "dual users" or current snus users who have quit smoking referred to as "switchers". Comparison of results focused on presentation of results from prior studies that compared effect estimates in dual users and switchers to effect measures in former and/or current smokers. This section assessed the following outcomes: oral and pharyngeal cancer, oral cancer, esophageal cancer and subtypes, pancreatic cancer, stomach cancer and subtypes, lung cancer, overall cardiovascular disease, incident and fatal ischemic heart disease and MI, nonfatal MI, incident and fatal stroke, sudden cardiac death, metabolic syndrome, diabetes prevalence and incidence, acute myeloid leukemia, and all-cause mortality.

Dual users compared to never tobacco or never snus/smoke

The majority of endpoints had statistically non-significant results for the comparison of dual users to never tobacco or never snus/smoke, however eight endpoints varied in evidence. Results did not exist for oral and pharyngeal cancer. Lung cancer had evidence of a lower risk in dual users, while four endpoints (non-fatal MI, fatal stroke, total mortality-related outcomes, and pancreatic cancer) had evidence of an increased risk. Two endpoints (IHD/MI incidence and mortality) had mixed evidence of increased risk and statistically non-significant results. The remaining ten outcomes have statistically non-significant results only. Notably endpoints with statistically significant increased, decreased, or mixed evidence of risk in dual users did not have evidence for significant risk compared to smokers and/or no evidence of statistical interaction.

Dual users compared to smokers

Except for three endpoints (oral and pharyngeal cancer, lung cancer, and pancreatic cancer), all studies present some evidence of statistical non-significance either through statistical comparison, tests of interaction, or effect measures that overlap confidence intervals. Dual users compared to smokers was not assessed in two endpoints (lung cancer, pancreatic cancer) due to a lack of smoking effect estimates. Oral and pharyngeal cancer was the only study to report increased risk in dual users, although with evidence of statistically non-significant interaction. Two endpoints (fatal stroke and fatal IHD/MI) did not have a statistical comparison reported but had evidence of a statistically non-significant interaction between smoking and snus use. Two endpoints (diabetes incidence and total mortality related outcomes) had mixed evidence of lower risk and statistical non-significance. Five endpoints (non-fatal MI, SCD, MetSy, Diabetes prevalence, AML) had neither a statistical comparison between dual users and smokers or an assessment of interaction, however all of these had dual user effect measures that overlapped the confidence interval for the smoker effect measure suggesting no statistically significant difference in relative risks. The remaining six endpoints (IHD/MI incidence, oral, esophageal, stomach, overall cardiovascular disease, and incident stroke) had statistically non-significant results assessed through a statistical test.

Effects in switchers and comparison to smokers

Only ten endpoints had evidence for switchers in this report: non-fatal MI, incident and fatal IHD/MI, diabetes incidence and prevalence, oral cancer, overall cardiovascular disease, stroke incidence, sudden cardiac death, and metabolic syndrome.

Switchers compared to never tobacco or never smoke/snus

Only evidence for non-fatal MI suggests an increased risk for switchers. Evidence for IHD/MI incidence is mixed with studies suggesting increased risk and statistical non-significance. Notably, these two endpoints (IHD/MI incidence and non-fatal MI) have evidence suggesting a significant lower risk in dual users compared to smokers. The remaining eight endpoints have evidence of statistical non-significance through a statistical test.

Switchers compared to current smokers

In the comparison of switchers to current smokers, evidence for all endpoints suggested either lower risk, mixed evidence of lower or non-significant risk, or statistical non-significance. Four endpoints (non-fatal MI, IHD/MI incidence, overall cardiovascular disease, and incident stroke) had lower risk, while one endpoint (Fatal IHD/MI) had mixed evidence of lower or non-significant risk. The remaining five endpoints had evidence that suggested statistical non-significance due to effect measures overlapping confidence intervals or a statistical test.

Switchers compared to former smokers

All studies had evidence suggesting statistical non-significance either due to a statistical test or effect measures overlapping confidence intervals.

Section 4 – Non-clinical Toxicological Studies with Snus

Nine potentially relevant non-clinical toxicological and *in vitro* studies were identified in the July 28, 2017 literature search. Of the nine, five were identified as relevant, with four excluded for reasons including nonuse of Swedish Match snus product(s), or previous inclusion in the 2013 ENVIRON report.

Like the 2013 report, some of the new studies included genotoxicity, mutagenicity, and cytotoxicity endpoints investigated *in vitro*, as well as an *in vivo* study of rats. New endpoints included *in vitro* effects on platelet function (adhesion) and aneuploidy (abnormal number of chromosomes), and an *in vivo* study of potential cardiovascular and developmental effects of Swedish snus on zebrafish embryos.

Consistent with previous findings, one study of the combined effect of three Swedish snus products (one of which was not Swedish Match brand) indicated that Swedish snus may be mutagenic (increased mutation revertants), genotoxic (increased micronuclei), and cytotoxic (lower cell viability) *in vitro*. Another *in vitro* study of the potential genotoxicity of Swedish snus did not report a statistically significant increase in aneuploid HPV-positive keratinocytes. A third *in vitro* study reported a reduction in platelet adhesion to fibrinogen and collagen for 10% Ettan snuff extract. The potential clinical significance of these results is unclear, and it remains unknown to what extent any of the *in vitro* effects from these studies may be relevant to humans *in vivo*.

In an *in vivo* study of rats that consumed a tobacco slurry of Swedish snus, consistent with previous findings in animals as well as oral changes in humans, non-cancerous soft tissue changes in the forestomach were observed including cell proliferation, and a thickening of the basal region of squamous epithelium. In a new study of the potential cardiovascular and developmental effects of Swedish snus on zebrafish embryos, a variety of toxic effects including early embryonic mortality, developmental delay, defects in lymphatics development and ventricular function, and aneurysm development were observed following injection with Swedish snus extracts. Aside from the potential differences between human and zebrafish embryos, the conditions for which the embryos were exposed in this study (injection) is not necessarily representative of potential real-world exposure of human embryos as a result of the mother using snus.

1. INTRODUCTION AND PROTOCOL

1.1 Introduction

Ramboll (formerly ENVIRON) was asked and funded by Swedish Match to conduct a systematic review of the literature relating to the health effects of Swedish snus, as part of an update to the 2013 ENVIRON report. The funders had no role in study design, data collection, and analysis of this review.

The previous review included studies published through December 31, 2012, as well as some relevant articles published in early 2013. The objective of this review was to identify and evaluate all original primary scientific studies published since December 1, 2012 through July 28, 2017, and not included in the previous review, to comprehensively update previous conclusions contained within the following specific sub-sections of the 2013 ENVIRON report (Review of the Scientific Literature on Snus (Swedish Moist Snuff)):

- Section 4: Non-Clinical Toxicological Studies with Snus
- Section 5: Human Health Effects of Snus (including all previous and new endpoints)
- Appendix VII (to Section 5): Comparison of Risks from Dual Use, Switching, and Quitting

This updated report includes a summary of the conclusions from the document listed above (which is comprehensive through December 2012), a presentation of new information (if available) for each endpoint, and an updated evaluation of the total available evidence and conclusion. Newly identified human health endpoints were presented with their own new summary, evaluation, and conclusion. This review and update of the 2013 ENVIRON report is intended to be systematic, with the methods clearly and transparently presented so the literature searches and evaluations could be replicated. This systematic review is intended to comply with all relevant guidelines of the Preferred Reporting Items for systematic Reviews and Meta-Analyses (PRISMA) statement, a well-established and highly-regarded standard for the reporting of systematic reviews and meta-analyses.[1] The 27-item checklist of this protocol is provided in Appendix A, with relevant page numbers cited for each item on the checklist.

The systematic review update to Section 5 of the 2013 ENVIRON report included the following steps:

- Development of a protocol, and a relevant and comprehensive search strategy;
- Systematic literature searches;
- Screening of potentially relevant literature identified in the comprehensive searches, including the application of inclusion and exclusion criteria;
- Detailed evaluation of literature deemed potentially relevant from the initial screening;
- Data abstraction from relevant new studies, and quality assessment of individual analyses;
- Quality assessment of all previously identified studies from the 2013 ENVIRON report;
- Qualitative synthesis of the total available evidence (Section 2);

[1] For more information, visit http://www.prisma-statement.org/.

- Evaluation of the health effects of continued smoking in comparison with switching and dual use (Sections 3);
- Preparation of written report.

Any potentially relevant human studies identified in the update to Section 5 of the 2013 ENVIRON report (Section 2) were included in the update to Appendix VII (Section 3). The methods/protocol involved in the update to this appendix are described in detail in Section 3.

1.2 Methods & Search Results

1.2.1 Overview

The purpose of this update is to identify and evaluate all new literature on the human health effects of Swedish snus, as well as *in vitro* and *in vivo* toxicology studies of Swedish snus. This section describes in detail the steps taken to identify all relevant literature, abstract relevant data, and evaluate and report upon the reviewed literature.

1.2.2 Literature Identification and Screening

1.2.2.1 Relevant Literature Definitions

Relevant literature for this update included publications pertaining to the topics described in section 1.2.1, that have been published and/or made publicly available after December 1st, 2012 and were not included in the 2013 ENVIRON report.

Attention was paid to the snus product evaluated within publications, as publications considered relevant will have evaluated the exposures, use, and/or perceptions of Swedish snus in particular. Studies of other or unknown brands of snus were not included or evaluated in this review, with the exception of Swedish or Norwegian studies that do not disclose the brand of snus or type of smokeless tobacco evaluated. Due to Swedish Match's dominant market share in these countries, Ramboll reasonably assumed that the vast majority of snus and/or smokeless tobacco used in these countries was likely Swedish snus.

In addition to an update to the human health effects literature published after December 1, 2012, a retrospective literature search on the human health effects of Swedish snus was also conducted without a start date through December 1, 2012. This was done because of a lack of a reproducible systematic approach regarding the literature search strategy described in the 2013 ENVIRON report. Any potentially relevant studies identified through this search that were not included in the 2013 ENVIRON report were evaluated and included in this update if deemed relevant.

The publication types considered for this update included:

- Peer-reviewed primary studies;
- Secondary sources, including reviews, meta-analyses, government and non-government organization reports, and survey reports (human studies only);
- Publicly available primary data sources, including scientific abstracts, clinical trial data, and academic theses providing relevant results.

The peer-reviewed literature considered for this report includes epidemiological studies, human clinical studies, and toxicology studies. Secondary sources, such as reviews, meta-analyses, and government reports, were used as supporting evidence of that presented in the primary literature when forming conclusions for the human health effects of snus. Due to the extensive use of Swedish snus in countries such as Sweden and Norway, relevant studies also included those published in languages other than English. Potentially relevant non-English studies were considered for inclusion in the final evaluation if the studies could be translated into English.

1.2.2.2 Literature Databases and Search Terms

Structured searches in PubMed/MedLine (http://www.pubmed.com), Scopus (http://www.scopus.com/), and ClinicalTrials.gov (http://clinicaltrials.gov/) were used to identify the relevant literature spanning across the disciplines and publication types of interest. Additionally, searches of select, pre-determined government and non-government organization websites were also conducted to identify reports of primary data not traditionally captured in literature databases. The searches were completed on July 28, 2017.

Our objective was to capture all Swedish snus-related literature in one step to allow us to be as systematic and comprehensive as possible in updating the literature. Thus, following exploratory searches of the National Library of Medicine's PubMed database, we developed search terms for these topics that were general and broad, and designed to capture all relevant literature on Swedish snus. Each batch of search results were saved and imported into Mendeley[2] reference manager software for additional review, screening, and tagging (categorizing). Details of these literature searches are provided in Appendix B. The numbers of articles saved from each search and database were documented. Mendeley includes an automated feature by which duplicates are eliminated; the tables in Appendices B, C, and D also include the total number of unique articles that required screening.

The bibliographies of potentially relevant reviews, meta-analyses, and reports were also reviewed in order to identify publications not otherwise captured by the initial search queries. No additional articles were identified in this way.

1.2.2.3 Inclusion and Exclusion Criteria

Articles imported into Mendeley were initially screened according to their title, abstract, and key words. Following the initial review of this information, the article was labeled with pre-determined "inclusion" or "exclusion" tags to reflect the reviewers' initial judgment regarding potential relevance. Full-text copies of articles marked for inclusion were ordered, reviewed, and abstracted in detail, while articles marked for exclusion were not reviewed further, unless re-reviewed during QAQC (see Section 1.2.3.1). If a reviewer was unsure of an article's overall relevance, the article was initially included as "check" so that it could be reviewed further. The intention of this approach was to help minimize the number of missed relevant articles prior to the full-text review.

[2] For more information, visit http://www.mendeley.com.

Table 1-1 describes the inclusion and exclusion criteria used in this review and lists the "tags" used in Mendeley to label publications determined to be potentially relevant. Only one tag was applied per article.

Table 1-1: Inclusion and Exclusion Criteria for Updated Search

Topic / Mendeley Tag	Criteria
Included Studies (Potentially Relevant)	
Health	Publications evaluating the human health effects of Swedish snus • Primary epidemiology studies of any health effect • Involves use of Swedish snus, or smokeless tobacco use in a Scandinavian country
Tox	Toxicology or *in vitro* studies involving Swedish snus
Meta/Review	Relevant commentaries, reviews, and/or meta-analyses that will be reviewed for additional publications not originally captured by the source, and/or provide supporting evidence to the primary health effects data
Check	Publications requiring additional discussion or consideration by the reviewing team; these articles were converted into another inclusion or exclusion tag following discussion
Excluded / Non-Relevant Studies	
Not a study	Publications that are not primary studies and do not provide evidence related to the human health effects or toxicology of Swedish snus. • May include commentaries, editorials, policy-related articles, etc. that otherwise do not provide reliable primary scientific evidence.
Not snus	Health and/or tobacco use-related publications that do not consider exposure to Swedish snus. • May include studies of non-Swedish snus (e.g., snus from brands other than Swedish Match), smokeless tobacco as a group, cigarettes, or other unrelated or grouped exposures
Use	Publications involving primary data that evaluate the use patterns related to Swedish snus in human populations
Risk Perception	Publications evaluating the risk perceptions of Swedish snus
Other KAB	Studies on knowledge, attitudes, or beliefs related to Swedish snus that do not include an evaluation of health risk perceptions of Swedish snus
Animal/cell	Toxicology or *in vitro* studies involving tobacco/tobacco component exposures other than Swedish snus
Chemistry	Studies of the chemical composition of Swedish snus
Misc	Any other non-relevant publications

Table 1-2 describes the inclusion and exclusion criteria used in the retrospective literature search on the human health effects of Swedish snus through December 1, 2012 and lists the "tags" used in Mendeley to label publications determined potentially relevant. Only one tag was applied per article.

Table 1-2: Inclusion and Exclusion Criteria for Retrospective Health Effects Literature Search through December 1, 2012

Topic / Mendeley Tag	Criteria
Included Studies (Potentially Relevant)	
Health	Publications evaluating the human health effects of Swedish snus • Primary epidemiology studies of any health effect • Involves use of Swedish snus, or smokeless tobacco use in a Scandinavian country
Meta/Review	Relevant reviews, and/or meta-analyses that will be reviewed for additional publications not originally captured by the source, and/or provide supporting evidence to the primary health effects data
Check	Publications requiring additional discussion or consideration by the reviewing team; these articles were converted into another inclusion or exclusion tag following discussion
Excluded / Non-Relevant Studies	
Commentary	Publications that are not primary studies or formal reviews/meta-analyses on the health effects of Swedish snus. • May include commentaries, editorials, policy-related articles, etc. that otherwise do not provide reliable primary scientific evidence.
Not snus	Health and/or tobacco use-related publications that do not consider exposure to Swedish snus. • May include studies of non-Swedish snus (e.g., snus from brands other than Swedish Match), smokeless tobacco as a group, cigarettes, or other unrelated or grouped exposures
Duplicate	Duplicate studies that have already been tagged/categorized.
Exclude	Any other non-relevant publications

1.2.3 Preliminary Literature Screening Results

Detailed screening results of the updated literature searches and for the retrospective human health effects literature search through December 1, 2012 are provided in PRISMA diagrams in Appendices C and D, respectively. After conducting the literature search update (described in Appendix B), and after removing duplicates, we identified 1,428 articles that potentially related to the human health effects or toxicology of Swedish snus. Following the preliminary screening of these articles, 1,309 were excluded, with 119 identified as potentially relevant requiring further review.

After conducting the retrospective literature search of the health effects literature through December 1, 2012, we identified 4,037 articles for further screening after most duplicates were automatically removed. Following the preliminary screening of these articles, 3,713 were excluded, with 324 identified as potentially relevant requiring further review.

1.2.3.1 Quality Assurance/Quality Control (QA/QC) of Screened Literature

An independent reviewer conducted an initial QA/QC review following the review of the first 100 publications by each reviewer. The reviewer blindly selected 10 (10%) of the screened publications and documented their own determination regarding inclusion or exclusion. Following this initial QA/QC check, an error rate of 0% was identified for both the updated search and the retrospective search of the health effects literature. Since no error patterns were identified, the preliminary screening progressed.

Following the screening of all publications in the databases, an independent reviewer randomly screened 10% of excluded references and 20% of the included. Following the QA/QC review of the updated search results, none of the excluded articles were determined to be potentially relevant except for two that were changed to "Meta/Review," and no serious patterns of disagreement were observed.

Following the QA/QC review of the retrospective health effects search results, seven studies previously included in the 2013 ENVIRON report were re-categorized to excluded. This suggested that the screeners were conservative in their inclusion of potentially relevant studies and did not indicate any serious screening issues. However, two of the 380 excluded studies reviewed during QA/QC were identified as potentially relevant (a 0.52% error rate). To determine whether a pattern of missed relevant studies might exist, the relevant studies from the 2013 ENVIRON report were compared to those that were excluded in the retrospective search and no further missed relevant studies were identified. This suggested that no serious patterns of disagreement existed.

1.2.4 Full-Text Literature Review and Abstraction Results

Detailed screening results of articles identified as potentially relevant following the preliminary screening of articles related to the updated, and retrospective health effects literature search through December 1, 2012 are provided in PRISMA diagrams in Appendices C and D, respectively.

Following the retrieval and/or purchase of publications initially identified as potentially relevant, each full-text publication was reviewed in detail. 53 studies were ultimately included in the qualitative synthesis. These included 47 "Health" studies (two of which were identified in the retrospective search that had not been previously included in the 2013 ENVIRON report), five "Tox" studies, and one "Meta/Review" study.

The detailed review of articles relevant to the update of Section 5 of the 2013 ENVIRON report (articles tagged as "Health") included abstraction of information according to a pre-determined template and an overall determination of evidence quality from the article. Information was abstracted from each publication using the template in Appendix E, and the abstraction table is provided in Appendix F. The process by which evidence quality is rated from new articles and integrated into the conclusions from the previously published reports (where applicable) is discussed in Section 1.3.

92 "Health" studies were reviewed in detail, and 47 were excluded for various reasons including the following:

- Included in the 2013 ENVIRON report
- No health outcomes evaluated
- Did not include an evaluation of Swedish snus (e.g., cigarettes, combined tobacco, non-relevant brands or tobacco types, etc.)
- Non-relevant study (e.g., case report, use-behavior, non-relevant commentary, animal study)
- Commentaries

47 relevant primary studies on the human health effects of Swedish snus were identified and included in the qualitative syntheses (including two additional studies identified from the retrospective literature search through December 1, 2012).

1.2.4.1 Quality Assurance/Quality Control (QA/QC) of Abstracted Data

Following abstraction, a QA/QC review of the "Health" data was conducted by a team member of 20% of the studies abstracted. This review involved documentation of any potential omission or other errors. Although all relevant results were included for nearly every abstracted study that was reviewed, some minor omissions involving various study data were identified for eight of the nine abstracted studies. For this reason, all remaining abstracted data was reviewed for accuracy and completeness, and any omissions or errors were corrected. All excluded studies were also re-reviewed to confirm that they were not improperly excluded.

1.3 Guidelines for Rating Evidence and Forming Health-Related Conclusions through Weight of Evidence Evaluation

This section describes the manner in which Ramboll 1) critically evaluated the quality of individual analyses presented within human health-related studies and 2) evaluated the total evidence across studies examining the same relationships (e.g., all studies, both old and new, related to the same outcome). These two steps assisted with the update and summary of the total body of human evidence (described in Section 1.1).

1.3.1 Critical Evaluation of Individual Analyses

As part of the data abstraction process, a "quality rating" was applied to each analysis[3] that examined a tobacco use behavior and health endpoint (Table 1-3). We developed these quality rating guidelines/criteria specifically for evaluation of epidemiology studies (primarily observational) involving tobacco-related exposures. These criteria were partially adapted from the Institute of Medicine's (IOM) (2003) Gulf War and Health, Volume II report, and were based on standard differences in characteristics and potential limitations of epidemiology studies. Although FDA does not endorse

[3] The word "analysis" used here to reflect the idea that a single study may include multiple, possibly unrelated analyses of different outcomes, and/or different measures of exposure.

specific methods or tools for assessing quality or synthesizing evidence, these criteria are consistent with FDA's informal recommendations on interpreting relevant studies presented at the October 17, 2016 public seminar on the PMTA for ENDS (FDA 2016). The quality rating helped to anchor an individual analysis' relative importance within the overall causal determination involving all similar studies, old and new. The individual analysis rating considered the study's overall quality (e.g., objectives, study methods, outcome and exposure measurement), as well as the robustness of the analysis in question (e.g., statistical power, control of confounding and potential biases, exposure definition).

This approach helped to account for the variation of strength that a similar study may present for individual analyses; though an individual study may be of high quality overall, the strength of each individual analyses may differ within that study. For example, a study reporting results for multiple outcomes may have sufficient power to detect changes in risk for a common outcome but may not have sufficient power with respect to a less common outcome. In this scenario, the study's risk estimate for the more common outcome may provide stronger evidence of an association compared to the risk estimate for the less common outcome. Different ways of analyzing data may also affect the strength of evidence provided from a study. For example, while an analysis of Swedish snus use controlled for cigarette smoking may have more statistical power, a risk estimate from an analysis of exclusive Swedish snus users might be more relevant, but also more imprecise. Thus, the strength of evidence of a specific analysis within a given study will be assessed using a fixed rating scale and guidelines; the use of such tools is consistent with the approach outlined by PRISMA.

Table 1-3: Quality Ratings for Individual Analyses

Evidence	**Definition/Guidelines**
Strong	• Evidence originates from a well-designed study (e.g., study methods adequately described, reasonable sample size, well-designed large randomized controlled trial, cohort, or case-control study); • Effect estimate is precise and calculated using sufficient statistical power; • Exposure is relevant to study question (e.g., analysis of exclusive Swedish snus users with sufficient statistical power, and may account for changes over time); • Bias and confounding (appropriate for the specific exposure and endpoint) can be reasonably ruled out.
Moderate	• Evidence originates from a study with some quality-related limitations (e.g. limited sample size, some methodological flaws); • Effect estimate is imprecise or calculated using limited statistical power, possibly due to origin from a smaller cohort or case-control study; • Exposure is relevant, but may not be ideal (e.g., an estimate with high precision may involve an analysis of Swedish snus users adjusted for smoking, and may not account for changes in use behavior over time); • Evidence may not be entirely free of bias, including confounding. However, adjustment for other confounder(s) may indirectly mitigate potential confounding.
Weak	• Evidence may originate from a cross-sectional analysis, a very small cohort or case-control study, or an otherwise methodologically flawed study; • Evidence may be imprecise, perhaps due to the estimate's low statistical power, • Exposure is not well defined, or may likely include mixed tobacco use; • Evidence subject to a high likelihood of bias and/or confounding.

1.3.2 Weight of Evidence Evaluation of the Total Evidence for a Specific Relationship

Following the quality determination of newly identified analyses, Ramboll integrated the new findings (where applicable) with previously established evidence and conclusions. The synthesis of the total body of human evidence to form conclusions was based on the following guidelines adapted from the Institute of Medicine's (IOM) (2003) Gulf War and Health, Volume II review (Table 1-4). Determinations for new relationships previously unexamined were also developed by following these guidelines. The IOM (2003) guidelines were chosen specifically because of their focus on epidemiology studies (primarily observational), and conclusion language that is relevant to describing potential relationships between an exposure and disease.

The objective of this review was to form conclusions based on an evaluation of the available human evidence. The studies discussed here assessed differences in prevalence, incidence or mortality related to different levels of snus use (ranging from none to frequent or heavy use). Although no individual study can determine a causal relation, all of these studies contribute to our knowledge of the potential effects of snus use when considered in the broader context of other research (epidemiological as well as chemical and toxicological). Epidemiological studies of the highest quality contribute the most to a causality determination. The design and careful planning and conduct of the study are important in considering a study's contribution to the weight of evidence for the determination of a causal association between exposure and outcome in humans. Epidemiological study designs include intervention studies and several types of observational studies. The study participants' exposure status is under the control of the investigator in intervention studies such as clinical trials. There are no intervention studies of the long-term health effects of snus use in humans, but this methodology was used to assess several short-term, so-called acute, health effects. Evidence of the potential long-term health effects of snus comes from a variety of types of observational studies including: cohort, case-control, and cross-sectional.

Because of the relative lack of experimental evidence involving Swedish snus for most of the studied endpoints, and our consideration of mostly observational human evidence in forming these conclusions, our goal was to evaluate potential associations, rather than causal relationships. An association is present when evidence suggests that two variables are related (or correlated), while a causal relationship exists when the evidence is sufficient to indicate that a direct relationship exists between one variable and another (e.g., the exposure causes a particular disease). As stated by IOM (2003), sufficient evidence of a causal relationship includes the following:

> "Evidence from available studies is sufficient to conclude that a causal relationship exists between exposure to a specific agent and a specific health outcome in humans, and the evidence is supported by experimental data. The evidence fulfills the guidelines for sufficient evidence of an association [see table 1-4 below] and satisfies several of the guidelines used to assess causality: strength of association, dose–response relationship, consistency of association, biologic plausiblility, and a temporal relationship."

The highest category of evidence for a positive association included in our guidelines was "Sufficient Evidence of an Association," whereas the highest category of evidence for no association is "Limited/Suggestive Evidence of No Association." A category such as "Sufficient Evidence of No Association" is not included, in part due to philosophical reasons. It is not possible to prove a negative, and an absence of evidence is not necessarily evidence of an absence of a potential effect. For these

reasons, IOM (2003) states that "the possibility of a very small increase in risk after exposure studies cannot be excluded," even when several well-conducted studies do not show an association. This may result in a body of evidence that varies in quality and amount for endpoints in this category.

Table 1-4: Total Evidence Integration Guidelines

Adapted from the IOM *Gulf War and Health, Volume II* review.

Conclusion	Guidelines
Sufficient Evidence of an Association	• Evidence from available studies is sufficient to conclude that there is a positive association • A causal relationship is at least suspected • Consistent positive association from human studies in which chance and bias, including confounding, could be ruled out with reasonable confidence • For example, several well-conducted studies report consistent positive associations. This may include 2 studies providing "strong" evidence of an association, or a mix of a single study providing "strong" evidence, and 2 or more studies providing "moderate" evidence of an association • Epidemiological data suggests a dose-response relationship between exposure and health endpoint
Limited/Suggestive Evidence of an Association	• Evidence from available human studies suggests an association, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence • This may include at least one study providing "strong" evidence, and/or at least two studies providing "moderate" evidence of an association between the exposure and the outcome • Alternatively, several studies providing weak evidence (e.g., cross-sectional), but a consistent positive association, and results are probably not due to bias, including confounding (studies may be methodologically flawed in different ways)
Limited/Suggestive Evidence of No Association	• Evidence from well-conducted studies is consistent in not showing a positive association after exposure of any magnitude • Conclusion is limited to the conditions, magnitudes of exposure, and length of observation in available studies • This may include at least one study providing "strong" evidence of a null association, or at least two studies providing "moderate" evidence of a null association that is reliably measured within reason (i.e., reasonably narrow confidence intervals) • Alternatively, several studies providing weak evidence (e.g., cross-sectional), but a consistent null association, and results are probably not due to bias, including confounding • Possibility of a very small increase in risk from exposure studied cannot be excluded
Balanced/Mixed	• Approximately equal amounts of evidence suggesting an association and providing null results that are reliably measured within reason (i.e., reasonably narrow confidence intervals) • Not necessarily based on quantity of studies suggesting particular association(s) • At least some "moderate" or "strong" evidence from available studies
Inadequate/Insufficient	• Evidence from available studies is of insufficient quantity, quality, or

Evidence to Determine Whether an Association Exists	consistency to permit a conclusion regarding the existence of an association

2. SYSTEMATIC REVIEW OF THE HUMAN HEALTH EFFECTS OF SNUS

2.1 Introduction

This section serves as an update to Section 5 of the 2013 ENVIRON report, which involves the absolute risks of Swedish snus. Further details of previously reviewed studies can be found in that report. As noted in Section 1.2.4, 47 new studies (those not previously included in the 2013 ENVIRON report) on the human health effects of Swedish snus were identified and included in the qualitative synthesis conducted in this section. The health endpoints evaluated in these studies are numerous, exceeding 100 distinct endpoints, under a variety of endpoint categories including body weight, cancer, cardiovascular effects and disease, dental and non-cancer oral effects, diabetes and metabolic syndrome, gastrointestinal effects, and reproductive effects, among many other studies not included in these categories. As noted previously, this section presents a brief summary from the 2013 ENVIRON report, followed by a detailed evaluation of any new studies, information regarding the quality rating that we applied to the individual studies (old and new), and an overall discussion and conclusion based on the quality rating and conclusion guidelines outlined in Section 1.3.

2.2 Non-Neoplastic Oral Effects

2.2.1 Dental Effects and Periodontal Disease

2.2.1.1 Dental Conditions

Summary from 2013 ENVIRON Report

Of the eight cross-sectional studies of dental effects, two reported a statistically significant association with the use of snus and dental caries and tooth loss (Hirsch et al. 1991) and tooth wear (Ekfeldt et al. 1990). Neither study accounted for the potential confounding effects of socioeconomic status, or dietary or oral hygiene habits. Several studies that did account for these potential confounding factors did not find a relationship between the use of snus and dental caries (Hugoson et al. 2012; Rolandsson et al. 2005) or for tooth loss (Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005). None of the five studies that investigated the relationship between snus use and dental plaque reported a statistically significant relationship between the two (Bergstrom et al. 2006; Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005; Wickholm et al. 2004). Three out of those five studies accounted for socioeconomic status, or dietary or oral hygiene habits (Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005).

Newly Identified Studies

Two studies on the dental effects of Swedish snus have been published since the 2013 ENVIRON report (Hellqvist et al. 2012; Hellqvist et al. 2015). Hellqvist et al. (2012) evaluated the potential effect of Swedish snus on plaque pH in a clinical cross-over study of 10 Swedish adults. Intraoral pH increased following use of four nicotine-containing snus products, including the Swedish Match product, General Original Portion. Plaque pH decreased among three of six nicotine-free snus products (including the old recipe of the Swedish Match product, Onico snus, but not the newer Onico product), and all 10 products differed significantly from a sucrose control ($p<0.001$, area under the curve) (the plaque pH dropped much further in the sucrose control compared to the snus products). The authors noted that a lowering of plaque pH can cause demineralization of the dental hard tissue (enamel and

dentine), and that in the present study, there "appears to be a relationship between the content of fermentable carbohydrates in the snus and the pH fall in dental plaque." However, the biological relevance of short-term changes in pH as observed in this study is unknown, and in all products, plaque pH was statistically significantly higher compared to a sucrose control. The quality of evidence presented in this study was rated as weak based on the relevance to the risk of long-term dental effects such as caries, as well as the small number of participants included in the study.

Hellqvist et al. (2015) evaluated the effects of Swedish snus on plaque pH, plaque index, caries, number of decayed and filled tooth surfaces, and other factors related to the development of caries in a cross-sectional study of 101 exclusive snus users of 10 or more years and 100 non-users of tobacco for 10 or more years living in or near Karlstad, Sweden. Among a sample of 10 snus users and 10 non-users, non-users experienced a more pronounced drop in plaque pH compared to snus users, though this difference was not statistically significant. When snus users placed snus under the lip and then rinsed with sucrose, the pH fall was statistically significantly smaller than when no snus was present in the mouth. Among the larger study population, there were no significant differences between snus users and non-users with respect to plaque index (as well as when considering upper front teeth only), enamel caries, manifest caries, number of decayed and filled tooth surfaces (as well as when considering upper front teeth only), cariogram value, buffer capacity, *Mutans streptococci* in saliva, and *Lactobacilli* in saliva. Snus users, however, did have a higher ($p=0.005$) salivary secretion rate compared to non-users. The authors concluded that there were no statistically significant differences in prevalence of dental caries between snus users and non-users, with "only minor differences regarding caries-associated factors." Although the authors did not account for potential confounding variables in the models, they noted that there was no statistically-significant difference between snus users and non-users regarding tooth-brushing habits and approximal cleaning with toothpicks and interdental brush. There was also no significant difference in the intake of candy, sweets, and soft drinks between the two groups, although use of dental floss was more frequent among non-users, and visits to dental clinics were less frequent among tobacco users. In the current study, the authors reported that "poor oral hygiene was the main risk factor for caries development and that the main risk factor for poor oral hygiene was intellectual disability." Due to the small number of participants, unadjusted results, and cross-sectional design, the evidence quality from this study was rated as weak.

Quality Rating of all Studies

Study	**Endpoint(s)**	**Evidence Quality Rating**
Bergstrom et al. 2006	Dental plaque	Weak
Ekfeldt et al. 1990	Tooth wear	Weak
Hellqvist et al. 2012	Intraoral pH	Weak
Hellqvist et al. 2015	Plaque pH, plaque index, caries, number of decayed and filled tooth surfaces, and other factors related to the development of caries	Weak
Hirsch et al. 1991	Dental caries, tooth loss	Weak
Hugoson and Rolandsson 2011	Tooth loss, dental plaque	Weak
Hugoson et al. 2012	Dental caries	Weak
Monten et al. 2006	Tooth loss, dental plaque	Weak

Rolandsson et al. 2005	Dental caries, dental plaque	Weak
Wickholm et al. 2004	Dental plaque	Weak

Discussion and Conclusions

Although study findings were summarized in the 2013 ENVIRON report, standardized conclusions were not provided. A discussion of the new studies as well as standardized conclusions that consider the old and new evidence are provided below.

Dental Caries and Caries-associated Factors

The findings reported by Hellqvist et al. (2015) provide additional evidence of no association between the use of snus and dental caries. Furthermore, Hellqvist et al. (2015) reported no differences in the number of caries or plaque index between snus users and non-users when considering only the upper teeth, where snus is typically placed against. The authors also reported no differences in caries-associated factors such as cariogram value, buffer capacity, *Mutans streptococci* in saliva, and *Lactobacilli* in saliva. Intraoral or plaque pH either increased (Hellqvist et al. 2012) or showed a less pronounced drop (Hellqvist et al. 2015) following use of snus. Given that a drop in pH is associated caries development, this evidence suggests that snus does not increase the risk through this mechanism.

Though Hirsh et al. (1991) reported a signification association between snus use and dental caries, the authors did not account for potentially important confounders, and acknowledged that a definitive conclusion could not be made based on this. Several of the available studies controlled for or assessed important potential confounding factors such as socioeconomic status or oral hygiene habits (Hellqvist et al. 2105; Hugoson et al. 2012; Rolandsson et al. 2005; Hugoson and Rolandsson 2011; Monten et al. 2006). These studies did not report any differences in risk of dental caries or caries-associated factors between snus users and non-users. Though no prospective cohort or case-control studies are available, several descriptive studies, although rated as weak, have consistently shown no association between snus use and dental caries and caries-associated factors.

The studies on snus use and dental caries and caries-associated factors provide *limited/suggestive evidence of no association* between snus use and dental caries.

Tooth Wear

No new studies were identified since publication of the 2013 ENVIRON report.

There is *inadequate/insufficient evidence to determine whether an association exists* between snus use and tooth wear given that only a single, weak study exists.

Tooth Loss

No new studies were identified since publication of the 2013 ENVIRON report.

Three cross-sectional studies (Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005) that accounted for important confounders reported no association between the use of Swedish snus and tooth loss (the average number of teeth in Swedish snus users was statistically significantly higher compared to non-users in the Hugoson and Rolandsson 2011 study, and similar to non-users in the other two studies). The one study that did not account for these important confounders reported an association between Swedish snus use and tooth loss (Hirsch et al. 1991), but the authors

acknowledge that a definitive conclusion could not be made because of this. Given that the studies that controlled for important confounders consistently reported no association between Swedish snus use and tooth loss, there is *limited/suggestive evidence of no association*.

2.2.1.2 Gingivitis

Summary from 2013 ENVIRON Report

Of six cross-sectional studies of gingivitis, gingival index, or gingival bleeding, one reported a significant association between a higher gingival index and the use of snus (Modeer et al. 1980). The authors of this study did not report whether oral hygiene habits or sociodemographic variables differed between snus users and non-users of tobacco. The mean gingival index of snus users was 1.10 compared to 0.89 among non-users (a gingival index of 2 or 3 is considered gingivitis). Among the five studies that reported no association with gingivitis or other endpoints associated with gingivitis (Bergstrom et al. 2006; Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005; Wickholm et al. 2004), three of the five accounted for either oral hygiene habits and/or socioeconomic variables (Hugoson and Rolandsson 2011; Monten et al. 2006; Rolandsson et al. 2005).

Newly Identified Studies

A single study on the potential relationship between use of Swedish snus and gingival index was published since the 2013 ENVIRON report (Hellqvist et al. 2015). Hellqvist and colleagues (2015), described previously, reported that snus users had significantly higher gingival index values compared to non-users for the whole dentin (20.4% of snus users had a GI index of 2 or 3 vs. 14.4% among non-users, p=0.009) and for the upper front teeth (14.9% of snus users had a GI index of 2 or 3 vs. 7.7% among non-users, p=0.003).

Quality Rating of all Studies

Study	**Evidence Quality Rating**
Bergstrom et al. 2006	Weak
Hellqvist et al. 2015	Weak
Hugoson and Rolandsson 2011	Weak
Modeer et al. 1980	Weak
Monten et al. 2006	Weak
Rolandsson et al. 2005	Weak
Wickholm et al. 2004	Weak

Discussion and Conclusions

Most of the available studies, including those that accounted for important confounders reported no association between the use of snus and gingivitis. Two studies, including a new study published by Hellqvist et al. (2015) reported significant associations between snus use and a higher gingival index. Hellqvist et al. (2015) noted that use of dental floss and visits to dental clinics was less frequent among snus users compared to non-users, which could explain this finding. Given that all the studies that did account for socioeconomic status and/or oral hygiene habits reported no association, the evidence suggests that there is *limited/suggestive evidence of no association* between snus use and gingivitis.

2.2.1.3 Gingival Recession

No new studies were identified since publication of the 2013 ENVIRON report.

Quality Rating of All Studies

Study	Evidence Quality Rating
Andersson and Axéll 1989	Weak
Hugoson and Rolandsson 2011	Weak
Monten et al. 2006	Weak
Wickholm et al. 2004	Weak

Discussion and Conclusions

Of three cross-sectional studies that compared gingival recession among snus users and non-users of tobacco, one reported that snus use was associated with gingival recession (Monten et al. 2006). Of the two other studies, one reported that the prevalence of gingival recession among snus users and non-users was not significantly different (Wickholm et al. 2004), while the other reported a significantly lower percentage of sites with gingival recession ≥ 1 mm among snus users compared to non-users (adjusted for sociodemographic variables) (Hugoson and Rolandsson 2011). A fourth study found that loose snuff was significantly associated with gingival recession compared to the use of portion-bag snuff, while the authors provided no comparison of the effects of loose or portion-bag snuff use with non-use of tobacco (Andersson and Axell 1989). Given the inconsistent results and the cross-sectional nature of the existing studies, there *is inadequate/insufficient evidence to determine whether an association exists* between snus use and gingival recession.

2.2.1.4 Periodontal Disease

No new studies were identified since publication of the 2013 ENVIRON report.

Quality Rating of All Studies

Study	Evidence Quality Rating
Bergstrom et al. 2006	Weak
Hugoson and Rolandsson 2011	Weak
Julihn et al. 2008	Weak
Kallestal and Uhlin 1992	Weak
Monten et al. 2006	Weak
Rolandsson et al. 2005	Weak
Wickholm et al. 2004	Weak

Discussion and Conclusions

In all six cross-sectional studies and the one case-control study (Kallestal and Uhlin 1992), snus use was not associated periodontal disease or individual indicators of periodontal disease. Most studies, with only two exceptions (Bergstrom et al. 2006; Kallestal and Uhlin 1992), adjusted, or accounted for, socioeconomic status or oral hygiene habits. The five remaining studies accounted for either socioeconomic factors (Hugoson and Rolandsson 2011; Julihn et al. 2008; Wickholm et al. 2004) or oral hygiene habits (Monten et al. 2006; Rolandsson et al. 2005). Therefore, although the quality of the studies was rated as week, the consistent results, including among those that adjusted for

important confounders, suggests that there is *limited/suggestive evidence of no association* between snus use and periodontal disease.

2.2.2 Oral Mucosal Effects

2.2.2.1 Snuff Dipper's Lesion

No new studies were identified since publication of the 2013 ENVIRON report.

Quality Rating of All Studies

Study	Evidence Quality Rating
Andersson et al. 1989	Weak
Andersson et al. 1990	Weak
Andersson et al. 1991	Weak
Andersson et al. 1994	Weak
Andersson et al. 1995	Weak
Andersson and Axéll 1989	Weak
Andersson and Warfvinge 2003	Weak
Axéll 1976	Weak
Axéll et al. 1976	Weak
Axéll 1987	Weak
Axéll and Hedin 1982	Weak
Axéll and Henricsson 1985	Weak
Axéll 1993	Weak
Frithiof et al. 1983	Weak
Hirsch et al. 1982	Weak
Larsson et al. 1991	Weak
Martensson 1978	Weak
Mornstad et al. 1989	Weak
Rolandsson et al. 2005	Weak
Roosaar et al. 2006	Weak
Rosenquist et al. 2005	Weak
Salonen et al. 1990	Weak
Wallstrom et al. 2011	Weak

Discussion and Conclusions

Although much of the studies employ a cross-sectional or case-series design, there is a general consensus from the available literature that Swedish snus causes a characteristic type of oral mucosal lesion; and in this causal relationship, there is *sufficient evidence of an association*. However, the literature also demonstrate that the oral mucosal lesion caused by snus use typically regress following cessation of snus use, or among long-time users who do not change their snus habits, with no evidence that they progress to cancer, even with long-term use.

2.2.2.2 Leukoplakia

No new studies were identified since publication of the 2013 ENVIRON report.

Discussion and Conclusions

Confusion exists surrounding the use of the term leukoplakia, especially as related to the use of oral snuff. This is reflected in the various terms used to describe the condition in snuff users such as snuff dipper's lesion, oral leukoplakia, smokeless tobacco lesions, smokeless tobacco keratosis (Bouquot 1994; Greer 2006) and tobacco pouch keratosis (Neville and Day 2002). These differences in terminology, their varying definitions, and the multiple number of classification systems used to grade the severity of these lesions, combine to make assessment of the literature difficult. Due to these current difficulties, the available literature is currently the evidence provided in the current literature is *inadequate/insufficient to determine whether an association exists.*

2.2.2.3 Dysplasia

No new studies were identified since publication of the 2013 ENVIRON report.

Quality Rating of All Studies

Study	Evidence Quality Rating
Frithiof et al. 1983	Weak
Hirsch et al. 1982	Weak

Discussion and Conclusions

Two studies that comprise only snus users reported dysplasia in the population; 5 cases in 21 users in one study (Frithiof et al. 1983) and 9 in 50 users (Hirsch et al. 1982) in the other. Due to the lack of valid comparison groups (i.e. snus non-users), there is *inadequate/insufficient evidence to determine whether an association exists* with respect to snus use and dysplasia.

2.2.2.4 Miscellaneous Oral Changes

No new studies were identified since publication of the 2013 ENVIRON report.

Quality Rating of All Studies

Study	Evidence Quality Rating
Axéll and Hedin 1982	Weak

Discussion and Conclusions

Axéll and Hedin (1982) examined whether snus use was associated with increased oral melanin pigmentation. Among 1,541 individuals examined, 42 were snus users and the prevalence of pigmentation in snus users (4.7%) was not significantly higher than that among non-users of tobacco (3.0%). Axell and Hedin (1982) concluded that the use of snus did not significantly elevate the prevalence of oral melanin pigmentation. Given that the only study to date is of weak quality and reported no association, there is *inadequate/insufficient evidence to determine whether an association exists* between snus use and oral melanin pigmentation.

2.2.2.5 Biological Markers Associated with Oral Cancer in Oral Lesions from Swedish Snus Users

No new studies were identified since publication of the 2013 ENVIRON report.

Quality Rating of All Studies

Study	Endpoint(s)	Evidence Quality Rating
Ibrahim et al. 1996	P53 protein expression	Weak
Merne et al. 2002	p53 protein expression p21 protein expression PCNA protein expression Ki-67 protein expression	Weak
Schildt et al. 2003	p53 protein expression PCNA protein expression Ki-67 protein expression bcl-2 protein expression	Weak
Wedenberg et al. 1996	p53 protein expression	Weak
Wood et al. 1994	p53 protein expression	Weak

Discussion and Conclusions

p-53 expression

Five studies investigated p-53 protein expression in tissue samples of oral lesions from snus users as compared to tissues samples from snus non-users (Ibrahim et al. 1996; Merne et al. 2002; Schildt et al. 2003; Wedenberg et al. 1996; Wood et al. 1994). All these studies were constrained by weak methodology, including small sample sizes and inability to control for potential confounding factors such as alcohol consumption. In addition, all but one of the studies (Schildt et al. 2003) used methods that could not distinguish between wildtype and mutant p53 proteins. Two studies detected significantly increased p53 expression in snuff-induced lesions, compared to healthy tissue (Wedenberg et al. 1996; Wood et al. 1994), while one did not (Merne et al. 2002). Two studies showed a low (13-14%) frequency of p53 expression in snuffers' lesions (Ibrahim et al. 1996; Merne et al. 2002). The remaining study (Schildt et al. 2003), which analyzed oral squamous cell carcinoma tumor samples in a case-control study, found no positive association between snus use and p-53 positive tumors. Given the mixed results, and limitations present in the studies, there is *inadequate/insufficient evidence to determine whether an association exists* between snus use and p-53 protein expression levels.

2.3 Cancer

2.3.1 Head and Neck Cancer

2.3.1.1 Oral and Pharyngeal Cancer

Summary from 2013 ENVIRON Report

The available evidence suggests that use of Swedish snus is not associated with an increased risk of oral cancer. Results of high-quality epidemiological studies specifically examined the possibility that use of snus causes oral cancer and found no relationship; only one study yielded a statistically significant association with oral cancer (Roosaar et al. 2008). Several meta-analyses restricted to Swedish snus did not report a significantly increased risk of oral cancer, and other public health committees have agreed that snus does not increase the risk of oral cancer (Rodu and Jansson 2004; Stratton et al. 2001; Boffetta et al. 2008; Lee 2011; Lee and Hamling 2009b).

Newly Identified Studies

One study relating Swedish snus use to oral cancer has been published since the 2013 ENVIRON report. Hirsch et al. (2012) conducted a case series study of 16 male Swedish snuff users diagnosed with oral squamous cell carcinoma. All patients used snus for a mean duration of 42.9 years (range: 8-71 years) prior to diagnosis and were diagnosed at a mean age of 72.9 years. Six of the patients had a history of smoking conventional cigarettes. The authors noted that all patients developed cancer at the "exact anatomical location where the snuff quid was placed daily" (Hirsch et al. 2012). The generalizability and validity of these results, however, are limited by the study's design and participant selection. The participants were selected for study participation due to their referral and treatment at seven specialty clinics in Sweden, and do not reflect a representative sample of Swedish snus users. Given the limitations related to possible selection bias, the quality of evidence presented in this study was rated as weak.

Quality Rating of All Studies

Study	**Endpoint(s)**	**Evidence Quality Rating**
Oral Cancer		
Ahlbom 1937	Oral squamous cell carcinoma	Weak
Axell et al. 1978	Oral cancer	Weak
Hirsch et al. 2012	Oral squamous cell carcinoma	Weak
Lewin et al. 1998	Oral cavity	Moderate
Luo et al. 2007	Oral cancer, corresponding to ICD-7 codes 140 (lip); 141 (tongue); 143 (floor of mouth); and 144 (oral cavity, not otherwise specified). Analyses did not include cancers of the salivary glands, pharynx, or larynx.	Moderate
Rosenquist et al. 2005*	Oropharyngeal squamous cell carcinoma (OOSCC), corresponding to ICD-7 codes 141 (tongue), 143 (floor of mouth), 144 (oral cavity, not otherwise specified) and 145 (oropharynx)	Moderate
Schildt et al. 1998b*	Squamous cell oral cancer, corresponding to ICD-7 codes 140 (lip), 141 (tongue), 143 (floor of mouth), 144 (oral cavity, not otherwise specified), 145 (oropharynx)	Moderate
*Grouped with oral cancer because the outcome definitions only included part of the pharynx.		
Oral and Pharyngeal Cancer		
Boffetta et al. 2005	Oral/pharyngeal cancer: cancers of the oral cavity and pharynx (ICD-7 codes 141–148)	Moderate
Lewin et al. 1998	Oral cavity; Pharynx	Moderate
Roosaar et al. 2008	Oral and pharyngeal cancer, corresponding to ICD-7 codes 140-148	Moderate

Discussion and Conclusions

Because the definitions of oral cancer differ from study to study, we conducted separate evaluations for oral cancer and oral and pharyngeal cancer.

Oral Cancer

The new study published by Hirsch et al. (2012) contributes little to the greater understanding of a potential relationship between snus use and oral cancer, as the study provides weak evidence. Similar to two older studies (Ahlbom 1937; Axell et al. 1978) reviewed in the 2013 ENVIRON report, risk of oral cancer cannot be estimated from these studies. The cohort study conducted by Luo et al. (2007) provided no evidence of an association between exclusive ever, current, or former snus use and oral cancer, as well as no evidence of an increasing risk of oral cancer with increased consumption of snus. A statistically significant protective effect against oral cancer was observed among all snus users in the cohort, adjusted for age, BMI, and smoking. This study, however, was rated as moderate due to the lack of control for important potential confounding factors such as alcohol. Three case-control studies similarly did not observe a statistically significant increased risk of oral cancer (Rosenquist et al. 2005; Schildt et al. 1998b), all of which adjusted for alcohol consumption, an important potential confounder. Furthermore, Rosenquist et al. (2005) and Schildt et al. (1998), did not observe any statistically significant evidence of an exposure response relationship between snus use and oral cancer. The evidence provided by these four moderate quality studies is *limited/suggestive of no association* between snus use and oral cancer.

Oral and Pharyngeal Cancer

The three studies on oral and pharyngeal cancer included the appropriate study design and representative study populations, though most were limited by a small number of cases and low statistical power. Nonetheless, risks of oral and pharyngeal cancers were not significantly increased within a study of exclusive snus users providing moderate evidence (Roosaar et al. 2008), or among studies that presented smoking-adjusted risks among snus users (Boffetta et al. 2005; Lewin et al. 1998). Boffetta et al. (2005) was the only study that did not control for alcohol consumption, an important potential confounder. The only statistically significant increased risk of oral and pharyngeal cancer was reported by Roosaar et al. (2008), but only among all cohort members, adjusted for smoking, and not among exclusive snus users, as noted previously. For both analyses, however, the number of available cases were small, and confidence intervals were imprecise. Overall, given that several well-conducted studies providing moderate quality evidence consistently showed no association between snus use and oral and pharyngeal cancer after exposure of any magnitude, particularly among exclusive snus users, we concluded that the evidence is *limited/suggestive of no association*. Results from several meta-analyses also support this conclusion (Boffetta et al. 2008; Lee 2011; Lee and Hamling 2009b).

2.3.1.2 Esophageal Cancer

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

Four epidemiology studies have examined the relationship between snus use and esophageal cancer (Boffetta et al. 2005; Lagergren et al. 2000; Lewin et al. 1998; Zendehdel et al. 2008); one study, of the Swedish Construction Worker cohort (Zendehdel et al. 2008), reported evidence of a significant association with one type of esophageal cancer (squamous cell, the subtype most strongly associated with smoking), but not another type (esophageal adenocarcinoma). The meta-analysis that used this

squamous cell finding result reported an increased summary risk estimate (Boffetta et al. 2008), whereas the meta-analyses that used the combined cell type risk estimates from the individual studies did not report an increased summary risk estimate for esophageal cancer (Lee 2011; Lee and Hamling 2009b). Overall, the epidemiology studies suggest no association between snus use and esophageal cancer, but limitations in the available studies, and inconsistent results of the meta-analyses indicate a need for additional study of this outcome.

Quality Rating of All Studies

Study	**Endpoint(s)**	**Evidence Quality Rating**
Boffetta et al. 2005	Esophageal cancer	Moderate
Lagergren et al. 2000	Esophageal adenocarcinoma; esophageal squamous-cell carcinoma	Moderate
Lewin et al. 1998	Esophagus	Moderate
Zendehdel et al. 2008	Esophageal cancer, corresponding to ICD-7 code 150. The cancer subtype was further separated into esophageal adenocarcinoma and esophageal squamous-cell carcinoma.	Moderate

Discussion and Conclusions

Four studies providing moderate evidence examined the association between snus use and esophageal cancer (Boffetta et al. 2005; Lagergren et al. 2000; Lewin et al. 1998; Zendehdel et al. 2008). Of these, three studies of Swedish or Norwegian populations did not identify a statistically significant and increased risk of esophageal cancer among snus users in any exposure group (Boffetta et al. 2005; Lagergren et al. 2000; Lewin et al. 1998). However, a 2008 study of the Swedish Construction Worker's cohort identified an increased risk of esophageal squamous cell carcinoma among never smokers who exclusively used snus (10 cases, RR=3.5; 95% CI: 1.6-7.6), ever-smokers, and current smokers (Zendehdel et al. 2008), while a case-control study did not report an alcohol-adjusted statistically significant increased risk for adenocarcinoma or squamous cell carcinoma (Lagergren et al 2000). Although the Zendehdel et al. (2008) study is strengthened by the investigators' analysis of a large cohort (including approximately 336,000 construction workers) and complete, lengthy follow-up (mean 22.2 years), this study is limited by its one-time evaluation of each participants' tobacco use behaviors, low number of exposed cases, and the lack of information related to participants' alcohol consumption behaviors.

A meta-analysis conducted by Boffetta and colleagues (2008) reports a statistically significant and elevated relative risk of esophageal cancer among snuff users when considering the results of five studies. One of the five studies considered US smokeless tobacco users, while the other four studies considered Scandinavian populations (snus users), including that of Zendehdel and colleagues (2008). More recent meta-analyses considering only Scandinavian populations (Lee 2011; Lee and Hamling 2009b), do not report statistically significant summary relative risks for this relationship, primarily due to the selection of different relative risks from the Zendehdel (2008) study. The relative risk from the Zendehdel (2008) study that should be used in a meta-analysis for esophageal cancer is the subject of debate (Lee and Hamling 2009a).

Overall, the available studies provide *balanced/mixed evidence of an association* between snus use and esophageal cancer overall and esophageal squamous cell carcinoma, and *limited/suggestive evidence of no association* between snus use and esophageal adenocarcinoma.

2.3.1.3 Cancer at Other Sites in the Head and Neck

No new studies were identified since publication of the 2013 ENVIRON report.

Discussion and Conclusions

One case-control study of Swedish men conducted by Lewin and colleagues examined the association between snus use and cancers at other sites in the head and neck (Lewin et al. 1998). Specifically, the study concluded that compared to never users of snus, ever users of snus do not have significantly increased risks for general "cancer of the head and neck," (RR=1.1; 95% CI 0.7-1.5), nor do ever users of snus experience increased risks of laryngeal cancer (RR=0.9; 95% CI 0.5-1.5) (Lewin et al. 1998). Although this study provided moderate quality evidence of a lack of an association to support a relationship between snus use and cancers at other sites in the head and neck, the available data is *inadequate/insufficient to determine whether an association exists* based on this single study.

2.3.2 Pancreatic Cancer

Summary from 2013 ENVIRON Report

Two cohort studies suggest that use of Scandinavian smokeless tobacco could be associated with increased risk of pancreatic cancer among some subgroups of the population (Boffetta et al. 2005; Luo et al. 2007). However, there are inconsistencies between the two studies with respect to the specific subgroups at risk (only individuals who were also current smokers in one study (Boffetta et al. 2005) vs. only never-smokers of tobacco in the second study (Luo et al. 2007)). As with esophageal cancer, the authors of one of the available meta-analyses (Boffetta et al. 2008) chose different risk estimates from (smoking adjusted and never-smoking snus user estimates), whereas other researchers who combined like risk estimates did not observe an increased risk of pancreatic cancer among snus users, nor among smokeless tobacco users in the US and other Western populations (Lee et al. 2011; Lee and Hamling 2009b). Combined with evidence from a recent pooled analysis of the risk of pancreatic cancer among smokeless tobacco users in other Western populations (Bertuccio et al. 2011), the available evidence suggests that snus and other smokeless tobacco forms are not associated with pancreatic cancer.

Newly Identified Studies

Update searches identified one new study that investigated the potential relationship between use of Swedish snus and pancreatic cancer (Araghi et al. 2017). Araghi et al. (2017) conducted a pooled cohort study of 424,152 male participants from nine cohort studies. Data were pooled from the Swedish Collaboration on Health Effects of Snus Use, and participants were followed up through linkage to health registries. The cohorts included in the analysis included the Swedish Construction Worker Cohort; Malmo Diet and Cancer Study; Multinational Monitoring of Trends and Determinants in Cardiovascular disease (MONICA) study; National March Cohort, Scania Public Health Cohort; Stockholm Public Health Cohort; Vasterbotten Intervention Programme (VIP); and the Work, Lipids, and Fibrinogen Study. Participant recruitment began as early as 1978, and participants were followed through 2013. Thirty percent of the 418,448 total participants reported ever having used snus at study entry and 321 of these ever users were diagnosed with pancreatic cancer. Compared to never-

users of snus (n=1,1203, 1) current snus use, 2) ever snus use, and 3) former snus use were not individually associated with a significantly increased risk of pancreatic cancer, nor was an association observed at any intensity (<4, 4-6, and 7+ cans/week) or duration (<5, 5-<10, 10-<15, 15-<20, and 20+ years) of snus use. The authors reported hazard ratios generally equal to or lesser than 1. Adjustment for smoking behaviors yielded similar results; analyses of exclusive, never-smoking snus users did not suggest increased pancreatic cancer risks compared to never users of snus. All analyses were adjusted for attained age, smoking (for non-exclusive snus user analyses), and BMI. Additional analyses among ever, former, and current users that were further adjusted for alcohol consumption, physical activity, and the interaction between alcohol consumption and smoking showed similar results. The authors of this study concluded that their "findings, from the largest sample to date, do not support a role of snus use in the development of pancreatic cancer in men… [the findings] point to tobacco smoke constituents other than nicotine or its metabolites, i.e. carcinogens associated with combustion, as the causal agent explaining the increased risk of pancreatic cancer in smokers." This study had several strengths, including its prospective design, relatively large sample size, examination of potential dose-response relationships, and control for important confounders. A limitation of this study was that tobacco use was assessed only at baseline, which could have contributed to potential misclassification of exposure and consequent bias towards the null.

Quality Rating of all Studies

Study	**Endpoint(s)**	**Evidence Quality Rating**
Araghi et al. 2017	Pancreatic cancer, corresponding to ICD-7 code 157 and ICD-10 code C25.	Strong
Boffetta et al. 2005	Pancreatic cancer	Moderate
Heuch et al. 1983 (updated by Boffetta et al. 2005)	Pancreatic cancer, including histologically verified cases	Weak
Luo et al. 2007	Pancreatic cancer, corresponding to ICD-7 code 157.	Moderate

Discussion and Conclusions

The new study published by Araghi et al. (2017) provides strong evidence of a lack of an association between snus use and pancreatic cancer. In contrast to Luo et al. (2007) and Boffetta et al. (2005), this study controlled for alcohol consumption, an important potential risk factor for pancreatic cancer, and included a larger study population and exposed cases. The evidence provided by the three other studies on snus and pancreatic cancer are limited, and contradictory (Boffetta et al. 2005; Heuch et al. 1983; Luo et al. 2007). The Araghi et al. (2017) study provides strong support of our previous conclusion that the available evidence is *limited/suggestive of no association* between use of snus and pancreatic cancer.

2.3.3 Stomach Cancer

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

No studies found that use of snus was associated with any significant increase in risk of overall or cardia stomach cancer (cardia is the upper portion of the stomach) (Boffetta et al. 2005; Hansson et al. 1994; Lagergren et al. 2000; Ye et al. 1999; Zendehdel et al. 2008), but one study found an elevated risk for the noncardia subtype of stomach cancer (Zendehdel et al. 2008). These data suggest no association between snus use and stomach cancer overall, but additional research will help confirm whether the finding for the noncardia subtype is real.

Quality Rating of All Studies

Study	**Endpoint(s)**	**Evidence Quality Rating**
Boffetta et al. 2005	Stomach cancer	Moderate
Hansson et al. 1994	Gastric cancer	Moderate
Lagergren et al. 2000	Adenocarcinoma of the gastric cardia	Moderate
Ye et al. 1999	Newly and histologically confirmed gastric cardia cancer, distal stomach cancer (of the intestinal and diffuse type), and total gastric and cardia cancer	Moderate
Zendehdel et al. 2008	Cardia and non-cardia stomach cancer, corresponding with ICD-7 code 151	Moderate

Discussion and Conclusions

Overall Stomach Cancer

A statistically significant elevated risk of overall stomach cancer among snus users was not reported in two case-control studies (Hansson et al. 1994; Ye et al. 1999) and a cohort study (Boffetta et al. 2005) of moderate quality. Only Ye et al. (1999) examined the risk of overall stomach cancer among exclusive snus users, while the other two studies controlled for smoking. Ye et al. (1999) additionally controlled for alcohol consumption, an important potential confounder. Overall, the available studies provide *limited/suggestive evidence of no association* between use of snus and overall stomach cancer.

Cardia Stomach Cancer

Among the two case-control studies (Lagergren et al. 2000; Ye et al. 1999) and cohort study (Zendehdel et al. 2008) of moderate quality that examined the potential relationship between snus use and cardia stomach cancer, none reported any statistically significant increase in risk. The authors of the two case-control studies controlled for alcohol consumption, an important potential confounder, and reported no significant trend in risk of cardia cancer with increasing intensity or duration of snus use. Zendehdel et al. (2008), however, was the only study that included an analysis among never-smokers, while the two case-control studies controlled for other tobacco use among snus users. Overall, these three studies provide support of our previous conclusion that the available studies provide *limited/suggestive evidence of no association* between use of snus and cardia stomach cancer.

Non-Cardia Stomach Cancer

The potential relationship between non-cardia stomach cancer and snus use was examined in a case-control (Ye et al. 1999) and cohort study (Zendehdel et al. 2008), both of moderate quality. Ye et al. (1999) did not report elevated risks of non-cardia stomach cancers including distal gastric cancer of

the intestinal type, and distal gastric cancer of the diffuse type. Zendehdel et al. (2008) reported a statistically significant increased risk of non-cardia stomach cancer among never-smoking snus users overall, and in participants aged 70 or older (but not among participants under age 70). These results were based on few cases (n=8 cases among snus users overall, and n=5 in the older age group). The authors did not observe an elevated risk of non-cardia stomach cancer among total participants or among ever-smokers, adjusted for smoking. Neither study included adjustments for alcohol consumption, an important potential confounder. Overall, the available studies provided *inadequate/insufficient evidence to determine whether an association exists* between snus use and non-cardia stomach cancer.

2.3.4 Colorectal and Anal Cancer

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

Nordenvall and colleagues (2010) examined the impact of smoking and snus use on anal and colorectal cancer incidence among 336,381 males in the Swedish construction worker cohort. There was no excess risk of colon (RR=1.08; 95% CI: 0.91-1.29), rectal (RR=1.05; 95% CI: 0.85-1.31), or anal (RR=0.61; 95% CI: 0.07-5.07) cancer among exclusive users of snus. No dose-response relationships were observed based on duration of snus use at inclusion, however a significantly elevated risk was observed for the left-sided colon sub-site among snus users with 35-44 years of total estimated snus use at inclusion and during follow-up. A significant excess was not observed among the group with at least 45 years of total estimated snus use. The authors commented that the results among the 35-44 year group were imprecise, that multiple significance testing may have generated borderline significant results by chance, and that larger studies were warranted.

Quality Rating of All Studies

Study	Endpoint(s)	Evidence Quality Rating
Nordenvall et al. 2010	Colon cancer; right-sided colon cancer; left-sided colon cancer; cancer of the rectum; cancer of the anus	Strong (Colon and Rectal Cancer) Moderate (Anal Cancer)

Discussion and Conclusions

The evidence for colon and rectal cancer presented by Nordenvall et al. (2010) was rated as strong, due to the prospective design large number of participants investigated/high statistical power, long follow up, restriction to pure snus users, and evaluation of a potential duration-response relationship. Based on this, and the results presented above, the Nordenvall et al. (2010) study provides *limited/suggestive evidence of no association* between use of snus and colon and rectal cancer.

The evidence for anal cancer was rated as moderate, due to the observation of only a single anal cancer case observed among pure snus users, which resulted in hazard ratios with wide confidence intervals. For this reason, the Nordenvall et al. (2010) study provides *inadequate/insufficient evidence to determine whether an association exists* between snus use and anal cancer.

2.3.5 Kidney and Bladder Cancer

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

The cohort study conducted by Boffetta and colleagues (2005) also presents data on the relationship between snus use and development of kidney and bladder cancers. The authors concluded that the use of snus (either current or former) was not associated with any increase in the risk of kidney or bladder cancer. In fact, current snus users had a significantly lower risk of kidney cancer than did never-users (RR=0.47; 95% CI: 0.23-0.94).

Quality Rating of All Studies

Study	Endpoint(s)	Evidence Quality Rating
Boffetta et al. 2005	Kidney and urinary bladder cancer	Moderate

Discussion and Conclusions

Elevated risks of kidney or bladder cancer were not observed in the cohort study conducted by Boffetta et al. (2005). Relative risks were below 1.0 for ever and current users of snus for both kidney and bladder cancer, including a statistically significant decreased risk of kidney cancer among current snus users. This prospective study included over 10,000 Norwegian men, though the available evidence was rated as moderate quality due to the lack of analyses among exclusive snus users, and adjustment for potential confounders (relative risks were adjusted only for age and other tobacco use). The available evidence suggests a decreased risk of these cancers among snus users, with potential confounding from smoking unlikely to have biased the results towards a lower risk. However, given that only one moderate quality study was available, the available study provides *inadequate/insufficient evidence to determine whether an association exists* between snus use and kidney or bladder cancer.

2.3.6 Lung Cancer

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

Three large cohort studies have collected data on the relationship between use of snus and lung cancer (Boffetta et al. 2005; Bolinder et al. 1994; Luo et al. 2007). These studies found no evidence that use of snus increases the risk of lung cancer.

Quality Rating of All Studies

Study	Evidence Quality Rating
Boffetta et al. 2005	Moderate
Bolinder et al. 1994	Moderate
Luo et al. 2007	Moderate

Discussion and Conclusions

Three large cohort studies, two involving participants of the Swedish Construction Worker cohort (Bolinder et al. 1994; Luo et al. 2007), and the third involving 10,000 Norwegian men (Boffetta et al. 2005), reported that use of snus was not associated with a statistically significant increase in the relative risk of lung cancer. Furthermore, no trend was observed when the risk of lung cancer was evaluated by amount of snus consumed per day (Luo et al. 2007). Overall, the available studies provide *limited/suggestive evidence of no association* between use of snus and lung cancer.

2.3.7 Skin Cancer & Melanoma

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

Odenbro and colleagues (2005; 2007) examined the relationship between use of snus and several forms of skin cancer in two analyses of the construction worker cohort. An initial analysis (Odenbro et al. 2005) examined the effect of tobacco use on the risk of cutaneous squamous cell carcinoma (CSCC) among 337,311 male construction workers who were followed for 30 years. The authors found that snuff use was not associated with any increased risk; in fact, it was associated with a significantly decreased risk of CSCC (RR=0.64; 95% CI: 0.44-0.95).

In their second analysis, Odenbro and colleagues (2007) examined data from 339,802 male construction workers to determine whether tobacco use was associated with any of four types of melanoma, including all melanoma, cutaneous malignant melanoma (CMM), melanoma in situ (MIS), and intraocular malignant melanoma (IMM). Snuff-only users had a significantly reduced risk of CMM (RR=0.63; 95% CI: 0.48-0.81) and all melanoma (RR=0.65; 95% CI: 0.52-0.82), a non-statistically significant reduced risk of MIS (RR=0.64; 95% CI: 0.36-1.14), and there was no effect on IMM (RR=1.14; 95% CI: 0.43-3.07). Risk of CMM decreased with increasing duration of snuff use. The authors note that the biological mechanisms behind these findings are unclear, and that this cohort is relatively young, with some workers not reaching the mean age for melanoma diagnosis.

Quality Rating of All Studies

Study	**Endpoint(s)**	**Evidence Quality Rating**
Odenbro et al. 2007	All melanoma; cutaneous malignant melanoma (CMM); melanoma in situ (MIS); intraocular malignant melanoma (IMM)	Strong (all melanoma, CMM, MIS) Moderate (IMM)
Odenbro et al. 2005	Cutaneous squamous cell carcinoma (CSCC)	Strong

Discussion and Conclusions

The evidence for CSCC, all melanoma, CMM, and MIS presented by Odenbro et al. (2005; 2007) was rated as strong, due to the prospective design, large number of participants investigated/high statistical power, long follow up, restriction to pure snus users, and evaluation of a potential duration-response relationship. Relative risks of CSCC, all melanoma, and CMM decreased significantly with increasing duration of snus use. Although Odenbro et al. (2005) did not control for sunlight exposure, occupational sunlight exposure had been previously evaluated in this cohort, and no association was found. Odenbro et al. (2007), however, did control for this potential confounder. Based on these reasons, and the results presented above, these studies provide *limited/suggestive evidence of an inverse association* between use of snus and CSCC, all melanoma, and CMM, and *limited/suggestive evidence of no association* for MIS.

The evidence for IMM was rated as moderate, due to the observation of few reported cases, which resulted in relative risk ratios with wide confidence intervals. For this reason, the Odenbro et al.

(2007) study provides *inadequate/insufficient evidence to determine whether an association exists* between snus use and IMM.

2.3.8 Hematopoietic Cancer

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

Two analyses by Fernberg and colleagues (2006; 2007) investigated the role of tobacco use and BMI in the development of various hematopoietic malignancies. An initial study (Fernberg et al. 2006) evaluated the effect of these factors on the incidence of malignant lymphomas, specifically non-Hodgkin's lymphoma (NHL) or Hodgkin's disease (HD), among 335,612 male and female Swedish construction workers. There was no link between snuff use and risk of NHL, even among men who had used snuff for more than 30 years (incidence rate ratio (IRR)=0.69; 95% CI: 0.41-1.15). With respect to HD, the overall analysis did not show snuff use to be associated with significant increased risk. However, men who had used snuff for more than 30 years had a significantly increased risk of HD (IRR=3.78; 95% CI: 1.23-11.15). This is a novel finding that must be verified by additional studies, and it was based on only four cases, which limits the statistical power of the finding. Women who had ever used snuff were not at significantly increased risk of either NHL or HD, however, only one woman used snus out of 17,691 women surveyed in the cohort.

In their second study, Fernberg and colleagues (2007) investigated the role of tobacco smoking, oral moist snuff use, and BMI on the incidence of leukemia and multiple myeloma (MM) among 336,381 Swedish male construction workers. The authors reported that exclusive use of snuff was not associated with an increased risk of either acute lymphocytic leukemia (IRR=1.24; 95% CI: 0.39-4.01), acute myelogenous leukemia (IRR=0.81; 95% CI: 0.41-1.60), chronic myelogenous leukemia (IRR=1.17; 95% CI: 0.60-2.28), or multiple myeloma (IRR=0.92; 95% CI: 0.61-1.40), after adjustment for age and BMI.

Newly Identified Studies

A single case-control study that investigated the potential relationship between snus use and NHL, published prior to the 2013 ENVIRON report was identified during the retrospective literature search of the health effects of snus through December 1, 2012 (Hardell et al. 1994). The study consisted of men aged 25 to 85 years who were admitted to the Department of Oncology in Umea, Sweden between 1974 and 1978 with histopathologically verified NHL, including 105 cases in total, of which 35 were snuff users. The authors did not find a statistically significant increased odds of NHL among snus users (unadjusted odds ratio:1.5; 95% CI: 0.9-2.5). Because of the low number of exposed cases, and the lack of adjustment for potential confounders, the quality of this evidence was rated as weak.

Quality Rating of All Studies

Study	**Endpoint(s)**	**Evidence Quality Rating**
Fernberg et al. 2007	Acute lymphocytic leukemia (ALL); acute myelogenous leukemia (AML); chronic myelogenous leukemia (CML); multiple myeloma (MM)	Moderate (ALL, AML, CML) Strong (MM)
Fernberg et al. 2006	non-Hodgkin's lymphoma (NHL);	Strong (NHL)

	Hodgkin's disease (HD)	Moderate (HD)
Hardell et al. 1994	non-Hodgkin's lymphoma (NHL)	Weak

Discussion and Conclusions

Multiple Myeloma

The evidence for MM presented by Fernberg et al. (2007) was rated as strong, due to the prospective design, large number of participants investigated/high statistical power, long follow up, and restriction to pure snus users. Based on these reasons, and the results presented above, this study provides *limited/suggestive evidence of no association* between snus use and MM.

Leukemia (ALL, AML, CLL)

Fernberg et al. (2007) also reported that snus use was not associated with increased risk of leukemia (ALL, AML, CML). The overall cohort was large, though there were few cases of each of the leukemias and thus lowering statistical power. Based on this single study providing moderate quality evidence for these endpoints, there is *limited/suggestive evidence of no association* between snus use and ALL, AML, and CML.

Lymphomas (NHL and HD)

The observational analyses of NHL conducted by Fernberg et al. (2006) was rated as strong due to the prospective design, large cohort, long follow-up, restriction to pure snus users, and evaluation of a potential duration-response relationship. The evidence for HD was rated as moderate due to the low number of exposed cases in the duration-response analyses. No increased risks of NHL or HD were reported to be associated with snus use. The analyses were adjusted for age, and BMI. When the authors stratified by years of snus use, they reported a significant association between snus use for more than 30 years and HD. However, the statistical power was limited in that there were only four cases for this specific finding. The case-control study conducted by Hardell et al. (1994) also found no increased odds of NHL with snus use. However, due to the lack of control for any potential confounding variables, and limited statistical power (only 35 cases reported snus use), the study was rated as weak. Based on these two studies presenting analyses of varying quality, there is *limited/suggestive evidence of no association* between snus use and NHL, and *inadequate/insufficient evidence to determine whether an association exists* between snus use and HD.

2.3.9 Smoke-Related Cancer

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

The cohort study by Roosaar and colleagues (2008) presents data on the risk of smoke-related cancers among approximately 10,000 Swedish men. With respect to smoke-related cancers, a significantly elevated risk was observed among never-smoking ever-daily snus users (HR=1.6; 95% CI: 1.1-2.5). Contrary to what would be expected, a significantly elevated risk was not observed among snus users that included smokers, as smoking alone was significantly associated with both the development of any cancer and smoke-related cancers in the analysis. Residual confounding from smoking or misclassification of tobacco use are important concerns, nonetheless, the authors concluded that relative risks of the outcomes studied were consistently lower among snus users than those associated with smoking.

Quality Rating of All Studies

Study	Endpoint(s)	Evidence Quality Rating
Roosaar et al. 2008	"Smoke-related cancer," corresponding to ICD-7 codes 140-148	Moderate

Discussion and Conclusions

The study conducted by Roosaar and colleagues (2008) followed a large cohort of Swedish men for 29 years. Among snus users who never smoked, there was a statistically significant elevated risk of smoke-related cancer. However, among snus users who also smoked daily or occasionally, the risk for smoke-related cancer was not elevated. This study did not assess tobacco habits after study entry, and misclassification may have occurred due to changing of tobacco habits over the almost three-decade long study. Based on this single study, there is *inadequate/insufficient evidence to determine whether an association exists* between snus use and smoke-related cancer.

2.3.10 All Cancers

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

The cohort study by Bolinder and colleagues (1994) presented data on death due to any type of cancer among 84,781 male construction workers. There was no excess risk of cancer mortality among the 6,297 "smokeless tobacco (snuff)" users in this cohort. The study did not examine specific types of cancer, except for lung cancer, possibly due to relatively small numbers of cancers (there were only 96 malignancies among 6,297 snus users).

Roosaar and colleagues (2008) presented data on the risk of any type of cancer in addition to smoking-related cancers among approximately 10,000 Swedish men followed for 29 years. For any cancer type, no excess risk was observed among never-smoking, ever-daily snus users and snus users that included some smokers. Residual confounding from smoking or misclassification of tobacco use are important concerns, nonetheless, the authors concluded that relative risks of the endpoints studied were consistently lower among snus users than those associated with smoking.

Quality Rating of All Studies

Study	Endpoint(s)	Evidence Quality Rating
Bolinder et al. 1994	All cancers	Moderate
Roosaar et al. 2008	"Any cancer," corresponding to ICD-7 codes 140-209	Moderate

Discussion and Conclusions

The evidence presented by Bolinder et al. (1994) and Roosaar et al. (2008) regarding the association between snus use and any cancer was rated as moderate. The study conducted by Bolinder and colleagues used a large cohort of construction workers and reported a relatively small occurrence of cancer deaths. The risk estimates were adjusted for age and region of origin, and the authors found no effect on risk even after adjustment for area of residence, BMI, blood pressure, diabetes, and heart symptoms. The study conducted by Roosaar et al. (2008) did not report increased risks of all cancer in both a smoking-adjusted analysis and an analysis restricted to never-smokers. The risk models were

adjusted for calendar period, alcohol consumption, and area of residence. These two studies of moderate quality provide *limited/suggestive evidence of no association* between snus use and cancer.

2.4 Cardiovascular Effects (Risk Factors and Disease)

2.4.1 Risk Factors for CVD

2.4.1.1 Blood Pressure and Heart Rate

Summary from 2013 ENVIRON Report

Though there appears to be acute increases in heart rate and blood pressure, it is not clear if blood pressure is elevated among regular snus users. A single cross-sectional study reported higher mean blood pressure and heart rates among snus users (Bolinder and de Faire 1998), but several additional studies did not identify group differences when compared to nontobacco users (Eliasson et al. 1991; Bolinder et al. 1997a; Bolinder et al. 1997b; Angman and Eliasson et al. 2008; Wennmalm et al. 1991).

Although the available studies on hypertension were described in the 2013 ENVIRON report, standardized conclusions were not provided. A discussion of the new studies as well as standardized conclusions accounting for the old and new evidence are provided below.

Newly Identified Studies

Acute Effects

Three new studies were identified that examined the potential acute effects of Swedish snus on blood pressure, heart rate, and other effects on the heart (e.g., heart rate variability) (Morente-Sanchez et al. 2015; Ozga et al. 2016; Zandonai et al. 2016). Morente-Sanchez et al. (2015) conducted a double-blind randomized crossover study in which 18 nonsmoking, non-snus-using male amateur football players in Spain consumed either a 1.0 g portion (8 mg of nicotine) of Swedish Match brand Catch White Eucalyptus snus or placebo 40 minutes prior to a fitness test. The authors examined the effect of snus use on heart rate variability, among other performance-related endpoints. At 35-minutes following snus administration, the authors observed a statistically significant decrease in heart rate variability, with no significant changes observed during the placebo session. In particular, values were reduced for the following measures: R-R interval (RRi) ($P<0.001$), root mean square of successive differences (rMSSD) ($P=0.05$), and instantaneous beat-to-beat variability of the data (SD1) ($P=0.04$). The authors noted that these results "confirm that nicotine leads to a reduced vagal tone," in line with previous results among smokers.

Ozga et al. (2016) conducted a clinical study in which six men and five women (age 19-26) who reported fewer than 100 lifetime uses of tobacco and no tobacco in the past three months were given ascending doses of nicotine in the form of Swedish Match brand General White Large snus. The session lasted for five hours, with 20-25 minutes separating the end of a pouch and the start of the next pouch. Nicotine doses ascended from 0.0, 1.6, 3.2, 4.8, 6.4, to 8.0 mg. Statistically significant main effects of dose were observed across dose groups during the experimental session including a decrease in heart rate, and increases in systolic and diastolic blood pressure. Significant dose-time interactions were also observed for heart rate and systolic blood pressure. Heart rate generally decreased from pre- to post-dose for the initial snus doses, but increased toward the end of the session. Systolic blood pressure increased from pre- to post-dose at nearly every active dose, though

these increases were significant only for the final, 8.0 mg nicotine dose. Little to no change was observed in diastolic blood pressure during the session, except following the final dose, where diastolic blood pressure was significantly higher than after all other doses.

Zandonai et al. 2016 conducted a double-blind, randomized crossover study of 12 healthy, non-smoking and non-snus-using men (age 18-45). Participants received either Swedish Match brand Catch White Eucalyptus snus (8.0 mg nicotine), or a snus placebo. The authors examined a variety of factors, including potential heart rate and blood pressure changes during an endurance exercise activity following use of Swedish snus or snus placebo. Heart rate and systolic blood pressure did not differ significantly between the Swedish snus and snus placebo groups during the exercise, while diastolic blood pressure at time to exhaustion during the activity was significantly lower in the Swedish snus group (73.10 ± 8.53 mmHg) compared to the snus placebo group (80.70 ± 8.56 mmHg). The authors concluded that "nicotine induced diastolic hypotension at exhaustion."

Non-acute Effects

Two new studies were identified that examined the potential non-acute effects of snus use on blood pressure and heart rate (Bjorkman et al. 2017; Overland et al. 2013). Bjorkman et al. (2017) conducted a clinical study in which the potential effects of snus cessation after several years of use were examined in 24 participants with a history of snus use exceeding two years. The authors compared various endpoint measures between a snus cessation group (5 females, 19 males) and a group that continued to use snus as usual (2 females, 9 males). Although heart rate and blood pressure improved (decreased) following cessation of snus, there were no statistically significant differences in these measures between the cessation group and the control group that continued to use snus.

Overland et al. (2013) examined the potential relationship between snus use and cardiovascular risk factors in a cross-sectional study involving a general population sample of 25,163 participants from the 3rd wave of the Nord-Trondelag Health Surveys (HUNT3) in the county of Nord-Trondelag, Norway. Following adjustment for age, smoking, gender, education, physical exercise, and frequency of alcohol use, the authors reported a statistically significant higher systolic blood pressure among "extensive" snus users (b=1.98; 95% CI: 0.87, 3.1) compared to never-users of snus. No differences in systolic blood pressure were observed among former users, those who use snus "sometimes," or daily users compared to never-users of snus. No significant differences in diastolic blood pressure were observed between any of the previously mentioned snus use categories compared to never-users of snus. The authors noted that the associations observed in this study were "generally quite weak, and not particularly consistent."

Hypertension

A single new study examined the potential relationship between snus use and high blood pressure (Byhamre et al. 2017). Byhamre et al. (2017) examined the risk of metabolic syndrome and its components, including high blood pressure, among 880 Swedish compulsory school students who had attained the 9th grade (age 16) in 1981. This sample consisted of students from the municipality of Lulea, as part of the 27-year prospective Northern Swedish cohort. The participants completed self-administered questionnaires at baseline and follow-ups at ages 16, 21, 30, and 43. At age 43, participants underwent a health exam, the results of which were used to define the presence of metabolic syndrome in each participant. Tobacco use information was self-reported at baseline and at

each follow-up. The authors noted that health exams at age 16 were "insufficient to determine exact presence of the metabolic syndrome," and "could not exclude prevalent cases at baseline." They further noted, however, that only five of the 880 participants had a BMI of 30 or greater at age 16, and suggested that "the number was considered too low to alter the results significantly." Strictly speaking, this study did not meet the criteria for a prospective cohort study, unless one assumes that the effect of some prevalent cases of metabolic syndrome at baseline is negligible, and that only participants that used snus throughout all four periods are considered to ensure that initiation of snus use likely preceded development of metabolic syndrome. Regardless, analyses of metabolic syndrome components, including high blood pressure, appear to be cross-sectional. The risk of high blood pressure (≥130 mm Hg systolic and/or ≥85 mm Hg diastolic) for current snus users who have never smoked was statistically significantly elevated (odds ratios were around 2.0) only for crude analyses at ages 21, 30, and 43, and the risk was attenuated and no longer statistically significant (for all age groups) when the analyses were adjusted for sex, cumulative smoking, BMI at 16 years, socioeconomic status at 16 years, family history of diabetes, alcohol consumption at 43 years, and physical activity at 43 years compared to never-users of tobacco. The authors also reported that high blood pressure was associated with cumulative snus use over the four periods, though the association did not remain significant in the fully adjusted model. Given the lack of an association when analyses were adjusted for potential confounding variables, the authors noted that "this indicated that differences between non-tobacco users and snus users regarding the potential confounders, rather than snus itself, may explain the associations."

Quality Rating of all Studies

Study	**Endpoint(s)**	**Evidence Quality Rating**
Acute Effects		
Bolinder et al. 1997b	Heart rate and blood pressure	Moderate
Bolinder and de Faire 1998	Heart rate and blood pressure	Moderate
Hirsch et al. 1992	Heart rate and blood pressure	Moderate
Lunell and Curvall 2011	Heart rate	Moderate
Morente-Sanchez et al. 2015	Heart rate variability	Moderate
Ozga et al. 2016	Heart rate and blood pressure	Moderate
Rohani and Agewall 2004	Heart rate and blood pressure	Moderate
Sundstrom et al. 2012	Heart rate, blood pressure, and ventricular heart function.	Moderate
Zandonai et al. 2016	Heart rate and blood pressure	Moderate
Non-Acute effects		
Angman and Eliasson 2008	Blood pressure	Weak
Bjorkman et al. 2017	Heart rate and blood pressure	Moderate
Bolinder et al. 1997a	Heart rate and blood pressure	Weak
Bolinder et al. 1997b	Heart rate and blood pressure	Moderate
Eliasson et al. 1991	Heart rate and blood pressure	Weak
Janzon and Hedblad 2009	Blood pressure	Weak
Norberg et al. 2006	Blood pressure	Weak

Overland et al. 2013	Blood pressure	Weak
Sundstrom et al. 2012	Blood pressure	Weak
Wennmalm et al. 1991	Blood pressure	Weak
High Blood Pressure / Hypertension		
Bolinder et al. 1992	Hypertension	Weak
Byhamre et al. 2017	High blood pressure	Moderate
Hergens et al. 2005	Hypertension	Weak
Hergens et al. 2008a	High blood pressure and hypertension	Moderate
Janzon and Hedblad 2009	Hypertension	Weak
Norberg et al. 2006	Hypertension	Weak

Discussion and Conclusions

Acute Effects on the Heart and Blood Pressure

The findings reported in the three new studies on the acute cardiovascular effects of Swedish snus were mixed, and differed in some ways from most of the studies reviewed in the 2013 ENVIRON report. The newly published studies were limited due to a small number of participants, though they were strengthened by their experimental design. Additionally, all three were unique in that they are the first available experimental studies that examined the acute effects of snus on the heart and blood pressure of tobacco-naïve users. Evidence from all the available studies investigating acute effects, including those newly published, was rated moderate in quality.

With respect to heart rate, most of the available studies, indicate acute, transient increases in heart rate at least after 20 minutes or so following snus use. The results from the new study conducted by Ozga et al. (2016) are consistent with these findings in that heart rate increases were observed towards the end of the experimental session (though there was a decrease initially). The new study by Zandonai et al. (2016), however, reported no differences in heart rate during exercise between those who used Swedish snus and those who used a snus placebo. Overall, the available studies provide *limited/suggestive evidence of an association* between snus use and acute increases in heart rate.

Similarly, blood pressure tended to increase, particularly systolic, following consumption of Swedish snus in most of the available studies. Results from the new study by Ozga et al. (2016) are consistent with this, though the results from the new study by Zandonai et al. (2016) did not indicate an increase in blood pressure during exercise following snus use (a decrease in diastolic blood pressure was actually observed at time during exhaustion during the experiment). However, overall, the available studies provide *limited/suggestive evidence of an association* between snus use and acute increases in blood pressure.

Two other studies have examined the potential relationship between snus use and acute effects on ventricular heart function (Sundstrom et al. 2012), and heart rate variability (Morente-Sanchez et al. 2015). Smoking habits were not described in the Sundstrom et al. (2012) study. These studies provide *inadequate/insufficient evidence to determine whether an association exists* between snus use and either endpoint.

Non-Acute Effects on Heart Rate and Blood Pressure

Two new studies provided additional evidence of a positive relationship between snus use and increased heart rate and blood pressure. Though most of the available studies do not suggest a

relationship exists, two moderate quality studies are suggestive of an association, while most of the studies that do not suggest an association are of weak quality (with the exception of a single moderate quality study). Overall, the evidence of an association between snus use and a non-acute increase in blood pressure and heart rate is *balanced/mixed*.

High Blood Pressure / Hypertension

A single new, cross-sectional study reported an increased risk of high blood pressure in snus users compared to never-users of tobacco in crude analyses, but not in analyses adjusted for various potential confounders (Byhamre et al. 2017). Two other previously reviewed cross-sectional studies reported an increased risk of hypertension (Bolinder et al. 1992; Hergens et al. 2005). In another cross-sectional analysis, Hergens et al. (2008b) reported an increased risk of high blood pressure at baseline), but when those free of hypertension at baseline were examined prospectively, the risk of developing hypertension at follow-up among snus users was not elevated in the overall cohort. The authors of two additional studies that did not account for the potential confounding effects of smoking did not report a relationship between snus use and hypertension (Janzon and Hedblad 2009; Norberg et al. 2006). Overall, the evidence of an association between snus use and high blood pressure or hypertension is *balanced/mixed*.

2.4.1.2 Lipid Levels

Summary from 2013 ENVIRON Report

Several cross-sectional studies examined lipid measurements (high-density lipoprotein (HDL) or low-density lipoprotein (LDL)), triglycerides, or apolipoproteins (Bolinder et al. 1997a; Eliasson et al. 1991; Eliasson et al. 1995). One case-control study examined whether controls who were snus users had increased risk of hyperlipidemia compared to controls who never used snus, controlling for smoking in multivariate analysis (Hergens et al. 2005). None of these studies reported increased prevalence of these lipid measurements among snus users compared to the nontobacco users. Norberg et al. (2006) and Wallenfeldt et al. (2001) examined the potential relationship between snus use and triglyceride and cholesterol levels, but were excluded from this evaluation because the analyses were not adjusted for current smoking (29% of the population of snuff users studied were current smokers).

Newly Identified Studies

Three new studies were identified that examined the potential effects of snus use on blood lipid levels (Bjorkman et al. 2017; Byhamre et al. 2017; Overland et al. 2013). Bjorkman et al. (2017), described previously, conducted a clinical study in which the potential effects of snus cessation after several years of use were examined in 24 participants with a history of snus use exceeding two years. Although cholesterol levels (total, LDL) increased following cessation of snus, there were no statistically significant differences in these measures between the cessation group and the control group that continued to use snus. HDL levels remained relatively unchanged. The authors concluded that the "effects of snuff on CVD risk factors are unsettled."

Byhamre et al. (2017), described previously, conducted cross-sectional analyses of the potential relationship between exclusive snus use and raised/high triglycerides and low HDL cholesterol. In crude analyses, the authors reported statistically significant increased risks of raised triglycerides among snus users at age 16, 21, and 30, but not at age 43 (statistically significant odds ratios ranged from 1.83 to 2.21) compared to never-users of tobacco. After adjusting for sex, BMI at 16 years,

socioeconomic status at 16, family history of diabetes, alcohol consumption at age 43, and physical activity at age 43, none of these results remained significant. Compared with never-users of tobacco, no significant increased risk was observed for low HDL cholesterol among exclusive snus users in crude or adjusted analyses.

Overland et al. 2013, described previously, conducted a cross-sectional study and reported statistically significant higher levels of HDL cholesterol among snus users who use snus "sometimes," daily users, and extensive users compared to never-users of snus following adjustment for age, smoking, gender, education, physical exercise, and frequency of alcohol use. The authors referred to these results among snus users as "beneficial," and noted that "snus use was associated with more favourable HDL-cholesterol levels." No statistically significant difference was reported for former snus users. Compared to current exclusive snus users, never-users of tobacco had significantly lower HDL. Statistically significant higher levels of triglycerides were reported among former and "sometimes" snus users, but not among daily, or extensive snus users. Compared to current exclusive snus users, never-users of tobacco did not have significantly different levels of triglycerides. Though the authors noted that Norwegians who use snus extensively faced an increased risk of higher HDL cholesterol, they concluded that "the significant associations between snus use and the cardiovascular risk factors we found were generally quite weak, and not particularly consistent."

Quality Rating of all Studies

Study	**Endpoint(s)**	**Evidence Quality Rating**
Bjorkman et al. 2017	Cholesterol levels after cessation of snus	Strong
Bolinder et al. 1997a	Cholesterol, apolipoprotein, and triglyceride levels	Weak
Byhamre et al. 2017	Low HDL, raised triglycerides	Moderate
Eliasson et al. 1991	Cholesterol, and triglyceride levels	Weak
Eliasson et al. 1995	Cholesterol, and triglyceride levels	Weak
Hergens et al. 2005	Hyperlipidemia	Weak
Norberg et al. 2006	Triglycerides ≥ 1.7 mmol/L	Excluded
Overland et al. 2013	HDL, and triglyceride levels	Weak
Wallenfeldt et al. 2001	Cholesterol, and triglyceride levels	Excluded

Discussion and Conclusions

Most of the previously evaluated studies involved cross-sectional analyses of potential differences in lipid levels between tobacco user (and non-user) groups, including Swedish snus users (Bolinder et al. 1997a; Eliasson et al. 1991; Eliasson et al. 1995). No statistically significant differences were reported in any of these studies. Hergens et al. (2005) conducted a cross-sectional analysis of the potential risk of hyperlipidemia among snus users compared to never users of snus. No increased risk was observed among snus users. Due largely to the cross-sectional design of these studies, they were rated as weak.

Some results from one of three newly identified studies contradict findings from the earlier studies. Byhamre et al. (2017) reported an increased risk of raised triglycerides among snus users at age 16, 21, and 30, but not at age 43. This study was rated as moderate, though it would have otherwise been rated as weak since each individual analysis was cross-sectional, although there was an element of prospective follow-up given that the population was evaluated at different ages over the course of the participants' lives. The authors reported that snus users faced no increased risk of low HDL (i.e., good cholesterol) compared to never users of tobacco. Overland et al (2013) and Bjorkman et al. (2017) reported generally favorable results among snus users. For example, Bjorkman et al. (2017) conducted a clinical study (rated as strong) in which total and LDL cholesterol levels increased in regular snus users that stopped using it (though plasma levels were not significantly different from participants that continued using snus). Overland conducted a cross-sectional study (rated as weak) and reported higher levels of HDL (good cholesterol) in snus users compared to never-users of tobacco, with no differences in triglyceride levels observed.

Although most of the studies are cross-sectional, a single, strong clinical study supports the consistent lack of an association observed between snus use and increased levels of certain lipids (or a lack of an association with hyperlipidemia). Overall, there is *limited/suggestive evidence of no association* between snus use and unhealthy blood levels of lipids.

2.4.1.3 Other Indicators of Cardiovascular Disease Risk

Summary from 2013 ENVIRON Report

Biochemical or Physical Measures of Clotting

Several cross-sectional studies examined other biochemical or physical measures of clotting or of atherosclerosis among snus users compared to nontobacco users; these include indicators such as carotid artery diameters and lumen thickness, to which may indicate increased risk of CVD events (Bolinder et al. 1997a; Eliasson et al. 1991; Eliasson et al. 1995; Wennmalm et al. 1991). In these studies, none reported a significant difference between snus users and nontobacco users.

Two analyses of a population of healthy male firefighters showed no significant difference between smokeless tobacco users and non-users of tobacco with respect to measurements of carotid wall thickness, lumen diameter, or the presence of carotid plaques (Bolinder et al. 1997a) or an "atherogenic index" (Bolinder 1997). A cross-sectional study of clinically healthy men by Wallenfeldt and colleagues (2001) found no statistically significant association between use of oral moist snuff and any ultrasound-assessed measures of subclinical atherosclerosis (intima-media thickness in the carotid bulb, carotid artery, or femoral artery, or carotid or femoral plaques). However, Wallenfeldt et al. (2001) was excluded because approximately 29% the population of snuff users examined in the study were current smokers.

Additionally, an experimental study of 20 healthy, middle-aged men and women suggests that acute use of Swedish snuff may be associated with endothelial dysfunction, but the study's authors do not describe the smoking status of the participants, and therefore, the results of this study were previously excluded (Rohani and Agewall 2004). As this was a controlled, experimental study of the acute effects of snus, these results should have been considered relevant in the 2013 ENVIRON report, and are therefore being included in this update.

Measures of Fitness: Oxygen Uptake, Work Capacity, Cardiac Output

The results of four studies on the potential effects of snus use and oxygen uptake/work capacity were presented in the 2013 ENVIRON Report. No statistically significant difference in work capacity was observed between snus users and non-users of tobacco in three cross-sectional studies (Bolinder et al. 1997b; Bolinder and de Faire 1998; Wennmalm et al. 1991) and one experimental study (Hirsch et al. 1992).

Cardiovascular/circulatory symptoms
A large cross-sectional study of Swedish construction workers found a significantly higher risk of reporting cardiovascular/circulatory symptoms (i.e., breathlessness on slight effort, chest pain walking up hill, pain in the leg while walking, white finger symptoms) among "smokeless tobacco" users compared to nonusers of tobacco (Bolinder et al. 1992).

Allostatic Load
In a study of participants from the Northern Swedish Cohort, Gustafsson and colleagues (2011a) examined demographic and behavioral factors that affected allostatic load. In addition to biologic parameters such as systolic and diastolic blood pressure, fasting glucose, and blood lipid measurements in participants, salivary cortisol concentrations used as a measure of total cortisol secretion, were summed in an index used as a measure of allostatic load. Sociodemographic variables and behaviors, including snus use and smoking, were examined in a multivariate model as predictors of allostatic load. Smoking, but not snus use, was found to be a significant predictor of allostatic load (stress) in men. In women, neither tobacco type was significantly associated with allostatic load.

Newly Identified Studies

Two new studies were identified that examined the potential effects of snus use on other indicators of cardiovascular disease risk, including endothelial function (FMD) (Skaug et al. 2016) and cardiac output (Zandonai et al. 2016). Zandonai et al. (2016) conducted a double-blind, randomized crossover clinical trial in which 12 healthy male non-tobacco users used snus or a placebo during exercise. No significant difference between snus or snus placebo were observed for cardiac output (Zandonai et al. 2016).

Skaug et al. (2016) conducted a cross-sectional study involving 5,633 men and women from the HUNT Fitness study, a subset of participants from the third wave of the Nord-Trondelag Health Study (HUNT3). The authors excluded participants with established cardiovascular disease, and the healthiest subset of the population self-selected into the study. The authors examined the potential relationship between exclusive snus use and endothelial function (flow mediated dilation: percent difference in vessel diameter) compared to non-users of tobacco. This relationship was also examined by physical activity level (i.e., recommended, not recommended) and aerobic capacity (i.e., low, high). Although the authors noted that "snuff-users had a clear tendency towards lower endothelial function compared to non-users," there were no statistically significant differences in FMD between exclusive snuff users, including most subgroups (overall, recommended physical activity, high aerobic capacity, low aerobic capacity). The percent difference in vessel diameter was -0.83% (95% CI: -1.59, -0.06) lower in exclusive snuff users that did not attain the recommended physical activity level compared to non-users of tobacco (the only statistically significant result).

Quality Rating of all Studies

Study	**Endpoint(s)**	**Evidence Quality Rating**

Bolinder et al. 1992	Cardiovascular/circulatory symptoms (breathlessness on slight effort, chest pain walking up hill, pain in the leg while walking, white finger symptoms)	Weak
Bolinder 1997	Atherogenic index	Weak
Bolinder et al. 1997a	Atherosclerotic indices (Wall thickness, lumen diameter, plaque %), Fibrinogen levels	Weak
Bolinder et al. 1997b	Oxygen uptake/work capacity	Moderate
Bolinder and de Faire 1998	Oxygen uptake/work capacity, low	Weak
Eliasson et al. 1991	Fibrinogen levels, white blood cell count	Weak
Eliasson et al. 1995	Fibrinogen levels	Weak
Gustafsson et al. 2011a	Allostatic load	Moderate
Hirsch et al. 1992	Maximum work load	Moderate
Rohani and Agewall 2004	Impaired endothelial function (flow-mediated dilatation)	Moderate
Skaug et al. 2016	Endothelial function: FMD	Weak
Wallenfeldt et al. 2001	Atherosclerosis, C-Reactive Protein	Excluded
Wennmalm et al. 1991	Thromboxane A2 production, Maximum work load	Weak
Zandonai et al. 2016	Cardiac output	Moderate

Discussion and Conclusions

Biochemical or Physical Measures of Clotting

The authors of four cross-sectional studies, rated as weak due largely to the study design, reported no differences between blood levels of biochemical measures of clotting (e.g., thromboxane A2 production, fibrinogen) between snus users and non-users of tobacco (Bolinder et al. 1997a; Eliasson et al. 1991; Eliasson et al. 1995; Wennmalm et al. 1991).

An experimental study, rated as moderate, suggests that acute use of Swedish snuff may be associated with endothelial dysfunction, though the study's authors do not describe the smoking status of the participants (Rohani and Agewall 2004). The results of a new cross-sectional study indicated no statistically significant differences in FMD between exclusive snuff users, including most subgroups (overall, recommended physical activity, high aerobic capacity, low aerobic capacity), except for those who do not engage in recommended physical activity levels.

Two cross-sectional analyses (also rated as weak) of a population of healthy male firefighters showed no significant difference between snus users and non-users of tobacco with respect to measurements

of carotid wall thickness, lumen diameter, or the presence of carotid plaques (Bolinder et al. 1997a) or an "atherogenic index" (Bolinder 1997).

Although most of the available studies on biochemical and physical measures of clotting were cross-sectional, the results indicate a consistent lack of a statistically significant difference in these measures between snus users and non-users of tobacco. Although some indication of a potential effect of snus use on endothelial function was reported in two studies discussed above, limitations of these studies preclude the ability to draw conclusions. However, endothelial dysfunction is believed to precede the development of atherosclerosis (Hadi et al. 2005). Given that no associations were reported between snus use and other biochemical components of atherogenesis (clotting factors), and no associations were reported between snus use and physical markers of atherosclerosis, the evidence overall is *limited/suggestive of no association* between snus use and biochemical and physical measures of clotting and atherosclerosis.

Measures of Fitness: Oxygen Uptake, Work Capacity, Cardiac Output

No statistically significant difference in work capacity or oxygen uptake was observed between snus users and non-users of tobacco in three cross-sectional studies (Bolinder et al. 1997b; Bolinder and de Faire 1998; Wennmalm et al. 1991) and one experimental study (Hirsch et al. 1992). A newly identified experimental study reported no differences in cardiac output during exercise following snus use, compared to placebo (Zandonai et al. 2016). Though the three cross-sectional studies were rated as weak, the results from these studies support those reported in the two experimental studies (rated as moderate). Based on these five studies, there is *limited/suggestive evidence of no association* between snus use and measures of fitness including oxygen uptake, work capacity, and cardiac output.

White Blood Cell Count

Eliasson et al. (1991) conducted a cross-sectional study, and compared levels of white blood cells in snus users with non-users of tobacco. An elevated white blood cell count is associated with an increased risk of cardiovascular events including coronary heart disease and ischemic stroke risk. Eliasson et al. (1991) reported white blood cell counts that were not statistically significantly different between the two groups. Because there is only a single study, which was rated as weak due largely to the cross-sectional study design, there is *inadequate/insufficient evidence to determine whether an association exists* between snus use and white blood cell count.

Cardiovascular/circulatory symptoms

The cross-sectional study conducted by Bolinder et al. (1992) was rated as weak, due to the cross-sectional design, and lack of control for any potentially confounding variables beyond age. Therefore, this study presents *inadequate/insufficient evidence to determine whether an association exists* between snus use and the cardiovascular/circulatory symptoms described by the authors including breathlessness on slight effort, chest pain walking up hill, pain in the leg while walking, and white finger symptoms.

Allostatic Load

In a prospective study of participants from the Northern Swedish Cohort, Gustafsson and colleagues (2011a) reported that snus use, which was investigated as a potential confounding variable with SES, was not associated with allostatic load. Overall, this single moderate study provides

inadequate/insufficient evidence to determine whether an association exists between snus use and allostatic load.

2.4.2 Chronic Cardiovascular Disease

2.4.2.1 Heart disease

Summary from 2013 ENVIRON Report

Twelve studies have evaluated the relationship between use of snus and various chronic cardiovascular diseases (CVDs). The following conclusions can be made about the use of snus and its possible effect on the risk of heart disease.

Most studies have not revealed an increased risk of myocardial infarction (MI) or an overall increased risk of CVD. A single study (Bolinder et al. 1994) found an increased risk only for fatal MI in an analysis of the Swedish Construction Worker cohort, and an analysis of heart failure among snus users controlled for smoking observed an increased risk especially in men ages 75 years and older (Arefalk et al. 2011). A large, pooled analysis, which pooled data from many of the major Scandinavian cohorts, confirmed previous findings that the use of snus is not associated with an increased risk of MI, and noted that slight increases in fatal MI may be explained by confounding (Hansson et al. 2012). Though there are known acute effects of nicotine on the cardiovascular system, no increased risk of cardiovascular disease has been detected epidemiologically, with the possible exception of a moderate increased risk of death due to a CV event. This increased risk of mortality due to a CV event among snus users has only been observed in the Construction Workers Cohort in Sweden (Bolinder et al. 1994).

Newly Identified Studies

Two new studies were identified that examined

Arefalk and colleagues (2014) followed a cohort of 20,911 MI patients who were admitted to a Swedish coronary care unit between 2005 and 2009 to investigate the effects of quitting snus on cardiovascular mortality and events. The population included 1,799 post-MI snus users and 675 post-MI snus quitters. The risk of cardiovascular events was reduced by over half (HR=0.38; 95%: CI 0.11-1.32) and mortality due to cardiovascular events was similarly decreased (HR=0.56; 95% CI: 0.16-2.00), though these risk estimates were not statistically significant. In this model, covariates were adjusted for age, sex, past smoking, present sun exposure, occupation status, and participation in a cardiac rehabilitation program. This study presented some limitations, including a lack of analyses that included exclusive snus users due to the low number of exposed cases, as well as comparisons with never users of tobacco. In a letter to the editor, Rodu and Phillips (2015) noted that the mortality rate was higher among non-users compared to continuing snus users and snus quitters.

Hergens et al. (2014) examined the potential relationship between snus use and atrial fibrillation, using pooled data including 425 current exclusive snus users and 3,069 snus non-users from a total population of 127,907 Swedish males from seven prospective cohort studies. Study entry took place between 1978 and 2004, though follow-up information was not provided, and exposure assessment was unclear and likely done at a single timepoint for all cohorts. Compared with never-smoking non-current snus users, there was no elevated risk of atrial fibrillation in never-smoking current snus users

(HR=1.07; 95% CI: 0.97-1.19). However, this study design may have biased the results toward null due to the reference group including never-smoking former snus users.

Reviews and Meta-analyses of Heart Disease Due to Use of Snus

One systematic review and meta-analysis of the epidemiological literature on snus use and the potential effect on ischemic heart disease (IHD) was published since the 2013 ENVIRON report (Vidyasagaran et al. 2016), but only included studies detailed in the previous ENVIRON report. The search strategy included a wide geographic range for smokeless tobacco, but the risks of fatal and non-fatal IHD were reported separately for European studies, all of which were based in Sweden where snus is the conventional smokeless tobacco product used. Based on seven risk estimates from Sweden, the overall relative risk of IHD was 0.91 (95% CI: 0.83-1.01), and in contrast, the overall risk of IHD deaths was 1.38 (95% CI: 1.13-1.67) based on three risk estimates (Vidyasagaran et al. 2016). This elevated risk of IHD mortality was statistically significant (p=0.001) in snus users with the referent group as non-users with adjustments for former smoking and excluding current smokers as each study required. The calculated combined risk of ischemic heart disease based on seven risk estimates from Sweden was not statistically significant (P=0.09). This publication draws strength in its explicit review criteria excluding study designs not case-control nor cohort, as well as only including studies with effective control of confounding and thorough definitions of exposure and outcome. However, the authors were unable to adjust for alcohol consumption and other potential confounding effects including blood pressure, serum lipids, BMI, and diabetes.

Quality Rating of All Studies

Study	**Endpoint(s)**	**Evidence Quality Rating**
Arefalk et al. 2011	Heart failure	Moderate
Arefalk et al. 2014	Post-MI Cardiovascular events and mortality from cardiovascular events	Moderate
Bolinder et al. 1994	Cardiovascular disease and ischemic heart disease mortality	Moderate
Haglund et al. 2007	Fatal and nonfatal Ischemic heart disease	Moderate
Hansson et al. 2009	Ischemic heart disease; cardiovascular disease	Strong
Hergens et al. 2005	Nonfatal and fatal myocardial infarction	Moderate
Hergens et al. 2007	Nonfatal and fatal myocardial infarction, post-MI fatal cardiovascular disease	Strong
Hergens et al. 2014	Atrial fibrillation	Strong
Huhtasaari et al. 1992	Myocardial infarction	Moderate

Huhtasaari et al. 1999	Myocardial infarction, and fatal myocardial infarction alone	Moderate
Janzon and Hedblad 2009	First ever myocardial infarction or ischemic heart disease	Moderate
Johansson et al. 2005	Coronary heart disease	Moderate
Roosaar et al. 2008	Cardiovascular death	Moderate
Wennberg et al. 2007	Myocardial infarction, fatal myocardial infarction within 28 days, sudden cardiac death with survival less than 24 hours and less than 1 hour	Moderate

Discussion and Conclusion

Fourteen epidemiological studies were included in this examination on snus use and cardiovascular diseases and events: four case-control studies (Hergens et al. 2005; Huhtasaari et al. 1992; Huhtasaari et al. 1999; Wennberg et al. 2007) and ten cohort studies (Arefalk et al. 2011; Arefalk et al. 2014; Bolinder et al. 1994; Haglund et al. 2007; Hansson et al. 2009; Hergens et al. 2007; Hergens et al. 2014; Janzon and Hedblad 2009; Johansson et al. 2005; Roosaar et al. 2008).

Incident ischemic heart disease, myocardial infarction, and heart failure

Of ten studies reported in eleven publications investigating incidence of ischemic heart disease, myocardial infarction (all cases or non-fatal), or heart failure, none reported evidence of an increased risk among snus users (Hergens et al. 2005; Huhtasaari et al. 1992; Huhtasaari et al. 1999; Wennberg et al. 2007; Hergens et al. 2007; Janzon and Hedblad 2009; Johansson et al. 2005; Haglund et al. 2007; Hansson et al. 2009; Arefalk et al. 2011; Arefalk et al. 2014). Two studies by Huhtasaari and colleagues (1992, 1999) found no evidence of an increased risk of myocardial infarction with snus use in their population-based Northern Sweden case-control studies. Wennberg and colleagues (2007), reported a similar lack of risk of myocardial infarction compared to non-users of tobacco and Hergens et al. (2005) estimated a relative risk for first acute myocardial infarction among current snus users who had never smoked to be less than 1: 0.73 (95% CI 0.35-1.5). A cohort study followed 3,120 healthy men and examined the incidence of coronary heart disease over an average follow-up of 11.2 years (Johansson et al. 2005). Men who used snus daily but never smoked were not at a significantly increased risk of coronary heart disease after adjustment for age, physical activity, BMI, diabetes, and hypertension. A follow-up study with an expanded cohort also reported no statistically significant excess risk of ischemic heart disease (Haglund et al. 2007). Janzon and Hedblad (2009) conducted a population-based cohort study that included male and female residents, and reported no increased risk of first-ever myocardial infarction. Hansson et al. (2009) similarly reported no increased risk of incidence of ischemic heart disease among current or former snus users nor in heavy users (4 or more cans of snus per week) and longtime users (20 or more years of snus use). During follow-up of a cohort of snus-using patients admitted to a coronary care unit after a

myocardial infarction, the risk of cardiovascular events was nonsignificantly reduced by over half in those who quit snus at the start of the study (Arefalk et al. 2014). Using the Swedish Construction Worker Cohort and another community-based sample of elderly men, current snus use was not significantly associated with risk of heart failure in either cohort with full adjustment for covariates (Arefalk et al. 2011). Also using the Construction Workers Cohort, Hergens and colleagues (2007) observed no increased overall risk of myocardial infarction among snus users though they did find a and increased risk of fatal myocardial infarction (See section below: "Fatal myocardial infarction and/or sudden cardiac death").

Based on strong evidence of no association from two studies (Hansson et al. 2009; Hergens et al. 2007) and moderate evidence of no association from nine additional studies, there is *limited/suggestive evidence of no association* between snus use and incident ischemic heart disease, myocardial infarction, or heart failure.

Fatal IHD, MI, and/or Sudden Cardiac Death

Five studies investigated the association between snus use and fatal myocardial infarction and/or sudden cardiac death; two cohort studies reported evidence of a statistically significant association (Bolinder et al. 1994; Hergens et al. 2007) and four studies (two cohort and two case-control) did not (Haglund et al. 2007; Hergens et al. 2005; Huhtasaari et al. 1999; Wennberg et al. 2007). Hergens and colleagues (2007) extended the follow-up of Bolinder et al.'s (1994) Swedish construction workers cohort through 2003. Information on snus use was obtained from follow-up visits starting in 1978. The study presented strong evidence, with the relative risk for fatal myocardial infarction statistically significantly elevated among current snus users overall (RR=1.32; 95% CI: 1.08-1.61), and at the lowest and highest consumption levels investigated (of four). This increased risk at the highest consumption level was only evident in the older age group (age 55-65). Wennberg et al. (2007) reported that never-smoking snus users did not have an increased risk of either myocardial infarction or sudden cardiac death with survival less than 24 hours. A population-based case-control study in two Swedish counties reported a nonsignificantly elevated relative risk estimate (OR=1.7; 95% CI: 0.48-5.5) for fatal myocardial infarction among current snus users who had never smoked (Hergens et al. 2005).

Though most of the available studies suggest no association between snus use and fatal MI, two publications evaluating the same population reported an increased risk (Bolinder et al. 1994; Hergens et al. 2007). With one of these studies presenting strong evidence (Hergens et al. 2007), we concluded that there is *balanced/mixed evidence of an association* between snus use and fatal myocardial infarction or sudden cardiac death. However, given the clear lack of an association of snus with incident IHD or MI, it's unclear how use of Swedish snus could plausibly and directly cause an increase in the risk of fatal MI.

Incident Cardiovascular Disease

A single study conducted by Hansson et al. (2009) presented strong evidence of no association between never-smoking current snus use and incident cardiovascular disease (RR=1.00; 95% CI: 0.69-1.46). Statistically significant increased risks were also not observed in heavy users (4 or more cans of snus per week) or longtime users (20 or more years of snus use). Based on this evidence, we concluded that there is *limited/suggestive evidence of no association* between snus use and incident CVD.

Fatal Cardiovascular Disease

Four studies investigated the potential relationship between snus use and fatal cardiovascular disease (CVD). Two Swedish population-based cohort studies did not report a statistically significant association with snus use (Roosaar et al. 2008; Arefalk et al. 2014), and two studies of participants from the Swedish Construction Worker cohort did report an association (Bolinder et al. 1994; Hergens et al. 2007). Bolinder et al. (1994) reported increased risks of death from all cardiovascular diseases in the overall cohort, among smokeless tobacco users aged 35-45 years, but not among older participants aged 55-65 years. Hergens et al. (2007) conducted an expanded follow-up of this cohort, and reported that snuff users that had previously experienced a non-fatal MI during follow-up had a statistically significant increased risk of death from cardiovascular disease compared with never-tobacco users (RR=1.55; 95% CI: 1.19–2.01). Misclassification of exposure and bias toward the null are concerns in cohort studies with long or unclear follow-up, as tobacco use as well as other lifestyle habits can change over the years. In contrast to Hergens et al. (2007), Arefalk et al. (2014) followed coronary center patients post-MI, and reported a nearly halved risk of mortality due to cardiovascular events in those who quit snus compared with those who continued to use snus, though this finding was not statistically significant (Arefalk et al. 2014). Roosaar et al. (2008) did not observe a statistically significant increased risk of cardiovascular death among snus users.

Based on moderate evidence of no association from two population-based studies (Roosaar et al. 2008; Arefalk et al. 2014), and two studies involving the Swedish Construction Worker cohort presenting moderate (Bolinder et al. 1994) and strong (Hergens et al. 2007) evidence of an association between snus use and fatal CVD or fatal CVD post-MI, we concluded that there *balanced/mixed evidence of an association* between snus use and fatal CVD. However, as with fatal IHD/MI, given the clear lack of an association of snus with incident CVD, it's unclear how use of Swedish snus could plausibly and directly cause an increase in the risk of fatal CVD.

Atrial Fibrillation

One cohort study examined the association between snus use and atrial fibrillation and reported no evidence of an increase or decrease in risk when snus users were compared with never smoking, non-current snus users (Hergens et al. 2014). Even when snus users were stratified by never-smoker, current smoker, and former smoker, the study authors observed no association between snus use and atrial fibrillation. Age, BMI, and education were assessed as covariates, and made no difference in the final risk estimates. This study was strong in its large sample size and pooled cohort design, but limited in that exposure assessment of snus use was done at a single timepoint leading to potential non-differential misclassification of exposure and possible bias toward the null.

Based on this single publication presenting strong evidence, there is *limited/suggestive evidence of no association* between snus use and atrial fibrillation.

2.4.2.2 Stroke

Summary from 2013 ENVIRON Report

Seven analytic studies (two case-control and five cohort) were identified that examined the relationship between snus and risk of stroke. Males only were studied in all but two studies (Janzon and Hedblad 2009; Koskinen and Blomstedt 2006), though the study by Janzon and Hedblad had too few female snus users to report risk estimates. Thus, the findings from the studies are applicable

generally only to males. None of the studies found an increased risk of all stroke types combined among current or former snus users. No association between hemorrhagic stroke and snus use was observed in the two studies that examined this stroke type (Hergens et al. 2008b; Koskinen and Blomstedt 2006). In one study that examined ischemic stroke, an increased risk of ischemic stroke was observed among snus users, however, in this study, no dose-response relationship with ischemic stroke was observed, and analyses of this cohort have often produced significant findings where other studies have not (Hergens et al. 2008b). In the study by Hansson et al. (2009), the dose-response analysis was suggestive of a higher overall stroke risk for snuff users using four or more cans per week, but this finding was not statistically significant.

Newly Identified Studies

Hansson and colleagues (2014) examined the association between different types of snus use and stroke in a pooled cohort (the Swedish Collaboration on Health Effects of Snus Use) of 130,485 men who had never smoked in eight prospective cohort studies with follow-up ranging from 5 to 29 years. The vast majority of study participants, and stroke cases came from the Swedish Construction Worker cohort, at 99,308. The authors reported no statistically significant association between snus use and incident stroke. The hazard ratios after adjustment for age and BMI for first ever stroke in current snus users and former snus users with the referent group of never-users were 1.01 (95% CI: 0.89-1.14) and 0.88 (95% CI: 0.64-1.22), respectively. Similarly, no association was observed between current snus use unspecified stroke after adjustment for age and BMI, compared to noncurrent snus users (HR=1.1; 95% CI: 0.78-1.54). The association between 28-day case fatality for overall stroke in current snus users compared with never tobacco users, after adjusting for age, BMI, and year of diagnosis was not statistically significantly increased (1.42; 95% CI: 0.99-2.04). Hansson and colleagues (2014) also examined first ever stroke, ischemic stroke, hemorrhagic stroke, and unspecified stroke in snus users stratified by frequency of use (<4, 4-6, 7+ cans per week) and duration of use (<20 years and 20 or more years) compared with noncurrent snus users. The associations were not statistically significant, and the hazard ratios were close to 1. The authors reported a statistically significant elevated risk in mortality due to first-ever stroke and hemorrhagic stroke in current snus users compared with noncurrent snus users: HR=1.32 (95% CI: 1.08-1.61) and 1.76 (95% CI: 1.16-2.67), respectively, while a borderline-significant association was reported for ischemic stroke mortality (HR=1.29; 95% CI: 1.00-1.67). These three analyses were adjusted for age, BMI, and year of diagnosis, but the number of exposed cases were not provided. The authors further noted, however, that after exclusion of participants from the Construction Worker Cohort, the statistically significant associations between snus use and stroke mortality did not persist. The analyses of incident stroke types were rated as strong. The mortality analyses were rated as moderate, given that no information was provided on the number of exposed cases, and all reference groups included former snus users. Confidence intervals were also less precise, and the findings were largely driven by data from a single cohort (Construction Worker).

Reviews and Meta-analyses of Stroke Due to Use of Snus

One systematic review and meta-analysis (described previously in Section 2.4.2.1) of the epidemiological literature on snus use and the potential effect on stroke was published since the 2013 ENVIRON report (Vidyasagaran et al. 2016). Based on four risk estimates from Sweden, the overall relative risk of non-fatal stroke was 1.01 (95% CI: 0.90-1.13), and the overall risk of fatal stroke was 1.28 (95% CI: 0.98-1.68) based on three risk estimates (Vidyasagaran et al. 2016). This elevated risk was not statistically significant (P<0.07) in never-smoking snus users with the referent group of

never-users of tobacco. This publication draws strength in its explicit review criteria excluding study designs not case-control nor cohort, as well as only including studies with effective control of confounding and thorough clear and relevant definitions of exposure and outcome. However, the authors were unable to adjust for alcohol consumption and other potential confounding effects including blood pressure, serum lipids, BMI, and diabetes.

Quality Rating of All Studies

Study	**Endpoint(s)**	**Evidence Quality Rating**
Asplund et al. 2003	First ever fatal or nonfatal stroke (combined)	Moderate
Bolinder et al. 1994	Stroke mortality	Moderate
Haglund et al. 2007	Fatal stroke; nonfatal stroke	Moderate
Hansson et al. 2009	Incident stroke	Strong
Hansson et al. 2014	First ever: All types (fatal and nonfatal); 28-day case fatality for all types; ischemic (fatal and nonfatal); Hemorrhagic stroke (fatal and nonfatal)	Strong (incident) Moderate (mortality)
Hergens et al. 2008b	All types (all, fatal, and nonfatal); ischemic (all, fatal, and nonfatal); hemorrhagic (all, fatal, and nonfatal), unspecified (all, fatal, and nonfatal)	Moderate
Janzon and Hedblad 2009	Incident stroke	Moderate
Koskinen and Blomstedt 2006	Subarachnoid hemorrhage	Weak

Discussion and Conclusions

Eight epidemiological studies were included in this evaluation of snus use and stroke incidence and fatalities: two case-control studies (Asplund et al. 2003; Koskinen and Blomstedt 2006) and six cohort studies (Bolinder et al. 1994; Haglund et al. 2007; Hansson et al. 2009; Hansson et al. 2014; Hergens et al. 2008b; Janzon and Hedblad 2009). One study of a cohort of Swedish construction workers reported a statistically significant association between current snus use and fatal ischemic stroke (Hergens et al. 2008b). A large pooled cohort study of Swedish men showed a statistically significant elevated risk of fatal first-time stroke of all types, and hemorrhagic stroke, but not ischemic stroke in current snus users compared with noncurrent snus users (Hansson et al. 2014). However, other analyses conducted in this study comparing the stroke incidence in snus users and never tobacco users reported no statistically significant associations, and no dose- or duration-response effect of

snus use was observed for all stroke types combined, and subtypes (ischemic, hemorrhagic unspecified) (Hansson et al. 2014). Some limitations of this pooled cohort study include potential misclassification bias due to snus exposure measured only at baseline, and confounding from having former snus users in the referent group for some of the analyses (Hansson et al. 2014). Collectively, the other six studies identified in this review of snus use and stroke reported no evidence of an elevated risk of stroke or stroke fatality with snus use, even after adjustment for a variety of covariates. A recent review (Vidyasagaran et al. 2016) reported a no statistically significant overall risk of fatal or nonfatal stroke in snus users compared with non-users, which is consistent with findings of other meta-analyses conducted previously (Boffetta and Straif 2009; Lee 2007; Lee 2011).

Based on consistent observations of no increased risk of stroke incidence among one strong and several moderate studies, there is *limited/suggestive evidence of no association* between snus use and incident stroke, including the subtypes: ischemic and hemorrhagic.

Based on inconsistent findings related to fatal stroke, including the subtypes: hemorrhagic and ischemic, the available studies currently provide *balanced/mixed evidence for whether an association exists* between snus use and fatal stroke and its subtypes. However, as with fatal CVD and MI/IHD, given the clear lack of an association of snus with incident stroke, it's unclear how use of Swedish snus could plausibly and directly cause an increase in the risk of fatal stroke.

2.5 Metabolic Effects

2.5.1 Insulin Resistance and Type 2 Diabetes

2.5.1.1 Insulin Resistance or Impaired Glucose Tolerance

Summary from 2013 ENVIRON Report

The relationship between snus use and insulin resistance or impaired glucose tolerance was examined in five descriptive studies of risk factors for cardiovascular disease (Bolinder 1997; Eliasson et al. 1991; Eliasson et al. 1995; Persson et al. 2000; Wallenfeldt et al. 2001), one experimental study (Attvall et al. 1993), and two cohort studies (Eliasson et al. 2004; Norberg et al. 2006). Seven of the eight studies found no statistically significant associations between snus use and impaired insulin or glucose tolerance, including two studies that examined the association by the amount of snus used (Norberg et al. 2006; Persson et al. 2000).

One cross-sectional study (Eliasson et al. 1991) suggested that serum insulin levels may be somewhat higher in snus users compared to non-users of tobacco, though this study was also unclear in how the analysis was conducted. For this study (Eliasson et al. 1991) and other cross-sectional studies (Bolinder 1997, Eliasson et al. 1995, Persson et al. 2000), it is not possible to determine whether the snus use preceded or followed the observed effects on the insulin and glucose of the participants. Most the studies investigating snus use and insulin resistance or impaired glucose tolerance support the conclusion that snus use is not associated with measures of insulin resistance or glucose impairment.

Newly Identified Studies

Four studies of varying designs that examined the relationship between snus use and insulin resistance or glucose intolerance were published since the 2013 ENVIRON report (Bjorkman et al. 2017; Byhamre et al. 2017; Overland et al. 2013; Neumann et al. 2013). Bjorkman and colleagues

(2017) conducted a randomized controlled trial (details described previously in Section 2.4.1.1.) wherein the resting blood glucose and resting insulin measurements of 11 regular snus users who stopped using for over 6 weeks were compared with those of 10 regular snus users who served as controls. Neither the blood glucose (p-value not reported) nor the insulin measurements (p=0.093) were statistically significantly different between the cessation group and the continued use groups (Bjorkman et al. 2017). Per interaction and time effects from a RM ANOVA, insulin values were significantly higher post-test; however post-hoc analysis attributed this result to one individual with an extremely high post-snus cessation insulin measurement (Bjorkman et al. 2017).

A cohort study of students in Sweden who were followed from 1981 to 2008 (previously described) reported no statistically significant associations between snus use and impaired fasting glucose or type 2 diabetes at any of four follow-up times (age 16, 21, 30, or 43) (Byhamre et al. 2017) when comparing never-smoking snus users with never-users of tobacco. The exposed group consisted of snus users who never smoked but was relatively small in number. At age 16, the risk of having impaired fasting glucose or type 2 diabetes was 1.08 (95% CI: 0.59-1.97) and at follow-up at age 21 and 30, the risk estimates were similar: age 21 OR 1.28 (95% CI: 0.63-2.62), age 30 OR 1.01 (95% CI: 0.48-2.11). The odds ratio of having impaired fasting glucose or type 2 diabetes was lower for those followed until age 43, but not statistically significant: OR 0.38 (95% CI: 0.12-1.16) (Byhamre et al. 2017). In addition to the small number of individuals exclusively using snus used in the analyses, there is a possibility of residual confounding from changes in other variables over time that were not accounted for.

A larger cohort study of almost 30,000 adults aged 30, 40, or 50 in Sweden were examined in 1990-1999, and followed-up 10 years later as part of the Vasterbotten Intervention Program (VIP) (Neumann et al. 2013). The primary endpoint investigated was the progression of normal glucose tolerance to impaired fasting glucose, or to impaired fasting glucose and impaired glucose tolerance in snus users compared with those who were not currently using snus. After adjusting for a variety of covariates including sex, age, smoking, physical activity, BMI, blood pressure, and diet, the risk estimates were not statistically significant between groups. The odds ratio for having progressed from normal glucose tolerance to impaired fasting glucose was 0.92 (95% CI: 0.82-1.03), and the odds ratio for having progressed from normal to impaired fasting glucose and impaired glucose tolerance was 0.79 (95% CI: 0.59-1.05) (Neumann et al. 2013). Two of the limitations of this cohort study (Neumann et al. 2013) were that the snus exposure was only measured at baseline indicating possible misclassification of exposure due to potential changes in habits during follow-up, and that no comparisons were made with an exclusive snus-user group.

One cross-sectional study previously described in Section 2.4 investigating snus use and the effect on non-fasting glucose reported findings stratified by frequency of snus use and smoking habits (Overland et al. 2013). Overland and colleagues (2013) examined 849 exclusive snus users, 1214 daily snus users, 941 sometimes snus users, and 1265 previous snus users separately and concluded that, when compared with never snus users in linear regression analyses, there were no statistically significant associations with non-fasting glucose measurements: previous snus use b=0.7 (95% CI: -0.44, 1.85), sometimes snus use 1.01 (95% CI: -0.3, 2.32), daily snus use -0.51 (95% CI: -1.68, 0.66), extensive snus use -1.31 (95% CI: -2.7, 0.08). The analyses were adjusted for age, smoking, gender, education, physical exercise, and frequency of alcohol use. A major limitation of this study,

aside from the inherent limits of the cross-sectional design, was selection bias: the participation rate was 53%, and even lower in younger participants.

Quality Rating of All Studies

Study	**Evidence Quality Rating**
Bolinder 1997	Weak
Eliasson et al. 1991	Weak
Eliasson et al. 1995	Weak
Wallenfeldt et al. 2001	Weak
Attvall et al. 1993	Strong
Eliasson et al. 2004	Moderate
Norberg et al. 2006	Weak
Persson et al. 2000	Weak
Bjorkman et al. 2017	Strong
Byhamre et al. 2017	Moderate
Overland et al. 2013	Weak
Neumann et al. 2013	Moderate

Discussion and Conclusions

Twelve publications were included in this investigation of snus use and effects on insulin resistance and glucose intolerance: two experimental studies (Attvall et al. 1993; Bjorkman et al. 2017), four cohort studies (Eliasson et al. 2004; Norberg et al. 2006; Byhamre et al. 2017; Neumann et al 2013), and five cross-sectional studies (Bolinder 1997; Eliasson et al. 1991; Eliasson et al. 1995; Wallenfeldt et al. 2001; Persson et al. 2000; Overland et al. 2013). Of these studies, only one cross-sectional study (Eliasson et al. 1991) reported evidence suggesting that insulin levels may be higher in snus users compared to those who do not use tobacco. This study was limited in that it was not possible to determine whether snus use preceded or followed the observed increase in insulin and that the analysis did not adjust for diet and lifestyle factors that could influence insulin levels.

Each study included in this section was limited in its final conclusions regarding the effects of snus on insulin and glucose in the body as measured in a group of participants. For example, Overland and colleagues (2013) reported cross-sectional analyses using a population-based group, but the participation rate was low and suggested possible selection bias. The two experimental studies (Attvall et al. 1993, Bjorkman et al. 2017) were limited in sample size and follow-up, and Attvall and colleagues (1993) did not evaluate snus use without excluding the potential impact of smoking. Some of the limitations of the cohort studies were potential confounding from current or past concurrent smoking (Norberg et al. 2006), limited power due to small numbers of exposed individuals (Byhamre et al. 2017), and possible misclassification of exposure due to long follow-up without reassessment of habits after baseline (Neumann et al. 2013). However, based on consistent findings of no association

among most of the studies, including all three rated as moderate in quality, there is *limited/suggestive evidence of no association* between snus use and insulin resistance and glucose intolerance.

2.5.1.2 Diabetes

Summary from 2013 ENVIRON Report

Five studies of varying designs have evaluated the relationship between Swedish snus use and type 2 diabetes (Eliasson et al. 2004, Ostenson et al. 2012, Hergens et al. 2005, Wandell et al. 2008, Persson et al. 2000). Conclusions regarding the association between snus use and diabetes were inconsistent.

Eliasson and colleagues (2004) report a population-based cross-sectional study with prospective follow-up providing odds ratios of prevalence and incidence. At study entry, the prevalence of diabetes was significantly higher among smokers compared to never-tobacco users, but the prevalence was not significantly elevated among snus users. Furthermore, no cases of diabetes developed (incidence) among consistent exclusive snus users, but odds ratios for incidence of diabetes associated with exclusive smokers or ex-smokers were significantly elevated compared to non-tobacco users regardless of adjustment for confounders. Another prospective study (Ostenson et al. 2012) found that snus use was associated with type 2 diabetes after adjustment for smoking, while a significant association was not observed among never-smoking snus users.

The population-based cross-sectional study (Wandell et al. 2008) examined the effect of snus use and smoking on risk of diabetes among 1,859 men aged 60 years. Wandell and colleagues (2008) reported that the prevalence of newly diagnosed diabetes was not significantly elevated among any category of snus use based on 78 participants diagnosed with diabetes. The only risk factors found to be associated with newly diagnosed diabetes were waist size and high alcohol consumption. The second cross-sectional study included 8,128 Swedish men, half of whom had a family history a diabetes (Persson et al. 2000). The authors found that exclusive-snus users had approximately a four-fold increased prevalence of type 2 diabetes compared to never-users of tobacco (OR 3.9; 95% CI: 1.1 – 14.3), based on four cases of diabetes among snus users (Persson et al. 2000). Hergens and colleagues (2005) conducted a cross-sectional analysis of the odds for having diabetes among the controls that participated in their population-based case-control study, which was 1.5 (95% CI: 0.76 – 2.9), based on six cases.

Newly Identified Studies

Three studies investigating the association between Swedish snus use and type 2 diabetes were published since the 2013 ENVIRON report (Byhamre et al. 2017, Carlson et al. 2017, Rasouli et al. 2017). One study also examined the association of snus use and incident latent autoimmune diabetes of adulthood (LADA) (Rasouli et al. 2017).

A cohort of students (described in Section 2.4.1.1) from the Swedish municipality of Lulea who attended 9th grade in 1981 were followed until 2008 (n=1,001) and assessed for risk of metabolic syndrome and its components including impaired fasting glucose and type 2 diabetes (Byhamre et al. 2017). The authors concluded that snus exposure in different life periods and cumulative snus exposure from age 16 to 43 were not associated with developing impaired fasting glucose or type 2 diabetes at or before age 43, with adjustment for covariates such as sex, cumulative smoking, BMI and SES at 16 years of age, family history of diabetes, and alcohol use and physical activity at 43

years of age (Byhamre et al. 2017). The exposed group consisted of snus users who never smoked at different ages, and the referent group included never-users of tobacco (Byhamre et al. 2017).

Carlsson and colleagues (2017) reported on a pooled set of five Swedish cohort studies lasting between 1991 and 2013. There was a total of 248 incident type 2 diabetes cases among current snus users and 118 cases among former users. Compared to never-tobacco users, current snus users had a borderline significant risk of having type 2 diabetes (HR=1.15; 95% CI: 1.00–1.32), after adjustment for age, calendar time, BMI, physical activity, level of education and alcohol consumption. Former snus users did not have a significant risk of developing the disease (HR=0.86; 95% CI: 0.71–1.05). The authors explored dose-response effect of snus use by stratifying by number of boxes consumed per week in current snus users: 1-2 boxes, 3-4 boxes, 5-6 boxes, 7 or more boxes, and 1-4 boxes or 4 or more boxes per week. There was a statistically significant elevated risk of incident type 2 diabetes in the group who used 5-6 boxes in a week (HR=1.42; 95% CI: 1.07–1.87) and the group who used 4 or more boxes per week (HR 1.43; 95% CI 1.15–1.79). When examining the relationship between duration of snus use and incident diabetes among current users, those with less than 30 years of snus use had a statistically significant elevated risk of having type 2 diabetes (HR=1.34; 95% CI: 1.03 – 1.73). The hazard ratio reported for those with 30 or more years of snus use was not statistically significant (HR=1.17; 95% CI: 0.98–1.39). The authors concluded that high snus consumption increases the risk of developing type 2 diabetes (Carlson et al. 2017).

The third study analyzed incident cases of type 2 diabetes (n=724), and cases of latent autoimmune diabetes of adulthood (LADA) (n=200) along with 699 population-based controls from ANDIS/ANDIU (All New Diabetes in Scania and Uppsala) and ESTRID (epidemiological study of risk factors for LADA and Type 2 diabetes), a sub-study of ANDIS (Rasouli et al. 2017). In addition to this case-control study based on the large-scale register of ANDIS/ANDIU, Rasouli and colleagues (2017) included cross-sectional analyses of HUNT3, a large Norwegian population-based survey performed between 2006 and 2008 that included information of snus use in participants 20 years of age or older (n=21,473 men). In both studies, the prevalence of ever-snus use was around 30% (HUNT (Norway): 28%; ESTRID (Sweden): 30%). Rasouli and colleagues (2017) reported no association between snus use and type 2 diabetes in either study: the odds ratios were 0.96 (95% CI: 0.67–1.37) and 0.91 (95% CI: 0.75–1.10) in Sweden and in Norway, respectively. When analyses were restricted to high snus consumers that were never-smokers, snus use was still not found to be associated with type 2 diabetes. After adjusting for educational level, alcohol consumption, and physical activity in Sweden, the risk for type 2 diabetes in snus users (using 10 or more boxes per year) remained similar: OR=1.02 (95% CI: 0.46–2.26). When investigating the association between LADA and snus use, analyses of the Swedish data yielded an odds ratio of 0.67 (95% CI: 0.24–1.86) among those using five or more boxes per week and 1.01 (95% CI: 0.45–2.29) among those with 10 or more box-years (consuming one box per day for a year). Using the Swedish data, the authors concluded that ever-smokers had an increased risk of type 2 diabetes (OR=1.59; 95% CI: 1.16–2.18) and in heavy smokers the risk was even greater (OR 2.20; 95% CI 1.40 – 3.45). Similar findings were reported in the Norwegian study: in only smokers, the risk for type 2 diabetes in smokers was 1.63 (95% CI: 1.36–1.96).

Quality Rating of All Studies

Study	**Evidence Quality Rating**
Eliasson et al. 2004	Weak

Ostenson et al. 2012	Moderate
Persson et al. 2000	Weak
Hergens et al. 2005	Weak
Wandell et al. 2008	Weak
Byhamre et al. 2017	Moderate
Carlsson et al. 2017	Strong
Rasouli et al. 2017	Moderate

Discussion and Conclusions

The eight studies reporting on the association between snus use and diabetes present conflicting conclusions (Byhamre et al. 2017; Carlsson et al. 2017; Eliasson et al. 2004; Hergens et al. 2005; Ostenson et al. 2012; Persson et al. 2000; Rasouli et al. 2017; Wandell et al. 2008). In a cross-sectional study, Wandell and colleagues (2008) reported that the only risk factors associated with newly diagnosed diabetes in their study of 60-year-old men were waist size and high alcohol consumption. Though this study was population-based and the prevalence of smokers and snus users in the cohort was comparable to the general Swedish population of the same age, one cannot effectively determine causality, as disease and exposure are measured simultaneously. Furthermore, the power to detect a potential association was low, evidenced by limited sample size and imprecise confidence intervals (Wandell et al. 2008). In contrast, Persson et al. (2000) included over 8,000 Swedish men in their study and found approximately a four-fold increased prevalence of type 2 diabetes in exclusive-snus users compared to never-users of tobacco. However, this was based on only four cases of type 2 diabetes in snus users. A cross-sectional analysis of the odds for having diabetes among the controls that participated in a population-based case-control study was not statistically significantly increased among snus users (Hergens et al. 2005).

Eliasson et al. (2004) reported no increased prevalence of diabetes among snus users, with no cases of diabetes observed in a follow-up study. This was based on data from over 3,300 men in Sweden, with adjustment for age and waist circumference (prevalence odds ratios). The findings in this study are limited due to the small number of diabetes cases. Ostenson et al. 2012 reported an association between diabetes and snus use in an analysis of snus users adjusted for smoking, but no significant association in never-smoking snus users. However, Ostenson and colleagues (2012) did not adjust for dietary confounders, the tobacco use and disease was self-reported at a single point in time rather than accounting for disease developing gradually over time. Furthermore, the study was not truly prospective in design; participants who were free of type 2 diabetes at baseline but diagnosed prior to the follow-up exam were not considered in the study.

Published after the 2013 ENVIRON report were two cohort studies: one concluded that there was no association between risk of type 2 diabetes or impaired fasting glucose with snus use (Byhamre et al. 2017) and the other reported that high snus consumption does have an association with developing type 2 diabetes (Carlsson et al. 2017). Both studies had their own limitations. Byhamre and colleagues' (2017) study followed about 1,000 Swedish teens until age 43, but there were only 37 exclusive-snus users at study-end follow-up. The study (Byhamre et al. 2017) adjusted for sex, cumulative smoking, BMI and SES at 16 years, family history, alcohol consumption and physical activity at 43 years, but confounding from changes over time, including socioeconomic status and

fluctuating tobacco habits was a possibility. Carlsson and colleagues (2017) pooled several cohort studies together, with diabetes incidence not assessed uniformly across studies, leading to possible underreporting and undiagnosed cases. Lastly, Rasouli and colleagues (2017) reported on two epidemiology studies in Sweden and Norway, concluding no association between snus use and diabetes or LADA, though there was a small number of diabetes cases among never-smokers (Rasouli et al. 2017).

Based on the conflicting findings of eight epidemiology studies with varying limitations, there is *balanced/mixed evidence for whether an association exists* between snus use and diabetes.

2.5.2 Metabolic Syndrome

Summary from 2013 ENVIRON Report

Three epidemiology studies investigated the relationship between use of snus and metabolic syndrome (MetSy) (Norberg et al. 2006, Wandell et al. 2008, Gustafsson et al. 2011). One follow-up study suggests that MetSy may be associated with heavy use of snus while the two other studies did not find an association between MetSy and use of snus.

Using data from a population-based longitudinal study of 16,492 adults in Sweden, Norberg and colleagues (2006) found that heavy snus consumption (more than four cans per week) was associated with increased risk of having developed MetSy 10 years later (OR=1.6; 95% CI: 1.26-2.15). Low education, physical inactivity, and former smoking were all associated with increased risk of MetSy after 10 years of follow up. However, the use of four or fewer cans of snus per week was not associated with developing MetSy. Snus use was associated with some individual elements of MetSy (high triglycerides and obesity) but not others (impaired glucose regulation, low HDL cholesterol, and hypertension). A conclusion about temporality of lifestyle habits and disease cannot be made because the study included those with MetSy at baseline. Furthermore, tobacco habits were only assessed at the start of the study, and habits likely changed during the 10-year follow-up period.

The population-based cross-sectional study by Wandell et al. (2008) mentioned previously also examined the effect of snus use and smoking on risk of MetSy among 1,859 men 60 years of age. The prevalence of MetSy was not significantly elevated among any category of snus users (formerly smoking current snus users, former snus users, current snus users, current dual users, and low and high consumption of snus). The number of snus users was low, thus limiting the power of this cross-sectional study (Wandell et al. 2008).

Gustafsson and colleagues (2011b) analyzed data from a Swedish prospective cohort study that enrolled 1,071 participants at age 16. Snus use was assessed at age 43 and, after adjusting for socioeconomic status, smoking, alcohol use, blood pressure, and BMI, it was not a significant independent contributor to the development of MetSy.

Newly Identified Studies

Since the 2013 ENVIRON report, one study was published investigating the association between snus use and the risk of MetSy (Byhamre et al. 2017). This cohort study enrolled all students who attained 9th grade in 1981 in the Swedish municipality of Lulea and followed them until they were 43 years old. 1,001 (94% of those still alive who enrolled in 1981) participants were a part of follow-up in 2008. Byhamre and colleagues (2017) evaluated the cohort at four ages: 16, 21, 30, and 43, and cumulative

snus use was defined as the number of life periods (1-4 corresponding to the periods between the ages at follow-up) with current snus use. After adjusting for sex, cumulative smoking, BMI, and SES at 16 years, family history of diabetes, alcohol consumption and physical exercise at 43 years, the authors concluded no association between MetSy at 43 years old and exclusive snus use at any of the four ages evaluated in the study (odds ratios ranged from 0.95 and 1.15, with confidence intervals ranging from around 0.5 to 2) with never-users of tobacco as the referent group. Furthermore, cumulative snus exposure during any of the life periods (odds ratios for all four periods hovered around 1 and were not statistically significant) and from age 16 through 43 was not associated with developing of MetSy at age 43 (Byhamre et al. 2017), though these calculations included smokers.

This study was limited in its follow-up, as MetSy risk factors may develop later in life than age 43. Though the cohort was relatively large at over 1000 participants at study end, it lacked power due to the small numbers of exclusive snus users and residual confounding from changes in other variables over time is possible. Overall, the study by Byhamre et al. (2017) supports the conclusion that snus use is unlikely to have an association with the development of MetSy.

Quality Rating of All Studies

Study	**Evidence Quality Rating**
Byhamre et al. 2017	Moderate
Gustafsson et al. 2011b	Moderate
Norberg et al. 2006	Weak
Wandell et al. 2008	Weak

Discussion and Conclusions

Three of the four epidemiology studies (Byhamre et al. 2017, Gustafsson et al. 2011b, Norberg et al. 2006, Wandell et al. 2008) exploring the association between MetSy and snus use identified in this report presented little evidence of a relationship between snus use and MetSy. The largest of the cohort studies (Norberg et al. 2006) reported that snus use of more than 4 cans per week was associated with risk of MetSy 10 years later at follow-up. Though this study is strong in its size and population-based design, the cohort included those with MetSy at baseline and only evaluated snus use at baseline when habits may have changed over the 10 years of follow-up. Gustafsson et al. (2011) and Byhamre et al. (2017) conducted studies using the same cohort of 16-year-olds that were followed until age 43. Both publications concluded no association between MetSy and snus use, though a major limitation of this cohort data is that risk factors for MetSy may manifest later in life than age 43. However, the cross-sectional study of 60-year-old men in Sweden (Wandell et al. 2008) similarly did not find a higher prevalence of MetSy in those who used snus.

Given that three of the four studies identified found no evidence of a relationship between snus use and the risk of metabolic syndrome, including two of moderate quality, there is *limited/suggestive evidence of no association* between snus use and MetSy.

2.5.3 Body Weight

Summary from 2013 ENVIRON Report

Numerous cross-sectional and prospective studies have examined the issue of body weight and obesity in association with snus and cigarette smoking. Among studies that controlled for past and current smoking, six of the seven found that BMI of snus users were no different than nontobacco users (Aro et al. 2010; Bolinder et al. 1997a (among younger snus users only); Bolinder et al. 1992; Engstrom et al. 2010; Rodu et al. 2004 (prospective analysis only); Sundbeck et al. 2009), while Hansson et al. (2011) observed that snus users were more likely to gain weight or become obese compared to non-users of tobacco, but not among those who took up snus during the follow-up period. Additionally, Rodu et al. (2004) reported a significantly higher BMI of snus users compared to non-users of tobacco in a cross-sectional analysis and Bolinder et al. (1992) reported a higher BMI among those older than 35 years of age. Two of the studies that looked only at exclusive snus users also reported that the waist-to-hip ratio (WHR) of snus users was not different from non-users of tobacco, in contrast to the known relationship between smoking and central adiposity (Audrain-McGovern and Benowitz 2011; Chiolero et al. 2008). Another nearly consistent finding is that former smokers had a higher BMI compared to non-users of tobacco (Aro et al. 2010 (not significantly higher compared to non-users of tobacco but higher than current smokers); Sundbeck et al. 2009) or smokers who quit during follow-up gained weight (Hansson et al. 2011; Rodu et al. 2004; Sundbeck et al. 2009). Weight gain among smokers who quit complicates the relationship between snus and weight gain as snus is often used as a smoking cessation aid, so it is therefore difficult to examine the expected contribution of smoking cessation to weight gain independently from any potential contribution of snus use.

The following conclusions can be made about use of snus and body weight:

- There is some evidence that suggests snus may be associated with higher BMI or weight gain, among studies that control for past and current smoking. However, overall, the results are mixed.
- Though the results of the two prospective cohort studies that eliminated the effect that smoking (especially former smoking) has on body weight are contradictory, neither reported an increased risk of becoming overweight or obese among non-tobacco users who began using snus during the follow-up period.

A mechanism of how snus could influence body weight remains to be elucidated. None of the studies investigated the relationship between snuff use and total energy intake, a potential confounder. Though a possible association may exist, additional investigations that account for past smoking, energy intake, and other relevant lifestyle behaviors, and that examine the potential effect of snus on metabolism would help clarify the role of snus, if any, on body weight.

Newly Identified Studies

Since publication of the 2013 ENVIRON report, four epidemiological studies examining the relationship between snus use and body weight were published (Bjorkman et al. 2017; Byhamre et al. 2017; Overland et al. 2013; Varga et al. 2013).

Bjorkman et al. (2017), described previously, ran a controlled experiment where 24 snus users of more than two years of daily snus use were tested for cardiovascular risk factors including BMI and body weight before and after six weeks or more following snus cessation. Eleven snus users, also with

more than two years of daily snus use, served as controls and maintained normal habits. Over the snus cessation period, mean body mass in kilograms increased significantly in both groups (snus cessation group: 1.4±1.7; control group: 0.5±1.1), but between groups, the increase was not statistically significant. There was very little change in BMI from baseline to end of snus cessation in both groups (Bjorkman et al. 2017).

A prospective cohort study, previously described, of sixteen-year-olds from Lulea, Sweden followed through age 43 (Byhamre et al. 2017) examined measures of metabolic syndrome including central obesity, which was defined as waist circumference ≥80 cm for women and ≥94 cm for men. Follow-ups were performed in 1983 (age 18), 1986 (age 21), 1995 (age 30), and 2008 (age 43). The BMI at baseline (age 16) did not vary based on snus or smoking use. Byhamre and colleagues (2017) did not find a significant risk increase for central obesity in current snus users who had never smoked compared with never-users of tobacco at any follow-up age: follow-up at age 16 had odds ratio 1.40 (95% CI: 0.83-2.35), age 21 OR=1.24 (95% CI: 0.65-2.34), age 30 OR=1.15 (95% CI: 0.61-2.15), age 43 OR=1.65 (95% CI: 0.76-3.58). These multivariate logistic regression calculations were adjusted for sex, cumulative smoking, BMI at 16 years, socioeconomic status at 16 years, family history of diabetes mellitus, alcohol consumption and physical activity at 43 years (Byhamre et al. 2017).

The third study investigating the association between snus use and body weight changes was a cross-sectional study of over 93,000 adults aged 20-39 in Norway (previously described, Overland et al. 2013). Compared with those who had never used snus, linear regression analysis found that extensive snus users and those who previously used snus were associated with having larger waist circumferences (b=1.38; 95% CI:0.59-2.17; b=0.78; 95% CI: 0.13-1.43, respectively). However, those who reported sometimes snus use and daily snus use had contradictory results: b=-0.29; 95% CI: -1.04-0.45; b=-0.32; 95% CI: -0.98, 0.35, respectively. The category of extensive snus users consisted of any participants who reported current daily snus use, a monthly consumption above the mean, and having used snus for more than five years. These analyses reported above were adjusted for age, smoking, gender, education, physical exercise and frequency of alcohol use. The authors acknowledge that the statistically significant findings are weak and inconsistent, as well as the association between snus use and waist circumference could be due to lifestyle factors or physiological changes. Overland and colleagues (2013) ran a post-hoc analysis with adjustment for age and gender of extensive snus users excluding daily smokers in order to investigate how previous smoking could affect waist circumference. Compared with a group of over 16,000 never-snus users, current extensive snus users who previously smoked (n=246) had larger waist circumferences (b=1.09, p=0.01) and current snus users who had never smoked (n=390) did not have this increase in waist size (b=1.09, p=0.06).

Another cross-sectional analysis examining snus use and body weight was based on data of 16,426 40, 50, and 60-year-olds pulled from the prospective, population-based cohort study GLACIER (Gene-Lifestyle Interactions and Complex Traits Involved in Elevated Disease Risk Study) from 1985 to 2004 (Varga et al. 2013). Using multivariate linear regression models adjusted for age and sex, snus use and BMI were positively related (b=0.35 kg/m^2, standard error=0.12; 95% CI: 0.12-0.58) when comparing current snus users to never snus users. As expected, when comparing current smokers to never smokers, smoking and BMI were inversely related (b=-0.46 kg/m^2, standard error=0.08; 95% CI -0.62—0.31, p<0.0001). the authors concluded, however, that "it seems more plausible that it is

the obesogenic correlates of snus (i.e., confounders) that underlie the association of snus with obesity, rather than a direct causal effect of snus."

Quality Rating of All Studies

Study	**Endpoints**	**Evidence Quality Rating**
Bjorkman et al. 2017	Body mass, BMI	Moderate
Byhamre et al. 2017	Central obesity (aka WC)	Moderate
Overland et al. 2013	Waist circumference	Weak
Varga et al. 2013	BMI	Weak
Aro et al. 2010	BMI	Weak
Bolinder et al. 1992	BMI	Weak
Bolinder et al. 1997a	BMI, waist-hip ratio	Weak
Engstrom et al. 2010	Underweight/Overweight/Obese	Weak
Sundbeck et al. 2009	BMI, WHR, WC	Weak
Hansson et al. 2011	Weight gain, obesity	Moderate
Rodu et al. 2004	Overweight	Moderate

Discussion and Conclusions

Because cessation of smoking is strongly linked with body weight changes, only studies that account for smoking are included in the discussion and final conclusions, as was done in the 2013 report.

BMI

In total, five studies investigated BMI in relation to snus use (Bjorkman et al. 2017, Aro et al. 2010, Varga et al. 2013, Bolinder et al. 1997a, Sundbeck et al. 2009) and results were contradictory. The single clinical trial (Bjorkman et al. 2017) found that mean body mass measured in kilograms increased significantly between baseline and after six weeks' snus cessation. However, when comparing the controls with the snus cessation group, there was no significant difference in body weight increase (Bjorkman et al. 2017). The authors did not observe a significant change in BMI from baseline to study end in the snus cessation group nor in the controls (Bjorkman et al. 2017). The other four studies examining BMI used cross-sectional analyses, which by design cannot determine temporality or causality due to disease and exposure measurements occurring simultaneously (Aro et al. 2010, Varga et al. 2013, Bolinder et al. 1997a, Sundbeck et al. 2009). Varga and colleagues (2013) found that snus use and BMI were positively related whereas smoking and BMI were inversely related based on information from over 16,000 participants in a population-based study. In a different population-based cross-sectional study, there was no difference in mean BMI among snus users compared with those who had never used tobacco products, though BMI was significantly lower among current smokers compared to the same group of never-users (Aro et al. 2010). The third population-based study (Sundbeck et al. 2009) reported no associations between snus use and overall obesity (as measured by BMI and abdominal obesity) compared with non-users of tobacco. A small cross-sectional study of 143 firefighters similarly found that snus users did not differ significantly from never-users with respect to BMI measurements (Bolinder et al. 1997a).

Four of the five studies examining BMI reported no statistically significant positive association between snus use and BMI (Bjorkman et al. 2017, Aro et al. 2010, Bolinder et al. 1997a, Sundbeck et al. 2009). Based on these results, including those from a single study presenting moderate evidence of no association there is *limited/suggestive evidence of no association* between snus use and BMI.

Underweight/overweight/obese

In a large cross-sectional study of construction workers, the prevalence of being overweight (BMI>26) was significantly elevated in those aged 36 or older but not among those 35 and younger when compared to non-users (Bolinder et al. 1992). In smokers, the prevalence of being overweight was not different from that of non-users. The prevalence of being underweight (BMI<22) did not differ from snus users to non-users, but among smokers, the prevalence of being underweight was significantly higher (Bolinder et al. 1992). A population-based cross-sectional study presented differing conclusions: snus use was not related to being overweight but being underweight was inversely associated with snus use (Engstrom et al. 2010). However, like Bolinder et al. (1992), smoking was positively associated with being underweight, though smoking was less common among overweight and obese participants. Though this study was strong in its size of over 34,000 men and women, 39% of those recruited did not participate, so selection bias was possible (Engstrom et al. 2010).

A cohort of 9,954 men was followed from 2002 to 2007 and examined exclusive snus use, and exclusive smoking, compared with those who had never used tobacco (Hansson et al. 2011). The authors found that snus use is associated with incident obesity (defined as BMI≥30 kg/m^2) during the study period. However, this study was limited in power due to its small number of obese participants (snus users n=21; smokers n=26). Rodu and colleagues (2004) followed up with 1,650 men at 13 years. Though the prevalence of being overweight (BMI≥27 kg/m^2) at study entry was slightly higher in snus users compared to those who had never used tobacco, the authors did not observe an increased risk of becoming overweight during follow-up of consistent, exclusive snus using men who were not overweight at study entry. Those who were formerly non-users of tobacco and took up snus during follow-up also did not have an increased risk of gaining weight.

The four studies examining the prevalence of being underweight/overweight/obese in snus users reported contradictory findings and each presented shortcomings including potential confounding (Bolinder et al. 1992, Engstrom et al. 2010, Hansson et al. 2011, Rodu et al. 2004). There is *balanced/mixed evidence for an association* between snus use and being or becoming overweight or obese, and *inadequate/insufficient evidence to determine whether an association exists* between snus use and being or becoming underweight.

Waist circumference and waist-to-hip ratio

Sundbeck and colleagues (2009) examined abdominal obesity in formerly smoking current snus users and found that abdominal obesity (a composite measurement of waist circumference and waist-hip-ratio) was greater in those with higher snus consumption; this positive association with abdominal obesity was not seen in those who used snus exclusively and had never smoked. This study did not account for important potential confounders such as alcohol consumption and energy intake (Sundbeck et al. 2009). Byhamre and colleagues (2017) also found no significant risk for central obesity (measured via waist circumference) in snus users who had never smoked compared with those who had never used tobacco. However, the number of exclusive snus users was small, which limited its statistical power. The authors adjusted for several confounders including alcohol consumption and

physical activity at age 43 (Byhamre et al. 2017). The small cross-sectional study of firefighters (Bolinder et al. 1997a) reported that snus users did not differ from never-users in waist-hip ratio. On the other hand, a larger cross-sectional study (Overland et al. 2013) reported that extensive snus users (consisting of current daily snus users, those who consumed more snus than the average, and those who had more than five years' snus use) and previous snus users were associated with having bigger waist circumferences. However, the authors' results for sometimes snus users were contradictory and not associated with bigger waist size, thus suggesting confounders at play that were not accounted for (Overland et al. 2013). Based on these studies, there is *balanced/mixed evidence for an association* between snus use and waist circumference or waist-to-hip ratio.

Weight gain/weight non-gain/intentional weight loss

Hansson and colleagues (2011) also measured weight gain over the course of five years and found that stable exclusive snus use during follow up was moderately associated with weight gain (defined as ≥5% increase in body weight) compared with never-users of tobacco as the reference group. Initiation of snus use during follow up was not associated with weight gain, though as mentioned above, the study was limited in power due to the small number of cases. Based on this single moderate quality study, there is *inadequate/insufficient evidence to determine whether an association exists* between snus use and incident weight gain.

2.6 Gastro Intestinal Effects

2.6.1 Heart burn and Gastroesophageal Reflux Symptoms (GERS), and Peptic Ulcer

Summary from 2013 ENVIRON Report

In a descriptive, cross-sectional study of approximately 40,000 subjects, Bolinder and colleagues (1992) found that Swedish users of "smokeless tobacco" (described as 'mainly moist snuff') did not have an elevated risk of peptic ulcer and that they had a significantly decreased tendency to suffer from heartburn compared to non-users. These findings were based on 5,014 Swedish smokeless tobacco users who had never been regular smokers and 23,885 Swedish participants who had never used any type of tobacco. The reason for the lower risk of heartburn in "smokeless tobacco" users was not clear, but the authors speculated that the high pH of moist snuff (8.5) could be important when saliva is swallowed.

Aro and colleagues (2010) also investigated the relationship between the use of snus and GERS and peptic ulcer. The results from this population-based cross-sectional study of a 2,860 sample of adults from two northern Swedish municipalities indicate that current or former use of snus use is not significantly associated with GERS or overall peptic ulcer disease (along with gastric ulcer and duodenal ulcer) compared to never-users of tobacco among never-smokers.

Newly Identified Studies

A single study on the potential relationship between use of Swedish snus and GERS was published since the 2013 ENVIRON report (Lie et al. 2017). Lie and colleagues (2017) conducted a cross-sectional analysis of 58,634 Norwegians living in the Nord-TrØndelag county and reported that while daily snus users, compared to snus never users, had reduced risk of GERS (OR=0.77; 95% CI 0.64-0.93), former snus users, those who used snus to quit or reduce cigarette smoking and those who used snus and cigarettes concurrently all had increased risks of GERS. Additionally, when stratified by age, snus users <30 years of age had an increased risk of GERS but those aged between 50-70 years

had a reduced risk. Noting the increased GERS risk among previous snus users and sub-groups of snus users, the author suggested that snus use could increase the risk of GERS.

Quality Rating of all Studies

Study	Endpoints	Evidence Quality Rating
Aro et al. 2010	GERS and peptic ulcer	Moderate
Bolinder et al. 1992	Heartburn and peptic ulcer	Weak
Lie et al. 2017	GERS	Weak

Discussion and Conclusions

The new study published by Lie et al. (2017) provides some evidence that there may be an association between snus use and increased risk of GERS. However, the evidence is not entirely consistent and relies on the assumption that the increased risk in former users and decreased risk in current daily snus users were a product of survivorship bias whereby those who developed GERS as a result of snus use stopped using snus. In contrast, evidence from both Aro and colleagues (2010) and Bolinder and colleagues (1992) is not suggestive of a relationship between snus use and peptic ulcer or GERS/heartburn. Given the limitations presented by all three cross-sectional studies, however, the evidence is *inadequate/insufficient to determine whether an association exists* between snus use and peptic ulcer or GERS/heartburn.

2.6.2 Crohn's Disease and Ulcerative Colitis

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

Persson and colleagues (1993) evaluated the relationship between the two types of inflammatory bowel disease (IBD), Crohn's Disease (CD) and ulcerative colitis (UC), and snus and also examined the role of cigarette smoking as a confounding or synergistic factor in the development of IBD. In this study, use of snus among never-smokers was not associated with any increase in risk of IBD. Among all participants (including those who were former or current smokers), ever-use of snus was associated with a two-fold increase in relative risk of both CD (RR=2.1; 95% CI: 1.0-4.6) and UC (RR=2.2; 95% CI: 1.1-4.4) after adjustment for age and cigarette smoking, but not for other potentially important factors that could be related to UC. However, only the finding for UC was marginally statistically significant, and was no longer significant when the analysis was restricted to never-smokers.

More recently, Carlens and colleagues (2010) conducted a cohort study, and examined the relationship between the use of snus and UC and CD among 277,777 male construction workers in Sweden. In this study, ever use of snus, adjusted for smoking, or among never-smokers was not associated with risk of UC (RR=1.1; 95% CI: 0.9-1.2 and RR=1.0; 95% CI: 0.8-1.2 respectively). With respect to CD, Carlens et al. found that ever use of snus, adjusted for smoking, or among never smokers, was not associated with risk of CD (RR=0.9; 95% CI: 0.8-1.1 and RR=1.0; 95% CI: 0.8-1.4 respectively). The authors also reported that a dose-response relationship of the amount of snus used was not observed.

Quality Rating of all Studies

Study	Endpoints	Evidence Quality Rating
Persson et al. 1993	Ulcerative Colitis and Crohn's Disease	Moderate
Carlens et al. 2010	Ulcerative Colitis and Crohn's Disease	Strong

Discussion and Conclusions

A case-control and a cohort study examined the relationship of UC and CD with oral moist snuff and cigarette smoking in Sweden. These studies found no increased risk of CD or UC associated with snuff use when the analysis was limited to never-smokers. Thus, the evidence supports a conclusion of *limited/suggestive evidence of no association* between snus use and risk of CD and UC.

2.6.3 Irritable Bowel Syndrome

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

Aro and colleagues (2010) also investigated the relationship between the use of snus and irritable bowel syndrome (IBS). The results indicate that current or former use of snus among never-smokers is not significantly associated with IBS compared to never-users of tobacco.

Quality Rating of all Studies

Study	Evidence Quality Rating
Aro et al. 2010	Moderate

Discussion and Conclusions

The results of a sole cross-sectional study indicate that current or former use of snus among never-smokers is not associated with irritable bowel syndrome (IBS) compared to never-users of tobacco. Based on this single study, however, the evidence is *inadequate/insufficient to determine whether an association exists* between snus use and risk of IBS.

2.6.4 Celiac Disease

Summary from 2013 ENVIRON Report

No studies on celiac disease were previously included in the 2013 ENVIRON report.

Newly Identified Studies

A single study on the potential relationship between use of Swedish snus and Celiac disease was published since the 2013 ENVIRON report (Ludvigsson et al. 2014). In an analysis of 199,185 participants from the Swedish Construction Workers' cohort, Ludvigsson and colleagues (2014) reported that ever use of snus was not associated with risk of celiac disease (RR=1.0; 95% CI: 0.78-1.28) after adjusting for age, sex, decade, and tobacco smoking.

Quality Rating of all Studies

Study	Evidence Quality Rating
Ludvigsson et al. 2014	Strong

Discussion and Conclusions

Although the authors did not evaluate an exclusive group of snus users, tobacco smoking was not associated with Celiac disease in this study, so potential confounding by smoking was not a major concern. Given the large sample size and prospective design of this study, the evidence was rated as strong, with the authors reporting no association between snus use and celiac disease. Therefore, this study provides *limited/suggestive evidence of no association* between snus use and Celiac disease.

2.6.5 Other Gastrointestinal Symptoms and Effects

No new studies were identified since publication of the 2013 ENVIRON report.

Quality Rating of all Studies

Study	Endpoints	Evidence Quality Rating
Aro et al. 2010	Gastrointestinal symptoms including dyspepsia, epigastric pain, abdominal pain, H. pylori infection, and esophagitis	Moderate

Discussion and Conclusions

Aro and colleagues (2010) investigated the relationship between the use of snus and other gastrointestinal symptoms including dyspepsia, epigastric pain, abdominal pain, *H. pylori* infection, and esophagitis. The results indicate that current or former exclusive use of snus is not significantly associated with any of these symptoms compared to never-users of tobacco. However, current use of snus was significantly associated with hyperplasia of the basal cell layer (OR=1.74; 95% CI: 1.02-3.00) and with elongation of papillae of the squamous epithelium at the esophago-gastric junction (OR=1.79; 95% CI: 1.05-3.05). Given that there was only a single cross-sectional study available on each of these endpoints, there is *inadequate/insufficient evidence to determine whether an association exists* between snus use and risks of these other gastrointestinal effects.

2.7 Pregnancy Outcomes and Reproductive Effects

2.7.1 Effects on Infants

Summary from 2013 ENVIRON Report

The Swedish Medical Birth Register was used to examine birth outcomes in a large number of pregnancies. Daily use of snus during pregnancy is associated with a modest reduction in average birth weight (though less than smoking), small-for-gestational-age birth, and increased risk of preterm delivery, stillbirth, and neonatal apnea.

These conclusions are consistent with the recent review by Rodu (2011), who also noted that while any form of nicotine should be avoided during pregnancy, the highest risks for the developing baby are associated with smoking.

Newly Identified Studies

No new studies for endpoints including small for gestational age, and neonatal apnea.

Stillbirths and Early Neonatal Mortality

A single study on the potential relationship between use of Swedish snus during pregnancy and risk of stillbirths was published since the 2013 ENVIRON report (Baba et al. 2014). In an updated analysis of the Swedish Medical Birth Register, Baba and colleagues (2014) reported a higher risk of stillbirth among women who used snus during the first trimester (OR=1.43; 95% CI: 1.02-1.99), with no effect of snus use on risk of stillbirth among the women who stopped using snus prior to the first antenatal visit (OR=0.73; 95% CI: 0.50-1.06).

Baba et al. (2014) also examined early neonatal mortality, defined as deaths occurring during the first week of life, and found that risk of nearly neonatal mortality was not elevated among those who used snus during the first trimester (OR=0.64; 95% CI: 0.30-1.37) or those who stopped using snus prior to the first antenatal visit (OR=1.15; 95% CI: 0.68-1.3).

Heartbeat Variability

A single prospective study on the potential relationship between use of Swedish snus during pregnancy and infant heartbeat variability was published in 2017 (Nordenstam et al. 2017). Nordenstam and colleagues (2017) reported that compared to the 19 infants of women who did not use tobacco or nicotine products, the 23 infants of women who used snus during pregnancy showed a higher Low Frequency to High Frequency ratio (p=0.006), but did not differ in electrocardiogram readings.

Oral Clefts

A single study on the potential relationship between use of Swedish snus during pregnancy and risk of oral clefts was published in 2014 (Gunnerbeck et al. 2014). Using the Swedish Medical Birth register data, Gunnerbeck and colleagues reported that the risk of all oral cleft malformations was increased among infants of women who reported use of snus in the first trimester compared to infants of women who did not use snus in the first trimester (OR=1.48; 95% CI: 1.00-2.21), though this finding was of borderline statistical significance. This appeared to be primarily driven by the increased odds of cleft lips (OR=1.61; 95% CI: 1.00-2.61) and not cleft palates (OR=1.26; 95% CI: 0.63-2.55) (Gunnerbeck et al. 2014). In contrast, the odds of all oral cleft malformations (OR=0.71; 95% CI: 0.44-1.14), including cleft lip (OR=0.77; 95% CI: 0.44-1.37) and cleft palates (OR=0.59; 95% CI: 0.24-1.43) were not elevated among infants of women who stopped using snus by 15 weeks gestation. No differences in rates of other malformations among infants with oral clefts were observed between infants of women who used snus in the first trimester and infants of women who did not use snus.

Preterm Birth

A single study on the potential relationship between use of Swedish snus during pregnancy and risk of preterm birth was published since the 2013 ENVIRON report (Dahlin et al. 2016). Using the Swedish Medical Birth register data, Dahlin and colleagues (2016) reported that pregnant women who reported snus use in the first trimester had elevated risk of extreme premature birth (OR=1.58; 95% CI: 1.14-2.21), very premature birth (OR=1.25; 95% CI: 0.98-1.59), and moderately premature birth (OR=1.21; 95% CI: 1.11-1.31), defined as <28 weeks, 28-31 weeks, and 32-36 weeks, respectively. In contrast, women who used snus 3 months prior to the pregnancy but had stopped prior to the first antenatal visit did not have elevated risk of extreme premature birth (OR=0.78; 95% CI: 0.52-1.16), very premature birth (OR=0.90; 95% CI: 0.71-1.15), or moderately premature birth (OR=0.95; 95% CI: 0.88-1.02).

Birthweight

Two studies on the potential relationship between use of Swedish snus during pregnancy and birthweight were published since the 2013 ENVIRON report (Juarez and Merlo 2013, Rygh et al. 2016).

Juarez and Merlo (2013) conducted an analysis of the Swedish Medical Birth Register using both a conventional observational approach and a "quasi-experimental" approach that examined sibling birthweights from sequential pregnancies. Compared to infants of women who never used snus, infants of women who used snus in both the first and third trimester were 47g lighter on average. However, infants of women who used snus in either the first or third trimester alone had similar birthweights compared to unexposed infants. The quasi-experimental sibling analysis included 144,017 mothers with two sequential pregnancies and reported similar results where infants of women who used snus during both pregnancies had lower birthweight compared to infants of women who did not use snus during either pregnancy.

Rygh and colleagues (2016) conducted an analysis of 10,583 births from the Sørlandet Hospital in Norway and reported that there was no statistically significant difference in birthweight between infants of women who used snus compared to infants of women who did not use snus. However, it is not clear what the authors defined as snus use in this analysis, nor were there other details on the methodology of the analysis.

Apgar Score

A single study on the potential relationship between use of Swedish snus during pregnancy and Apgar score, a measure of a newborn infants' health, in the infants was published in 2016 (Rygh et al. 2016). Rygh and colleagues (2016), described previously, reported that there was no statistically significant difference in Apgar scores between infants of women who used snus compared to infants of women who did not use snus. However, it is not clear what the authors defined as snus use in this analysis, nor were there other details on the methodology of the analysis.

Quality Rating of all Studies

Study	**Endpoints**	**Evidence Quality Rating**
England et al. 2003	Birth weight, small for gestational age, and preterm birth	Moderate
Baba et al. 2012a	Small for gestational age	Strong
Baba et al. 2012b	Preterm birth	Strong
Baba et al. 2014	Stillbirth, early neonatal mortality	Strong
Dahlin et al. 2016	Preterm birth	Strong
Gunnerbeck et al. 2011	Neonatal apnea, small for gestational age, and preterm birth	Strong
Gunnerbeck et al. 2014	Oral clefts	Moderate
Juarez and Merlo 2013	Birthweight	Strong
Nordenstam et al. 2017	Heart rate variability	Weak
Rygh et al. 2016	Birthweight, Apgar score	Weak

Wikstrom et al. 2010a	Preterm birth	Strong
Wikstrom et al. 2010b	Stillbirth, small for gestational age	Strong

Discussion and Conclusions

Stillbirths and Early Neonatal Mortality

With the new study published by Baba and colleagues (2014), two studies from the Swedish Birth Registry now report that snus use in the first trimester is associated with elevated risk of stillbirth (Wikstrom et al. 2010b, Baba et al. 2014). However, this new publication by Baba and colleagues (2014) only provided a limited update to the earlier publication by Wikstrom and colleagues (2014). Given the strong quality of the studies, however, we conclude that there is *limited/suggestive evidence of an association* between maternal snus use in the first trimester and increased risk of stillbirth.

A single strong study that evaluated the association between snus use and risk of early neonatal mortality reported no association (Baba et al. 2014), providing *limited/suggestive evidence of no association*.

Heartbeat Variability

A single new study reported that the Low Frequency to High Frequency Ratio in the infants of women who used snus during pregnancy was higher than that of the infants of women who did not use nicotine products during pregnancy (Nordenstam et al. 2017), but it was of weak quality due to the small number of participants in the study as well as the lack of control for potential confounders. Together with the observation that no differences in Low Frequency, High Frequency, and other electrocardiogram measures were noted between groups, our overall conclusion is that there is *inadequate/insufficient evidence to determine whether an association exists* between snus use during pregnancy and subsequent altered heartrate variability in infants.

Oral Clefts

A single new study reported an increased risk of oral clefts, in particular cleft lip was associated with maternal snus use in the first trimester (Gunnerbeck et al. 2014), although this finding was of borderline statistical significance, and other specific malformations, such as cleft palate, were not statistically significantly increased. However, the numbers of infants with specific malformations born to snus users were small. Overall, we conclude that there is *inadequate/insufficient evidence to determine whether an association exists* between maternal snus use in the first trimester and increased risk of oral clefts.

Preterm Birth

With the new study published by Dahlin and colleagues (2016), five studies from the Swedish Birth Register now report that snus use in the first trimester is associated with elevated risk of preterm birth (England et al. 2003, Wikstrom et al. 2010a, Gunnerbeck et al. 2011, Baba et al. 2012b, Dahlin et al. 2016). Similar to the stillbirth data, all publications on this topic came from the same cohort with overlapping participants. However, given the consistency of the results, large representative samples, as well as the overall quality of the studies, we conclude that there is *limited/suggestive evidence of an association* between maternal snus use in the first trimester and increased risk of preterm births.

Birthweight

The findings reported in the two new studies on maternal Swedish snus use and infant birthweight were mixed. Juarez and Merlo (2013) observed a decrease in birthweight associated with consistent snus use in the first and third trimester using the Swedish Birth Register, consistent with the prior study by England and colleagues (2003) of the same cohort. However, Rygh and colleagues (2016) reported that in their cohort of 10,583 births from Norway, no differences in birthweight were observed between infants of women who used snus during pregnancy compared to infants of women who did not use snus. However, the Rygh and colleagues (2016) did not report the methodology behind this analysis, which limits the interpretation of their results. Ultimately, given the relatively strong quality of the Swedish Birth Register studies, we conclude that there is *limited/suggestive evidence of an association* between maternal snus use and birthweight.

Small for Gestational Age

Being small for gestational age was defined as having a birth weight that was more than 2 standard deviations below the mean birth weight for gestational age, according to gender-specific Swedish fetal growth curves. The risk of having an SGA baby among snuff users was examined by England and colleagues (2003), and was found to be similar to that of nonusers of tobacco (OR=1.25; 95% CI: 0.72-2.17). By comparison, the risk was significantly increased among cigarette smokers (OR=2.99; 95% CI: 2.48-3.61). In the first expanded study, Wikström and colleagues (2010b) again observed that snuff use during pregnancy is not significantly associated with being SGA (OR = 1.17; 95% CI: 0.98-1.39). In the most recent expanded study, Baba and colleagues (2012a) concluded that both smoking, and to a lesser extent, use of snuff during pregnancy increased the risk of an SGA birth. The authors noted that both nicotine and tobacco combustion products are involved in the mechanisms by which maternal tobacco use during pregnancy increases the risk of SGA birth, and that products containing nicotine should be avoided during pregnancy. Women who used snuff (OR = 1.26; 95% CI: 1.09-1.46) or smoked (OR = 2.55; 95% CI: 2.43-2.67) during early pregnancy faced a significantly increased risk of SGA. Snuff use had a stronger association with preterm SGA (OR = 1.50; 95% CI: 1.13-1.98) than term SGA (OR = 1.21; 95% CI: 1.02-1.43), whereas the opposite was true for smoking (Preterm SGA OR = 1.85; 95% CI: 1.67-2.06, Term SGA OR = 2.76; 95% CI: 2.62-2.91). Women who stopped using snuff before their first visit to antenatal care had no increased risks of preterm or term SGA, and women who stopped using snuff later during pregnancy had no increased risk of term SGA. Given the relatively strong quality of the most recent and expanded study of the Swedish Medical Birth Register, we conclude that there is *limited/suggestive evidence of an association* between maternal snus use and small for gestational age.

Apgar Score

Given that the sole study that evaluated the association between maternal snus use and infant Apgar score presented weak evidence of no association with snus use, or even methodology associated with the analysis, there is *inadequate/insufficient evidence to determine whether an association exists*.

Neonatal Apnea

In an analysis of the Swedish Medical Birth Register, snuff use during pregnancy was significantly associated with an increased risk of neonatal apnea (OR = 1.96; 95% CI: 1.30-2.96) following adjusted for maternal age, height, parity, education, and tobacco use. Model 2 was further adjusted for cesarean delivery, gender, gestation age, and small for gestational age (Gunnerbeck et al. 2011).

Given the relatively strong quality of the Swedish Birth Register studies, we conclude that there is *limited/suggestive evidence of an association* between maternal snus use and neonatal apnea.

2.7.2 Maternal Effects

No new studies were identified since publication of the 2013 ENVIRON report.

Quality Rating of all Studies

Study	Endpoints	Evidence Quality Rating
England et al. 2003	Preeclampsia	Moderate
Wikstrom et al. 2010b	Antenatal Bleeding Preeclampsia	Strong
Wikstrom et al. 2010c	Preeclampsia Gestational Hypertension	Strong

Discussion and Conclusions

Antenatal Bleeding

Wikström and colleagues (2010b) investigated the relationship between the use of snuff during pregnancy and antenatal bleeding and reported that snuff use was not statistically significantly associated with antenatal bleeding (OR=1.15; 95% CI: 0.92-1.44). Given that this study presented strong evidence of no association, there is *limited/suggestive evidence of no association* between snuff use during pregnancy and antenatal bleeding.

Preeclampsia

England and colleagues (2003) reported that daily users of snuff were at significantly increased risk of preeclampsia compared to non-users of tobacco (OR=1.58; 95% CI: 1.09-2.27). In the expanded study of the same cohort, Wikström and colleagues (2010b) found that reported snuff use was not statistically significantly associated with preeclampsia (OR=1.11; 95% CI: 0.97-1.28). In addition, snuff use was not associated with the severity of preeclampsia. Given the strong evidence provided by Wikström and colleagues (2010b,c), there is *limited/suggestive evidence of no association* between snuff use during pregnancy and preeclampsia, but the evidence is somewhat inconsistent and came from a single cohort.

Gestational Hypertension

Wikström and colleagues (2010c) found that snuff use during pregnancy was not associated with risk of gestational hypertension (OR=0.89; 95% CI: 0.68-1.15). Given that this study presented strong evidence of no association, there is *limited/suggestive evidence of no association* between snuff use during pregnancy and gestational hypertension.

2.7.3 Effects on Male Fertility

Summary from 2013 ENVIRON Report

A single cross-sectional study does not suggest that the use of snus is associated with reproductive parameters in adolescent males (Richthoff et al. 2008). Though the authors' primary focus was on smoking, snus' potential association with male reproductive factors was investigated because it might have an impact directly or as a confounder or an effect modifier. None of the reproductive parameters

(semen parameters, seminal biochemical biomarkers, hormone levels) investigated were associated with snus use. The authors concluded that since tobacco smoking was associated with negative impacts on male reproductive parameters, it is unlikely that tobacco itself causes these impacts but rather the compounds that are released by smoking.

Newly Identified Studies

A single study on the potential relationship between use of snuff and male semen parameters was published since the 2013 ENVIRON report (Parn et al. 2015). Parn and colleagues (2015) reported that compared to 43 snuff non-users, 17 snuff users had decreased sperm concentration, total sperm count, motile sperm concentration, total motile sperm count, and percent motile sperm ($p<0.05$) in bivariate analyses. Given the known association between cigarette smoking and diminished semen quality, the observed decrease in semen quality among snuff users could have been confounded by past or current cigarette smoking.

Quality Rating of all Studies

Study	**Evidence Quality Rating**
Richthoff et al. 2008	Weak
Parn et al. 2015	Weak

Discussion and Conclusions

Both studies that evaluated the association between snus use and semen parameters were of weak quality due their small sample size, cross-sectional design, and inability to control for smoking status. Therefore, despite the associations observed by Parn and colleagues (2015), there is *inadequate/insufficient evidence to determine whether an association exists* between snus use and effects on male fertility.

2.8 Other Health Effects

2.8.1 Acoustic Neuroma

Summary from 2013 ENVIRON Report

No studies on acoustic neuroma were previously included in the 2013 ENVIRON report.

Newly Identified Studies

A single study that investigated the potential relationship between Swedish snus use and acoustic neuroma was published since the 2013 ENVIRON report (Palmisano et al. 2012). Palmisano et al. (2012) conducted a population-based case-control study with 451 patients with acoustic neuroma and 710 controls matched on gender, region and age. Of the acoustic neuroma patients, 78 were snus users, and 152 were non-users; in the control group 119 were snus users and 239 were non-users. Due to the low rate of female snus users (10 female users were identified in study population), only male users were used for analyses involving snus users. Using logistic conditional regression, odds ratios were estimated for ever-snus users, former snus users, and current snus users compared with never-users. Following adjustment for highest level of education and smoking status, all odds ratios for these snus user comparisons were around 1, indicating no statistically significant risk of developing acoustic neuroma. The authors also examined the potential effect of age of initiation, years since starting, total years, and years since cessation of snus use. Analyses of these subgroups also yielded

odds ratios close to 1, supporting the conclusion that snus use has neither a positive nor negative relationship with acoustic neuroma.

Discussion and Conclusion

This study had some potential selection bias in that 65% of recruited controls participated, compared with the higher participation rate of 84% among cases. A notable limitation of this study was that it did not include analyses among exclusive snus users, likely due to the relatively low number of study participants, although odds ratios were adjusted for smoking status. The quality of the evidence presented in this study was rated as moderate. Although the authors of this study noted that they "observed no evidence of a role for snuff tobacco consumption in acoustic neuroma etiology," the evidence from this single, moderate study is *inadequate/insufficient to determine whether an association exists*.

2.8.2 Acute Adverse Symptoms

Summary from 2013 ENVIRON Report

No studies on acute adverse symptoms were previously included in the 2013 ENVIRON report.

Newly Identified Studies

One study that investigated potential acute adverse symptoms associated with Swedish snus use was published since the 2013 ENVIRON report (Ozga et al. 2016). This was a pilot study, described previously, involving 11 never-tobacco users (defined as <100 uses/lifetime) who consumed six pouches of Swedish snus in ascending doses within a single session. Each pouch was consumed for 20 minutes with 25-minute pauses between snus pouches. Pre- and post-pouch assessments of drug effects and physiological response were measured to determine differences across dose groups. Subjective effects were measured using visual analog scale items via the Direct Effects of Nicotine Scale (DENS) and the Direct Effects of Tobacco Scale (DETS). Each participant consumed pouches containing 0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg of nicotine. Participants were asked to characterize 10 subjective effects with each dose: nausea, dizziness, lightheadedness, nervousness, sweatiness, headache, excessive salivation, heart pounding, confusion, and feeling weak. Out of these 10 measures, excessive salivation was the only measure that was significant for a main effect of time. Pre-pouch excessive salivation rated, on average, 6.7 and post-pouch was rated 20.6. The authors concluded that "the lack of reliable subjective effects may be the product of the dosing regimen or the relatively small sample size." In addition to small sample size, the successive administration of pouches could have led to "carryover effects" from nicotine in previous doses.

Discussion and Conclusions

The new study (Ozga et al. 2016) of 11 never-users of tobacco measuring physiological and subjective effects of Swedish snus provides moderate evidence that use of Swedish snus can result in excessive salivation, which is noted as a significant subjective effect, however the very small sample size is a major limitation of this study. Overall, there is *inadequate/insufficient evidence to determine whether an association exists* between use of Swedish snus, and the subjective symptoms examined in this study.

2.8.3 All-Cause Mortality

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

Two cohort studies have examined the relationship between the use of snus and all-cause mortality. Bolinder and colleagues (1994) investigated this relationship among 84,781 Swedish construction workers, and found a significant association between exclusive use of snus and all-cause mortality (adjusted for age and region of origin) among all subjects (RR=1.4; 95% CI: 1.3-1.8), and those aged 35-54 (RR=1.9; 95% CI: 1.6-2.4) at study entry, but not among subjects aged 55-65 (RR=1.2; 95% CI: 1.0-1.3) at study entry.

Roosaar and colleagues (2008) also evaluated the effects of the use of snus on all-cause mortality among 9,976 men from Uppsala County, Sweden. Ever daily use of snus (adjusted for smoking) was marginally significantly associated with an increased risk in all-cause mortality (HR=1.10; 95% CI: 1.01-1.21). Ever daily use of snus among never-smokers was also marginally significantly associated with an increased risk of all-cause mortality (HR=1.23; 95% CI: 1.09-1.40). Hazard ratios were adjusted for age, calendar period, area of residence, and alcohol consumption.

Quality Rating of all Studies

Study	**Evidence Quality Rating**
Bolinder et al. 1994	Moderate
Roosaar et al. 2008	Moderate

Discussion and Conclusions

While the overall hazard ratios among all subjects from both studies suggest a potential association between the use of snus and mortality from any cause, the evidence does not raise to the level off sufficient evidence of an association. Bolinder et al. (1994) did not account for any potential confounders such as lifestyle factors (e.g., alcohol consumption), and while Roosaar et al. (2008) adjusted for alcohol consumption, the authors did not adjust for other potentially important confounders such as dietary pattern, physical activity, BMI, or socioeconomic status. Given the myriad of potential causes of mortality, more evidence is clearly needed to establish a potential relationship with snus use. However, overall, the available studies currently provide *limited/suggestive evidence of an association* between snus use and all-cause mortality.

2.8.4 Amyotrophic Lateral Sclerosis (ALS)

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

Fang and colleagues (2006) used data from the Swedish construction workers cohort to evaluate the relationship between snus use, cigarette smoking and the development of ALS. The analysis involved 280,558 men who were followed for an average of 19.6 years. At study initiation, 13.6% of the participants were pure snuff users, 37.7% were pure smokers, and 17.3% were mixed snuff users and smokers. There was no increased risk of ALS among any group of tobacco users, including pure snus users (RR=0.6; 95% CI: 0.3-1.5); cigarette smokers (RR=0.7; 95% CI: 0.5-1.1); or mixed snus users and smokers (RR=0.9; 95% CI: 0.6-1.4), after adjusting for age and county of residence. The authors concluded that this study provides no evidence that tobacco use is associated with increased risk of ALS.

Discussion and Conclusions

This large cohort study (Fang et al. 2006) had many strengths, including a high prevalence of snus use, long and almost-complete follow-up of an average of 19.6 years, and adjustment for age and country of residence. However, the authors did not adjust for some potential confounders, such as socioeconomic status or alcohol consumption. Furthermore, tobacco habits were assessed only at study entry, and changes over time could affect the results. The number of ALS cases among snus users were low (six ALS cases in pure snus users, 30 cases in mixed snus/smokers, and 69 in the smoking-only group). Given these weaknesses, the evidence from this single cohort study is of moderate quality and thus there is *inadequate/insufficient evidence to determine whether an association exists.*

2.8.5 Chronic Pain Intensity

Summary from 2013 ENVIRON Report

Jakobsson (2008), using a cross-sectional study design, evaluated the relationship between tobacco use and pain intensity among 384 male and female participants from southern Sweden, who reported experiencing chronic pain for a duration of at least 3 months. At study initiation, 12.5% reported ever using snuff, while 52.1% reported ever smoking cigarettes. The author concluded that there was not significantly higher pain intensity among those who used moist snuff compared with those who did not.

Newly Identified Studies

One study investigating the relationship between snus use and pain intensity was published since the 2013 ENVIRON report (Jakobsson and Larsson 2014). The cross-sectional study included 2,000 randomly selected people aged 65 years or older living in Sweden and administered a postal questionnaire in 2011 with questions about demographic data, living conditions, tobacco use, health, and chronic pain (defined as pain lasting three months or longer) (Jakobsson and Larsson 2014). Most respondents (90.1%) were never snus users, about 5% were former snus users, 3.5% were daily snus users, and <1% were occasional snus users. With a 57% response rate (n=1,141), the study preformed multiple linear regression analyses identifying variables associated with pain intensity stratified by gender and frequency of snus use. Snus use and pain intensity were not associated for neither men nor women. However, older age and smoking daily were associated with higher pain intensity among both men and women.

Discussion and Conclusions

Based on the two studies exploring the relationship between snus use and pain intensity (Jakobsson 2008; Jakobsson and Larsson 2014), there is no association between snus use and pain intensity. However, both studies were cross-sectional in nature, so a causal relationship between exposure and effect cannot be determined using these studies alone. Furthermore, it is possible that selection and information biases, common features in this type of study design, may have been present and biased the results toward the null. Similarly, misclassification of exposure or outcome also may have skewed the results. Due to these limitations, the quality of evidence from these studies was rated as weak, and there is *inadequate/insufficient evidence to determine whether an association exists* between snus use and chronic pain.

2.8.6 Complications after Hernia Surgery

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

An analysis of the Swedish construction worker cohort sought to determine whether smoking, use of snus, or obesity affected the outcome of surgery (Lindstrom et al. 2007). The participants were 12,697 male construction workers who had undergone a first-time inguinal hernia repair. The overall complication rate following this surgery was low (2.9%). Snus use was not associated with significantly increased risk of postoperative complications, nor was it associated with any increase in the mean length of hospitalization. In contrast, current smokers had a 34% increased risk of postoperative complications compared to never-smokers, although their length of hospitalization was unaffected. The authors concluded that use of snus does not appear to affect the complication rate after hernia surgery.

Discussion and Conclusions

This single study (Lindstrom et al. 2007) is strong owing to its large size and prospectively collected data on tobacco use. There was likely some misclassification of study results due to failure of complete registration in the Swedish inpatient register. This is evidenced by the reported low overall rate of complications; however, the study results are likely unaffected since the misclassification of outcomes is likely nondifferential (about the same in the exposed and unexposed groups). The results were adjusted for age, calendar period, BMI, and acute surgery. Based on this study of strong quality, there is *limited/suggestive evidence of no association* between snus use and complications after hernia surgery.

2.8.7 Delayed Bone Healing

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

An analysis of the Swedish construction worker cohort was carried out to assess the effect of snus use and smoking on the time for bone healing (W-Dahl and Toksvig-Larsen 2007). The participants were 175 male patients who were subsequently operated on by tibial osteotomy using the hemicallotasis technique. The cohort comprised of 41 smokers, 21 oral snuff users, and 113 non-smokers/non-snus users, with habits documented preoperatively. There were no cases of delayed bone healing among snus users and the authors concluded that snus does not have the negative effects—such as delayed bone healing and increased risk of post-operative complications—associated with cigarette smoking.

Discussion and Conclusions

W-Dahl and Toksvig-Larsen (2007) found no evidence for delayed healing among oral snus users in a population of 175 male hospital patients who were operated on for knee deformity by tibial osteotomy. The results were adjusted for age, size of correction, and simultaneous bilateral surgery. However, limitations of the cohort study include the fact that there was no information on amount or duration of snus use or smoking, so dose-response analyses were not possible. With only this small cohort study presenting moderate quality evidence on the association between snus use and bone healing, there is *inadequate/insufficient evidence to determine whether an association exists.*

2.8.8 Gallstone Disease

Summary from 2013 ENVIRON Report

No studies on gallstone disease were previously included in the 2013 ENVIRON report.

Newly Identified Studies

A single cohort study of 58,402 participants from the Swedish Twin Registry examined the associations between smoking and smoke-free tobacco with gallstone disease (Katsika et al. 2007). 1,666 cases of twins with gallstone disease were reported. No significant associations were reported between current or previous smoke-free tobacco use and gallstone disease (OR=1.05; 95% CI: 0.49-2.23 and OR=0.62; 95% CI: 0.37-1.04). Conditional logistic regression analyses comparing cases to unaffected co-twins were also performed involving 1,527 gallstone disease cases where the same-sex co-twin did not have a history of gallstone disease. The odds ratios among twin pairs of having gallstone disease were not significant with previous or current use of smoke-free tobacco and were similar to the results for the overall cohort.

Discussion and Conclusions

The cohort study conducted by Katsika and colleagues (2007) had limited data on tobacco habits, especially in regard to smoke-free tobacco. Data on smoke-free tobacco was missing on approximately half of participants. Because of this major limitation, the power of the statistical analyses was low with only seven exposed cases in the overall cohort study. Furthermore, odds ratios were not adjusted for any potential confounders. The evidence presented in this study is weak, and provides *inadequate/insufficient evidence to determine whether an association exists* between snus use and gallstone disease.

2.8.9 General Health

Summary from 2013 ENVIRON Report

With respect to general health, Lee (2011) summarized two cross-sectional studies that investigated the relationship between the use of snus and general health outcomes that included frequent sick leave, long leave, and "best general health" (assessed by five indicators). Among these three outcomes, snuff use was significantly associated only with long leave. Another cross-sectional study reported that prevalence of snuff use was not significantly associated with poor or very poor self-rated health (Engstrom et al. 2010). Again, causality cannot be determined in these cross-sectional studies.

The two cross-sectional studies that Lee et al. (2011) summarized in his review included Bolinder et al. (1992) (frequent and long sick leave), and Halling et al. (2007) ("best general health", assessed by five indicators). The Bolinder et al. (1992) study and results were summarized in Appendix Q-1, and Halling et al. (2007) was not specifically cited or discussed in detail in the 2013 ENVIRON report. Therefore, these studies are discussed here, along with a newly identified study conducted by Eriksson and Ng (2015).

Newly Identified Studies

Bolinder et al. (1992) conducted a cross-sectional survey that involved 37,722 men from the Swedish Construction Worker cohort who received health examinations between 1971 and 1974. Among exclusive snus users that had never smoked cigarettes, snus use was significantly associated with long sick leave (OR=1.2; 95% CI: 1.1, 1.2), but not frequent sick leave (OR=1.1; 95% CI: 1.0, 1.2) following adjustment for age. Halling we al. (2007) also conducted a cross-sectional study involving 50- and 60-year old Swedes in two counties. Following adjustment for age, gender, place of living, social life, work, education, and marital status, snus use was not associated with "best general health", as assessed by a health index encompassing five items, compared to never-users of tobacco.

Eriksson and Ng (2015) conducted a cross-sectional analysis of the potential relationship between snus use and self-reported health as part of a cohort study of 33,621 men and women who participated in the Vasterbotten Intervention Program. The primary research focus of the study involved how changes in access to social capital influenced self-rated health in middle-aged men and women over time, however, snus was included as a covariate, and examined separately. Though no data were shown, and there was no control for potential confounders, the authors reported that men and women who were current snus users had higher odds of reporting poor self-rated health compared to those who did not smoke or use snus at baseline. No associations were observed during follow-up visits.

Quality Rating of all Studies

Study	Evidence Quality Rating
Bolinder et al. 1992	Weak
Engstrom et al. 2010	Weak
Eriksson and Ng 2015	Weak
Halling et al. 2007	Weak

Discussion and Conclusions

The new study published by Eriksson and Ng (2015) provides weak evidence of an association between snus use and general, self-reported health. Results among the other three available studies were mixed, and all consisted of a cross-sectional study design for which temporality cannot be determined. Bolinder et al. (1992) was the only other author to report a statistically significant association between snus use and measures of general health (frequent and long sick leave), though the results were adjusted only for age. Overall, the available studies provide *inadequate/insufficient evidence to determine whether an association exists* between snus use and general health measures.

2.8.10 Groin Hernias

Summary from 2013 ENVIRON Report

No studies on groin hernias were previously included in the 2013 ENVIRON report.

Newly Identified Studies

A single study that investigated the potential relationship between groin hernia repair and snus use was published since the 2013 ENVIRON report (Hemberg et al. 2017). The population-based longitudinal cohort study consisted of 102,857 adults from Vasterbotten county in Sweden whose data was collected between 1989 and 2013 in the Vasterbotten Intervention Study. 100,741 adults over the age of 40 were included for analysis. When compared to never-users of the same sex in multivariate Cox regression analyses, the hazard ratios all hovered around 1 and were statistically insignificant for all comparison groups: former snus users, <4 boxes per week, and 4 or more boxes per week. The authors concluded that "tobacco [snus] use is not a risk factor for requiring a groin hernia repair."

Discussion and Conclusions

A major limitation of the Hemberg et al. (2017) study is that the analyses of snus use did not adjust for smoking or age, which are associated with risk of groin hernia repair. The methodology of the study was unclear in that it lacked information on timing of exposure and outcome assessments. Though the study has adequate power due to its large population size, the data originated from an intervention program wherein individuals may change habits due to counseling while in the program. Furthermore, the intervention program involves only those older than 40, so participants who underwent groin hernia repair prior to joining the program were excluded. Lastly, the study does not address the association between snus use and groin hernias that may or may not require surgery. This single, moderate quality study provides *inadequate/insufficient evidence to determine whether an association exists.*

2.8.11 Multiple Sclerosis

Summary from 2013 ENVIRON Report

Although study findings from two studies on multiple sclerosis were summarized in the 2013 ENVIRON report (Carlens et al. 2010; Hedstrom et al. 2009), standardized conclusions were not provided. A discussion of the new studies as well as standardized conclusions that take into account the old and new evidence are provided below.

Newly Identified Studies

Two studies that investigated the relationship between multiple sclerosis (MS) and Swedish snus use were published since the 2013 ENVIRON report (Gustavsen et al. 2014; Hedström et al. 2013). The

smaller of these studies was a case-control study consisting of 756 MS patients in Norway and 1,090 healthy controls selected from the Norwegian Bone Marrow Donor Registry (Gustavsen et al. 2014). The study was conducted between 2011 and 2012, and analyses were split into two groups: those who were carriers of the HLA-DRB1*15:01 gene (positively associated with MS) and those who were not carriers. Overall, 11.4% of MS patients reported using snus vs. 15.6% among controls. The odds ratio of ever-snus users who were carriers of the HLA-DRB1*15:01 gene trended lower (0.60; 95% CI 0.27-1.32) than the odds of ever-snus users who were not carriers of the gene (0.88; 95% CI 0.39-2.0). Snus users included those who smoked, but analyses were adjusted for smoking. The authors reported a significant decreased risk of MS among snus users who were carriers of the HLA-DRB1*15:01 gene (OR 0.41; 95% CI 0.22-0.77), but this association was only seen in unadjusted analysis. Selection bias of the controls is likely present as bone marrow donors may be healthier than the general population (Gustavsen et al. 2014).

A pooled case-control study of 17,320 Swedish adults (7883 cases and 9437 controls) similarly found a decreased risk of developing MS in snus-users compared with those who had never used snus (Hedström et al. 2013). The 2005-2012 study captured snus use in use categories: <5 packet-years, 5-10 packet years, and >10 packet-years, with the referent group as non-users of snus. The odds ratio of developing MS was lower in those who had greater cumulative snus use (0.85 in those with less than 5 packet-years of use, 0.77 in those with 5-10 packet-years of use, and 0.57 in those who had greater than 10 packet-years of use). When stratified by sex and packet-years, the odds ratio for developing MS was lower in those with over 10 packet-years of use compared with those with only 5-10 packet-years. Notably, the study reported odds ratios for never smokers with 5-10 packet-years and more than 10 packet-years. The odds ratio was lower in never-smokers with more than 10 packet-years (0.45) compared to that of never-smokers with 5-10 packet-years (0.87). Current users who were also smokers had greater positive odds (1.19) of developing MS compared with those who used to smoke (1.42). These risk estimates are all statistically significant, with the exception of those reported for female snus users only. However, the authors note that only the results from unmatched analyses are reported due to the matched analyses being statistically insignificant, though trends were similar (Hedström et al. 2013).

Quality Rating of all Studies

Study	**Evidence Quality Rating**
Carlens et al. 2010	Strong
Hedstrom et al. 2009	Moderate
Hedstrom et al. 2013	Moderate
Gustavsen et al. 2014	Moderate

Discussion and Conclusions

The two new studies (Hedstrom et al. 2013; Gustavsen et al. 2014) support the findings from the 2013 ENVIRON report in which two studies reported no association between snus use and development of MS (Carlens et al. 2010; Hedstrom et al. 2009). A case-control study (Hedstrom et al. 2009) found a significant lower risk of developing MS in snuff users who smoked, after adjusting for age, sex, ancestry, residential area and smoking. The second study was a cohort of 277,777 males from the Swedish Construction Workers Cohort and found that ever use of snus was not associated with risk of MS after adjusting for smoking. However, the risk was marginally statistically significantly

increased among never-smoking snus users (Carlens et al. 2010), though no dose-response relationship was observed. The authors also noted that the increased risk among exclusive snus users may have been due to chance. Together, the four studies, all with significant power and results but with study-specific limitations, show *limited/suggestive evidence of no association* between snus use and MS.

2.8.12 Musculoskeletal Disorders

Summary from 2013 ENVIRON Report

No new studies were identified since publication of the 2013 ENVIRON report. Previously reviewed studies reported an increased risk of injury proneness (Heir and Eide 1997), disability pension due to musculoskeletal diagnosis (Bolinder et al. 1992), and disability pension due to neck or low back pain (Holmberg and Thelin 2006), and low back pain (Mattila et al. 2008) in snus users. However, Bolinder et al. (1992) also did not report an increased risk of low back pain in never-smoking snus users compared with non-tobacco users. Other results reported by Bolinder et al. (1992), pain in leg while walking, were not discussed in the 2013 ENVIRON report, but were summarized in Appendix Q-1, and are discussed here.

Heir and Eide (1997) investigated injury proneness in a prospective study of 480 male military conscripts. Snuff use was associated with a significantly increased risk of proneness to musculoskeletal injuries during training, adjusted for age and fitness (OR=2.31; 95% CI: 1.34- 3.99).

Bolinder and colleagues (1992) conducted a cross-sectional study among 37,722 Swedish construction workers and examined the prevalence of disability pension for musculoskeletal diagnoses among snus users. The risk of disability pension for musculoskeletal diagnoses was significantly increased in never-smoking snus users at both age 46-55 years (OR=2.8; 95% CI: 1.6-4.8) and 56-65 years (OR=1.5; 95% CI: 1.2-1.8). Bolinder and colleagues (1992) also examined the prevalence of low back pain within the past year among the 37,722 male Swedish construction workers. Among never-smoking snus users, the prevalence of low back pain within the past year was not significantly elevated (OR=1.1; 95% CI: 1.0-1.2). Furthermore, Bolinder et al. (1992) reported that the risk of having pain in leg while walking was slightly significantly increased in snus users compared with non-tobacco users (OR=1.2; 95% CI: 1.2-1.4). The analyses presented by Bolinder et al. (1992) were either stratified by age groups, or adjusted for age only.

Holmberg and Thelin (2006) examined long-term health outcomes associated with neck and back pain in a prospective cohort study of 1,347 Swedish farmers and rural non-farmers. They found that neck or low back pain at study entry was a significant predictor of consultation with a primary care doctor and sick leave during 12 years of follow-up. Snuff use was considered as a possible confounder; surprisingly, it was identified as a strong independent predictor of disability pension due to neck or low back pain (OR=3.46; 95% CI: 1.35-8.84). There is little information on snuff use and musculoskeletal symptoms; the authors note that this finding must be interpreted cautiously, and that further research is warranted.

Mattila and colleagues (2008) investigated low back pain in a cross-sectional study of 7,040 Finnish, male military conscripts. A significantly increased prevalence of low back pain was observed among smokeless tobacco users (not specified as Swedish snus), adjusted for age, perceived health, and disease during the past year (OR=1.4; 95% CI: (1.2-1.7).

Quality Rating of all Studies

Study	Endpoint(s)	Evidence Quality Rating
Heir and Eide 1997	Proneness to musculoskeletal injuries	Weak
Bolinder et al. 1992	Disability pension for musculoskeletal diagnoses, low back pain within past year	Weak
Holmberg and Thelin 2006	Disability pension due to neck or low back pain	Moderate
Mattila et al. 2008	Low back pain	Weak

Discussion and Conclusions

Of the four studies reporting on musculoskeletal disorders, two were cross-sectional studies (Bolinder et al. 1992; Mattila et al. 2008) and thus temporality of exposure and effect cannot be deduced based on the evidence. The small prospective cohort study of male military conscripts (Heir and Eide 1997) controlled for age and fitness, but confidence intervals were wide, and results were not adjusted for smoking. In a cohort study with 12 years of follow-up, Holmberg and Thelin (2006) identified a three-fold risk in disability pension due to neck or low back pain in snus users compared with non-users. Though this study (Holmberg and Thelin 2006) was moderate in its study design, the population was limited to a population of farmers and rural non-farmers and the results may not be appropriately representative of the general Swedish population. Based on the results of these four studies (Bolinder et al. 1992; Mattila et al. 2008; Heir and Eide 1997; Holmberg and Thelin 2006), there is *inadequate/insufficient evidence to determine whether an association exists* between snus use and various measures of musculoskeletal disorders.

2.8.13 Pain and Post-operative Nausea and Vomiting Following Surgery

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

Brattwall and colleagues (2010) examined the effects of snus use and smoking on pain and post-operative nausea and vomiting (PONV) following common day surgical procedures. The authors followed 355 patients during recovery and the first day at home, and found that PONV was significantly reduced during the early post-operative period among tobacco users (which included smokers and snus users). With respect to post-operative pain, no significant impact on incidence was observed for regular tobacco use. The number of regular tobacco users was not sufficient for further sub-group analyses of snus use or smoking individually.

Discussion and Conclusions

This single weak study exploring the effects of snus use on pain and PONV following surgery did not include analyses of snus use and smoking individually (Brattwall et al. 2010). The study lacks adjustment for smoking and thus does not evaluate snus exposure effectively. There is *inadequate/insufficient evidence to determine whether an association between snus use and pain and PONV*.

2.8.14 Parkinson's disease

Summary from 2013 ENVIRON Report

No studies on Parkinson's disease were previously included in the 2013 ENVIRON report.

Newly Identified Studies

Two studies that investigated the relationship between Swedish snus use and Parkinson's disease were published since the 2013 ENVIRON report (Liu et al. 2017, Yang et al. 2016). Starting in 1973-1974, a cohort of 20,333 residents free from Parkinson's disease, 15 years of age or older in Uppsala County, Sweden, was followed until 2012 (Liu et al. 2017). The authors reported that use of Swedish snus was associated with a reduced risk of developing Parkinson's disease in males (the association in females was not reported). With the referent group of those who never used tobacco daily, the hazard ratios for exclusive ever snus users of 10 years or less and more than 10 years were below 1: 0.51 (95% CI: 0.2-1.49) and 0.5 (95% CI: 0.23-1.1), respectively. When stratified by amount of snus use, snus use of 10 grams or less per day was associated with lower risk of Parkinson's disease (HR 0.33 95% CI 0.12-0.91) compared to more than 10 grams per day (HR 0.76 95% CI 0.35, 1.66) (Liu et al. 2017).

The second study (Yang et al. 2016) pooled seven cohort studies for a total of 351,640 participants followed from 1978 to 2013 in Sweden, with a mean follow-up of 16.1 years. Among men who had never smoked, ever-snus users had a statistically significant lower risk of Parkinson's disease compared with never-snus users (pooled hazard ratio 0.41; 95% CI: 0.28-0.61). This large cohort study also showed an inverse dose-response relationship between snus use and Parkinson's disease risk: light snus use (less than two cans per week) and moderate-heavy snus use (two or more cans per week) resulted in hazard ratios of 0.71 (95% CI: 0.35-1.43) and 0.41 (95% CI: 0.19-0.90), respectively, with never tobacco users (n=550) as the referent group (Yang et al. 2016).

Quality Rating of All Studies

Study	**Evidence Quality Rating**
Liu et al. 2017	Strong
Yang et al. 2016	Strong

Discussion and Conclusions

The two studies exploring the association between Parkinson's disease and snus use in this report were large cohort studies with sufficient statistical power (Liu et al. 2017, Yang et al. 2016). Both studies concluded that the use of Swedish snus was associated with a reduced risk of developing Parkinson's disease. There was a possibility of misclassification of exposure in both studies, as snus exposure was measured at baseline and may have changed over time. In this study (Yang et al. 2016), there was also a relatively small number of exposed cases. Based on the above two studies reporting a decreased risk of Parkinson's disease among snus users, there is *limited/suggestive evidence of an inverse association*.

2.8.15 Psychiatric Disorders

Summary from 2013 ENVIRON Report

Though some studies suggest snus may be associated with psychiatric disorders, this has not been universally observed, and all the studies are cross-sectional in nature, and simply report an

association; causality, including the issue of temporality cannot be determined based on these studies alone. Other results reported by Bolinder et al. (1992), involving "nervous problems," were not discussed in the 2013 ENVIRON report, but were summarized in Appendix Q-1 of that report. Bolinder et al. (1992), as well as newly identified studies are summarized and discussed below.

Newly Identified Studies

Identified in the 2013 ENVIRON report, Bolinder et al. (1992) reported a large cross-sectional study of male construction workers who received health examinations during 1971 through 1974. After excluding participants who used more than one type of tobacco product or were former smokers, 37,722 people were included in the analyses. The odds of having nervous problems was 20% higher (statistically significant) in those who used snus exclusively compared to non-tobacco users (95% CI 1.1-1.4). The term "nervous problems" is not defined. Due to the cross-sectional nature of the study, temporality cannot be determined. Furthermore, there was no adjustment for any potential confounders other than age, thus, the study is classified as having weak evidence for the relationship between snus and nervous problems.

The association between Swedish snus use and psychiatric disorders was reported in two studies published since the 2013 ENVIRON report. Munafo et al. (2016) investigated the potential relationship between snus use and non-affective psychosis and schizophrenia in a cohort study of 227,117 Swedish men from multiple national registers without a non-affective psychosis or schizophrenia diagnosis. The average age at conscript was 18.2 years and the age at the end of follow up was 26.1 years. After adjusting for smoking, snus users had an elevated risk of non-affective psychosis (HR=1.22; 95% CI: 1.00-1.48), though not statistically significant. For those who use snus exclusively, the risk of developing non-affective psychosis was statistically significantly elevated (HR=1.38; 95% CI 1.09-1.75). Hazard ratios for schizophrenia were not statistically significantly increased (Munafo et al. 2016).

Pedersen and von Soest (2014) reported on the relationship between snus use and depressive symptoms in two (2002 and 2010) pooled population-based cross-sectional studies of 6,217 Norwegian 16- and 17-year-olds. Compared with the group with no tobacco use, the risk of having depressive symptoms were significantly elevated in those with daily snus use (OR: 1.27; 95% CI 1.06-1.51, $p<0.05$) (Pedersen and von Soest 2014).

Quality Rating of all Studies

Study	**Endpoint(s)**	**Evidence Quality Rating**
Bolinder et al. 1992	Nervous problems	Weak
Edwards et al. 2011	Major depression	Weak
Engstrom et al. 2010	Psychological distress	Weak
Munafo et al. 2016	Non-affective psychosis and schizophrenia	Moderate
Pedersen and von Soest 2014	Depressive symptoms	Weak

Discussion and Conclusions

Non-affective Psychosis and Schizophrenia

The cohort study (Munafo et al. 2016) of over 200,000 Swedish men found that there was a significant elevated risk of developing non-affective psychosis and a nonsignificant, elevated risk of schizophrenia. However, due to the relatively low number (n=36) of exposed cases compared to the total cohort enrolled (227,117) and the reference group and follow-up period not precisely defined, this study is limited in its quality of evidence. Based on this single moderate study, there is *inadequate/insufficient evidence to determine whether an association exists* between snus use and non-affective psychosis or schizophrenia.

Nervous Problems and Psychosocial Distress

Two cross-sectional studies explored the potential association between Swedish snus and the development of nervous problems and psychological distress (Bolinder et al. 1992 and Engstrom et al. 2010, respectively). Bolinder and colleagues (1992) reported a statistically significant increase in risk of nervous problems compared with non-tobacco users. However, due to the cross-sectional nature of the study design, the temporality of exposure to Swedish snus and development of nervous problems cannot be determined. In contrast, Engstrom et al. (2010) reported a cross-sectional study which concluded that psychological distress and the use of Swedish snus was not significantly associated with psychosocial distress, as measured by the General Health Questionnaire (GHQ-12). Based on these two cross-sectional studies alone, there is *inadequate/insufficient evidence to determine whether an association exists* between snus use and these psychiatric endpoints.

Major Depression and Depressive Symptoms

Both studies investigating major depressive or depressive symptoms identified in this and the previous 2013 ENVIRON report conveyed a significant association with the prevalence of snus use (Edwards et al. 2011; Pedersen and von Soest 2014). However, both studies presented limitations: the main limitation being that the studies are cross-sectional and thus temporality cannot be elucidated. Edwards et al. (2010) did not adjust for smoking nor other types of potential confounders including neuroticism and socioeconomic status. The study of Norwegian adolescents (Pedersen and von Soest 2014) had a restrictive age group, and though response rates were high (91.0% in 2002 and 84.3% in 2010), the difference in response rates indicates that a proportion of the population is missed that may or may not be more disposed to using snus. Given these two small cross-sectional studies, there is *inadequate/insufficient evidence to determine whether an association exists* between snus use and major depression or depressive symptoms exists.

2.8.16 Respiratory Symptoms and Death

Summary from 2013 ENVIRON Report

Roosaar and colleagues (2008) found that ever daily use of snus (adjusted for smoking and among never-smokers) was significantly associated with an increased risk of death from respiratory disease among men aged 80 or older. The authors noted that the mechanisms of the observed excess risk of respiratory deaths in this age group could possibly be due to confounding from smoking and remain to be established.

Newly Identified Studies

Three studies that investigated the relationship between respiratory symptoms and snus use were published since the 2013 ENVIRON report (Bjorkman et al. 2017; Gudnadottir et al. 2017; Zandonai et al. 2016). Bjorkman and colleagues (2017) designed a clinical trial with 42 otherwise healthy snus users with over two years of daily use and doing regular exercise three or more times a week. Twenty-four patients were measured before and after stopping use of snus for over six weeks, and 11 snus users served as controls and continued their usual daily use. The peak value respiratory measurements were taken during maximal running tests: VO_2max, time to exhaustion, peak heart rate, volume of expired air, respiratory exchange ratio, blood lactate, and rating of perceived exertion for breathing and legs. The arithmetic means between the snus cessation group and the controls were not significantly different for any of these measurements, except for time to exhaustion ($P<0.000$) and blood lactate ($p=0.02$). Notably, the authors concluded that endurance exercise performance (VO_2max and maximal endurance time) was not affected by prolonged snus use (Bjorkman et al. 2017).

Gudnadottir et al. (2017) conducted a cross-sectional study of over 25,000 adult respondents who were randomly selected for a questionnaire in the Global Allergy and Asthma European Network survey in four Swedish cities in 2008. The participants were divided into three exposed groups: nonsmoking current daily snus users for six or more months, dual daily users (snus and smoking), former snus users who never smoked, and were compared with two groups: currently tobacco-free including former smokers and tobacco-free never-smokers. Analyses were adjusted for gender, age, BMI, study center, educational level, and physical activity. The risks of having some asthmatic symptoms (particularly wheezing and night-time chest tightness), chronic bronchitis, and chronic rhinosinusitis were significantly increased ($p<0.05$) in both nonsmoking current snus users and dual users when compared with currently tobacco-free participants (Gudnadottir et al. 2017). Risk of asthma and allergic rhinitis was significantly increased among nonsmoking current snus users (OR 1.51; 95% CI: 1.28-1.77; OR 1.17; 95% CI: 1.05-1.3), but not in dual users (OR 0.93; 95% CI: 0.65-1.33; OR 0.92; 95% CI: 0.75-1.13). With tobacco-free never-smokers as the reference group, never-smoking current snus users had increased risk of asthma (OR 1.49; 95% CI: 1.2-1.85), chronic bronchitis (OR 1.47; 95% CI: 1.21-1.78), chronic rhinosinusitis (OR 1.37; 95% CI: 1.11-1.7), and asthmatic symptoms. Overall, the authors reported an association between risk of asthma and current snus use, but observed no increased risk among smokers or dual users. For asthmatic and other respiratory symptoms, there was also an increased risk among snus users as well as among smokers and dual users (Gudnadottir et al. 2017).

Zandonai et al. (2016) conducted a double-blind, randomized crossover clinical trial in which 12 healthy male non-tobacco users used snus or a placebo during exercise. No significant differences between snus or snus placebo were observed for volume of expired air, VO_2, nor VCO_2. Furthermore, the mean respiratory exchange ratio (1.03±0.04) during exercise was the same for snus and placebo (Zandonai et al. 2016).

Quality Rating of All Studies

Study	**Endpoint(s)**	**Evidence Quality Rating**
Bjorkman et al. 2017	Respiratory measures	Strong
Gudnadottir et al. 2017	Asthma, asthmatic symptoms, chronic	Weak

	bronchitis, allergic rhinitis, chronic rhinosinusitis	
Roosaar et al. 2008	Respiratory death	Moderate
Zandonai et al. 2016	Respiratory responses (VE, VO2, VCO2)	Moderate

Discussion and Conclusions

Respiratory Performance During Exercise

Two clinical studies tested participants on respiratory performance during exercise (Bjorkman et al. 2017, Zandonai et al. 2016). One clinical trial had snus users stop using for a period of time (Bjorkman et al. 2017) so misclassification of exposure may have occurred due to participants' modification of behavior during follow-up. Snus abstinence was only tested at the very end of cessation, not throughout (Bjorkman et al. 2017). The second clinical trial (Zandonai et al. 2016) was limited in its sample size (only 12 participants). Despite these limitations, these clinical studies on snus use and respiratory performance provide *limited/suggestive evidence of no association* between snus use and respiratory performance during exercise.

Asthma and Other Respiratory Issues

Gudnadottir and colleagues (2017) conducted a large cross-sectional study of over 25,000 Swedish adults but the nature of the study design prevents any conclusion regarding the temporal relationship between snus use and the respiratory outcomes investigated. Furthermore, some analyses were based upon a tobacco-free comparison group that in actuality included nearly 27% former smokers and thus does not represent a true tobacco-free group (Gudnadottir et al. 2017). Based on this single cross-sectional study, there is *inadequate/insufficient evidence to determine whether an association exists* between snus use and asthma, asthmatic symptoms, chronic bronchitis, allergic rhinitis, or chronic rhinosinusitis.

Respiratory Death

The population-based cohort study conducted by Roosaar et al. (2008) is strong in its design (over 220,000 person-years), but did not adjust for confounding by dietary pattern, physical activity, and socioeconomic status that could have shifted the relative risks in any direction. Statistical imprecision is a second limitation, since the exposed cases were few and resulted in risk estimates with wide confidence intervals (Roosaar et al. 2008). This single cohort study lacked important information on covariates and provides *inadequate/insufficient evidence to determine whether an association exists* between snus use and respiratory death.

2.8.17 Rheumatoid Arthritis

Summary from 2013 ENVIRON Report

The cohort study conducted by Carlens and colleagues (2010) investigated the relationship between tobacco smoking and snus use and rheumatoid arthritis. Ever use of snus (adjusted for smoking) was not associated with risk of rheumatoid arthritis (RR=1.0; 95% CI: 0.9-1.2), nor was the use of snus among never-smokers associated with risk of rheumatoid arthritis (RR=1.2; 95% CI, 0.8-1.8). Smoking was significantly associated with an increased risk of developing rheumatoid arthritis.

Newly Identified Studies

Two studies that investigated the association between Swedish snus use and rheumatoid arthritis were identified since the 2013 ENVIRON report (Andersson et al. 2013; Jiang et al. 2014). Andersson et al. (2013) examined 2,800 patients enrolled from 1992-2005 and followed through 2010 in a longitudinal observational study of participants with early rheumatoid arthritis in southern Sweden. Fifty-one snus-using patients were identified and compared with 49 never-smoking controls using a composite score called the DAS28 (Disease Activity Score using 28-joint count) measuring the number of swollen and tender joints, erythrocyte sedimentation rate, and patient's global assessment. The snus users had statistically significant lower mean DAS28 scores ($p=0.001$) at 3 months' (2.0) and 6 months' follow-up (2.1), but not after 1, 2, or 5 years compared with never smokers (3 months: 3.7; 6 months: 3.2). These mean scores were statistically significantly different between snus users and never-smokers only after adjustment for socioeconomic class, disease duration, and number of previous disease-modifying anti-rheumatic drugs and biologics (Andersson et al. 2013). When comparing snus users with current smokers, clear trends were not evident.

The second study exploring the connection between snus use and rheumatoid arthritis was a case-control study consisting of 1,998 cases and 2,252 controls over the study period 1996 to 2006 (Jiang et al. 2014). The study calculated the odds ratios for three outcomes (rheumatoid arthritis, anti–citrullinated protein/peptide antibody positive rheumatoid arthritis, and anti–citrullinated protein/peptide antibody negative rheumatoid arthritis) in varying groups of snus users: ever, current, and former snus users, combined with never smoking, ever smoking, or [combined] light, former or never smoking habits. All odds ratios hovered around 1 and were not statistically significant. They were calculated using unconditional logistic regression models and were adjusted for cigarette smoking, alcohol consumption, and matching variables (Jiang et al. 2014).

Quality Rating of all Studies

Study	**Evidence Quality Rating**
Carlens et al. 2010	Strong
Andersson et al. 2013	Weak
Jiang et al. 2014	Moderate

Discussion and Conclusions

Two of the three studies evaluating snus use and rheumatoid arthritis concluded that there was no association (Jiang et al. 2014, Carlens et al. 2010). Jiang and colleagues' (2014) population-based case-control study enrolled incident rheumatoid arthritis cases with limited potential for selection bias as evidenced by high participation rates. The study lacked information on intensity of snus use (Jiang et al. 2014). The magnitude of selection and information biases that are common in case-control studies cannot be determined and may have skewed the results toward the null. The high-powered, prospective study conducted by Carlens et al. (2010) followed a large cohort of 277,777 male construction workers with relatively high prevalence of exposure, with long follow-up (mean 20 years) and limited recall and information bias. However, snus use was only estimated from a single visit and potential changes in tobacco habits were not recorded over time (Carlens et al. 2010).

One study reported a slight inverse relationship between snus use and rheumatoid arthritis as measured by composite measurement DAS28 (Andersson et al. 2013) that was no longer present at 1,

2, or 5 years' follow-up. Potential misclassification and recall bias were present because snus use was assessed retrospectively. Furthermore, the sample size was small at only 51 snus users and 49 never-smoking controls (Andersson et al. 2013). Based on a strong and moderate study showing a lack of an association between rheumatoid arthritis and snus use (Carlens et al. 2010, Jiang et al. 2014), and the single smaller study that concluded an inverse relationship using a composite scoring system early on in follow-up, there is *limited/suggestive evidence of no association* between snus use and rheumatoid arthritis.

2.8.18 Sarcoidosis

No new studies were identified since publication of the 2013 ENVIRON report.

Summary from 2013 ENVIRON Report

Carlens and colleagues (2010) also examined the relationship between tobacco smoking and snus use and sarcoidosis. Ever use of snus, adjusted for smoking, or among never-smokers was not associated with increased risk of sarcoidosis (RR=0.9; 95% CI: 0.8-1.5 for both). However, smoking was protective against developing sarcoidosis, which the authors note is consistent with findings from other studies.

Discussion and Conclusions

This cohort study (Carlens et al. 2010) was limited in its measure of exposure: tobacco habits were only measured at study entry but potential changes in tobacco habits over time could influence the results. Furthermore, due to the "healthy worker effect" in that construction workers may have specific exposures and characteristics which would restrict the generalizability of the results. However, this study provided strong evidence overall, and based on this single large study, there is *limited/suggestive evidence of no association* between snus use and risk of sarcoidosis.

2.8.19 Skin Conditions

Summary from 2013 ENVIRON Report

Wolk and colleagues (2009) investigated the relationship between a variety of risk factors, including smoking and smokeless tobacco use and plaque psoriasis in a case-control study in Stockholm, Sweden. No association was observed between current snus use and plaque psoriasis (OR=1.0; 95% CI: 0.6-1.9).

Newly Identified Studies

One study that investigated the relationship between Swedish snus use and skin conditions was published since the 2013 ENVIRON report (Wrangsjo et al. 2015). Wrangsjo and colleagues (2015) conducted a cross-sectional study of 47,931 randomly chosen adults from the Stockholm, Sweden population register in 2006. With a response rate of 58%, participants self-reported on their snus use, smoking, hand eczema and doctor-diagnosed psoriasis. After adjustment for potential confounders (stress, obesity, physical exercise) there was a statistically significant inverse association between daily exclusive snus use and reported hand eczema (prevalence proportion ratio 0.813; 95% CI 0.686-0.964, *p=0.017*) with the non-tobacco users as the referent group (Wrangsjo et al. 2015). In dual users (snus and smoking), the prevalence proportion ratio showed a slight positive association but was not statistically significant (PPR=1.187; 95% CI: 0.851-1.655, *p=0.313*). The authors concluded that there was no positive association between snus use and hand eczema. Only 3.3% of

respondents had doctor-diagnosed psoriasis, and with no potential confounders reported, there was no association reported between psoriasis and exclusive snus use (PPR=1.064; 95% CI 0.861-1.316, *p=0.566*).

Quality Rating of all Studies

Study	**Endpoint(s)**	**Evidence Quality Rating**
Wolk et al. 2009	Plaque psoriasis	Moderate
Wrangsjo et al. 2015	Hand eczema, psoriasis	Moderate

Discussion and Conclusions

The authors of two population-based studies in Sweden both concluded that there was no association between snus use and the development of psoriasis or eczema (Wolk et al. 2009, Wrangsjo et al. 2015). The case-control study (Wolk et al. 2009) was well designed; odds ratios were adjusted for age, sex, post code, body mass index, weight gain, alcohol, and smoking and the response rate was 88%. However, potential selection bias as a part of the case-control design cannot be fully accounted for, and the study was moderately-sized with less than 400 cases. Wrangsjo and colleagues (2015) performed a large cross-sectional study, but the response rate was low (58%), and temporality between exposure and outcome cannot be determined. Based on the two studies investigating psoriasis and hand eczema summarized above, there is *limited/suggestive evidence of no association* between snus use and these skin conditions.

2.8.20 Sleeping Problems

Summary from 2013 ENVIRON Report

Although Bolinder et al. (1992) investigated the association between snus use and sleeping disturbances, these results were not discussed in the 2013 ENVIRON report, but were summarized in Appendix Q-1, and are discussed below along with newly identified studies.

Newly Identified Studies

Bolinder and colleagues (1992) conducted a large cross-sectional study of male Swedish construction workers, previously described in Section 2.8.9 General Health. Compared with non-tobacco users, both snus users and smokers (15 or more cigarettes per day) had significantly elevated odds of reporting sleeping disturbances: snus users OR 1.2; 95% CI 1.1-1.4; smokers OR 1.8; 95% CI 1.7-2.0 (Bolinder et al. 1992).

Two cross-sectional studies that evaluated the potential association between snus use and sleeping problems were published since the 2013 ENVIRON report (Gudnadottir et al. 2017, Pettersson et al. 2016). The larger study (Gudnadottir et al. 2017) included 26,697 respondents aged 16 to 75 years from four Swedish cities who were randomly selected for a postal questionnaire in the Global Allergy and Asthma European Network survey in 2008. The authors concluded that snus users had an increased risk of some sleep problems (snoring, difficulty initiating sleep, excessive daytime sleepiness) but decreased risk of difficulty maintaining sleep, compared to current tobacco-free respondents not excluding former smokers. Non-smokers who had been using snus daily for six months or more had a significantly higher risk ($p<0.05$) of snoring (OR=1.41; 95% CI: 1.25-1.58), difficulty initiating sleep (OR=1.76; 95% CI: 1.56-1.99), excessive daytime sleepiness (OR=1.18; 95% CI: 1.07, 1.31), and use of medication for sleeping problems (OR=1.33; 95% CI: 1.07-1.65)

than tobacco-free former and never-smokers. The nonsmoking daily snus group had a decreased risk of difficulty maintaining sleep than current tobacco-free participants (OR=0.74; 95% CI: 0.66-0.83). Similar findings were reported for dual users (snus and smoking). Another exposed group were never-smokers who use snus daily for at least six months. Compared with tobacco-free never-smokers, snus users had significantly greater risk ($p<0.001$) of snoring (OR=1.53; 95% CI: 1.29-1.82), and difficulty initiating sleep (OR=1.71; 95% CI: 1.44, 2.03), and significantly decreased risk ($p<0.001$) of having difficulty maintaining sleep (OR=0.71; 95% CI0.59-0.84) and early morning awakening (OR=0.83; 95% CI: 0.67-1.04).

The second cross-sectional study consisted of 1,080 Swedish veterans from Kosovo and Afghanistan and 26,723 Swedes from a general population sample (Pettersson et al. 2016). Of the military participants, 297 were snus users while 2,886 of the general population sample used snus; veterans were three times more likely to use snus compared with Swedish civilians. The study combined veterans and the general population to evaluate sleep problems in the form of snoring, difficulty inducing sleep, difficult maintaining sleep, early morning awakenings, insomnia, and excessive daytime sleepiness, and adjusted for military assignment, age, sex, BMI, asthma, history, smoking history, educational level, and physical exercise. When daily snus users were compared against non-snus users, daily snus users had a statistically significant higher risk of having the following sleep problems: snoring (OR=1.28; 95% CI: 1.15-1.41), difficulty inducing sleep (OR=1.65; 95% CI: 1.48-1.83), excessive daytime sleepiness (OR=1.11; 95% CI: 1.02-1.22). Pettersson and colleagues calculated statistically significant lower risk of early morning awakenings (OR=0.81; 95% CI: 0.72-0.92) and difficulty maintaining sleep (OR=0.74; 95% CI: 0.67-0.82) in daily snus users compared with non-snus users.

Quality Rating of all Studies

Study	**Evidence Quality Rating**
Bolinder et al. 1992	Weak
Gudnadottir et al. 2017	Weak
Pettersson et al. 2016	Weak

Discussion and Conclusions

The three studies exploring the relationship between snus use and sleeping problems found that there may be a positive association for some sleeping issues and no association for others (Bolinder et al. 1992, Gudnadottir et al. 2017, Pettersson et al. 2016). Gudnadottir and colleagues (2017) reported that snus users specifically had increased risk of snoring, difficulty initiating sleep, excessive daytime sleepiness and decreased risk in other issues including difficulty maintaining sleep and early morning awakening in some groups. This is supported by the Pettersson et al. study wherein it was reported that there was evidence for an association between snus use and snoring, difficulty inducing sleep, and excessive daytime sleepiness and a decreased risk for difficulty maintaining sleep and early morning awakenings. However, due to the cross-sectional design of the studies, and inconsistent results for different types of sleeping issues, there is *inadequate/insufficient evidence to determine whether an association exists* between snus use and sleeping problems.

2.8.21 Survival Following a Cancer or MI Diagnosis

Summary from 2013 ENVIRON Report

The 2013 ENVIRON report included summary tables (Appendix H and Q-3) of data from the Nordenvall et al. (2013) study (previously cited as Nordenvall et al. 2012), but did not include a discussion in the report. The 2013 EVIRON report also had not identified relevant sensitivity analyses conducted by Hergens et al. (2007), which are relevant to the endpoint of survival following a non-fatal MI event. Nordenvall et al. (2013) and Hergens et al. (2007), as well as two newly identified studies (Arefalk et al. 2014; Wilson KM et al. 2016) are summarized and discussed below.

Newly Identified Studies

Hergens and colleagues (2007) extended the follow-up of the Swedish Construction Worker cohort through 2003 and examined mortality amongst those who experienced a nonfatal myocardial infarction during follow-up as part of a sensitivity analysis in the study. Information on "snuff" use was obtained from follow-up visits starting in 1978 as snuff use data before that date was deemed incomplete. Overall risk of dying from all causes following a non-fatal MI event was statistically significantly increased (RR=1.38; 95% CI: 1.11–1.71) among never smoking ever snus users, compared to never-users of tobacco, following adjustment for age, BMI, and region of residence.

Nordenvall et al. (2013) examined a subgroup of 40,230 men from the Swedish Construction Worker cohort that developed cancer during the study. Tobacco use information was collected from 1971 – 1992, and participants were followed until 2007 through the use of population and health registers. The cohort included 1,946 exclusive snus users and 9,578 never-users of any tobacco. Compared to never use of any tobacco at study entry, exclusive snus use was associated with a modest increased risk of death from any cause (HR=1.13; 95% CI: 1.05, 1.20), death from cancer at the same site as the primary cancer (HR=1.15; 95% CI: 1.05, 1.26), and death from causes other than cancer (HR=1.12; 95% CI: 1.01, 1.25). Hazard ratios were adjusted for age at cancer diagnosis, calendar period of diagnosis, cancer site, and BMI at study entry.

Wilson et al. (2016) examined a subgroup of 9,582 men from the same cohort who developed prostate cancer during the follow-up period through 2007. This cohort included 460 exclusive snus users and 2,762 never-users of any tobacco. Compared to never-users of any tobacco at study entry, exclusive snus use was associated with a modest increased risk of death from prostate cancer (HR=1.24; 95% CI: 1.03, 1.49) and death from any cause (HR=1.19; 95% CI: 1.04, 1.37). Hazard ratios were adjusted for age, time period of diagnosis, BMI, and time between examination and diagnosis.

Arefalk and colleagues (2014) followed a cohort of 20,911 MI patients who were admitted to a Swedish coronary care unit between 2005 and 2009 to investigate the effects of quitting snus on cardiovascular mortality and events. The population included 1,799 post-MI snus users and 675 post-MI snus quitters; comparisons were limited by the lack of exclusive snus users and never-users of snus. The risk of mortality from any cause among post-MI snus quitters following an MI event was reduced by almost half (HR: 0.55; 95% CI 0.31, 0.99) compared to those who continued to use snus in a model (Model D) adjusted for age, sex, smoking exposure, diabetes mellitus, hypertension, blood pressure, BMI, waist circumference, LDL/HDL ratio, type of MI, occupation status, physical activity (4 levels), participation in cardiac rehabilitation program, treatment with aspirin, treatment with any other platelet inhibitor (primarily clopidogrel), β-blockers, statins, and renin-angiotensin-aldosterone system inhibitors (angiotensin-converting enzyme inhibitor or angiotensin 2 receptor blocker). In the "main Model C," which included adjustment for age, sex, past and present smoking and sun exposure,

respectively, occupation status, participation in cardiac rehabilitation program, the result was similar, though it was not statistically significant (HR: 0.57; 95% CI 0.32, 1.02). Mortality due to non-cardiovascular events was similarly decreased using the model C adjustment factors (HR 0.43; 95% CI 0.15, 1.27).

Quality Rating of all Studies

Study	**Endpoint(s)**	**Evidence Quality Rating**
Arefalk et al. 2014	Overall, and non-CVD mortality following MI event	Moderate
Hergens et al. 2007	Overall, following MI event	Moderate
Nordenvall et al. 2013	Overall, primary cancer, and non-cancer mortality following cancer diagnosis	Moderate
Wilson KM et al. 2016	Overall, and prostate cancer mortality following prostate cancer diagnosis	Moderate

Discussion and Conclusions

Survival following a cancer diagnosis

Though these studies (Nordenvall et al. 2013; Wilson KM et al. 2016) were well conducted, and included large populations, they present some important limitations and design considerations. Neither study allows for the assessment of the risk of developing cancer among snus users because participants had already been diagnosed when selected for inclusion in the study. Instead, these studies assessed survival following diagnosis. Although the studies suggest a potential role for snus use in disease progression, increased risks were also observed for non-cancer deaths, and overall mortality. Furthermore, tobacco use was assessed only at study entry. Tobacco habits may have changed over time, and the authors were unable to confirm whether the participants were still users around the time of diagnosis and/or death. The time between study entry and diagnosis was potentially quite long. For example, Wilson et al. (2016) reported an average of 20 years. Additionally, given the relatively modest increases in risk among snus users, minor differences in risk factors (measured or unmeasured) for mortality between snus users and never-users of tobacco could explain these increases. The evidence provided by the two cancer studies was rated as moderate, but because these studies included participants from the same population and presented other limitations discussed previously, we concluded that the studies provide *inadequate/insufficient evidence to determine whether an association exists* between snus use and survival following a cancer diagnosis.

Survival following an MI diagnosis

The study conducted by Arefalk et al. (2014) included some mixed results, depending on the adjustment model used by the study authors. Furthermore, there was a limited number of never-smoking snus users, with no analyses conducted among exclusive users), and no comparisons with never-users of tobacco were presented. Although Hergens et al. (2007) reported an increased risk of mortality following an MI diagnosis of snus users compared to never-users of tobacco, the snus user group included ever users, and not necessarily current users of tobacco following MI diagnosis. Overall, although these studies were rated as moderate in quality, each provide evidence that is

limited in different ways, and overall, present *inadequate/insufficient evidence to determine whether an association exists* between snus use and survival following an MI diagnosis.

2.8.22 Tongue Abnormalities

Summary from 2013 ENVIRON Report

No studies on tongue abnormalities were previously included in the 2013 ENVIRON report.

Newly Identified Studies

A single study examined the relationship between Swedish snus use and tongue abnormalities, namely geographic tongue and fissured tongue (Dafar et al. 2015). Geographic tongue is defined by the loss of filiform papillae resulting in lesions in a map-like pattern, whereas fissured tongue is a condition where grooves or fissures develop in the dorsal and lateral surfaces of the tongue. Dafar et al. (2015) published a case-control (described as "retrospective cross-sectional") study that enrolled a total of 6,448 dental patients in Boras, Sweden from 2004 to 2006. Patients who were not referred to oral medicine specialists (examined by a general dental practitioner) totaled 130 with geographic tongue (mean age 59.9 years) and 62 with fissured tongue (mean age 65.9 years). A second group consisted of patients referred to oral medicine specialists, with 166 geographic tongue patients and 15 fissured tongue patients, but this group was not included in the analyses of interest. 1,029 patients (mean age 55.2 years) with no oral mucosal lesions served as controls. Snus use was significantly more prevalent among those with geographic tongue vs. controls (10.1% vs. 3.8%, *p-value*<0.01). No significant difference was observed in prevalence of snus use among those with fissured tongue. Multiple logistic regression analysis controlling for age and gender yielded a statistically significant 2.1 odds ratio (95% CI: 1.1, 4.35; *p-value*=0.025) of using Swedish snus and having geographic tongue or fissured tongue, compared with controls.

Discussion and Conclusions

This study (Dafar et al. 2015) demonstrates that snus use is associated with geographic tongue and fissured tongue. However, a major limitation of the study is that smoking was not controlled for in assessing the potential relationship between snus use and tongue abnormalities. Overall, the evidence shown in this study is weak and provides *inadequate/insufficient evidence to determine whether an association exists.*

2.8.23 Vitamin D Levels

Summary from 2013 ENVIRON Report

No studies on vitamin D levels were previously included in the 2013 ENVIRON report.

Newly Identified Studies

One study that investigated the association between Swedish snus use and vitamin D levels was published since the 2013 ENVIRON report (Oberg et al. 2014). This population-based cross-sectional study included 890 adolescents (475 boys and 415 girls) in Norway who attended school from September 2010 through April 2011. Vitamin D in serum was inversely associated with boys' snus use (*p-value*=0.01) but not with girls' snus use (*p-value*=0.1) reported via questionnaire. Snus use was reported in three categories: "Never", "Sometimes", and "Daily" use. Serum vitamin D levels were slightly lower in the "Sometimes" compared to "Daily" group, and both these groups had lower vitamin D levels than the "Never" group for boys. These linear trends in boys were statistically significant in

univariate analyses. The trend between vitamin D levels and girls' snus use was less clear, and statistically insignificant.

Discussion and Conclusions

A major flaw of the study (Oberg et al. 2014) is that it did not account for potential confounders, such as weight, exercise, and diet. The study population was fairly small and geographically limited. Based on the limited cross-sectional nature of the study and lack of adjustment for confounding factors, it cannot be concluded whether or not snuff affects serum vitamin D levels, and whether or not an association is dependent on lifestyle or biological mechanisms. This single, weak study provides *inadequate/insufficient evidence to determine whether an association exists.*

3. HEALTH RISKS OF DUAL USERS AND SWITCHERS COMPARED TO SMOKERS

3.1 Introduction

This section reviews the subset of studies that reported health effect estimates for snus users who concurrently smoke referred to as "dual users" or current snus users who have quit smoking referred to as "switchers". The effect estimates for dual users and switchers will be compared to effect estimates for former smokers and current smokers. In cases when one or both smoking and snus exposures are noted as "ever" exposure, the term "ever dual user" will be used. This is a distinct exposure as it was unclear whether exposure was ever concurrent.

The health outcomes considered for inclusion were those with the highest number of deaths attributable to smoking, as well as several additional health outcomes, as provided in the epidemiological studies. Though accounting for significantly fewer smoking-related deaths compared to some of the outcomes presented in 3-1, other outcomes were included in this analysis for a variety of reasons. Pancreatic cancer was included in this section due to ongoing controversy within the scientific community, though it accounts for only 1.7% of smoking-related deaths in the US annually. Although not confirmed as smoking-related outcomes by the US Surgeon General (USDHHS 2010), diabetes and metabolic syndrome were also included due to the significant burden of morbidity in the population, and high interest as potentially tobacco-related outcomes within the scientific community. Studies on all-cause mortality were also considered for inclusion. Oral cancer was included because it is commonly misperceived, by the general public and some within the scientific community, as an outcome related to Swedish snus, though numerous epidemiological studies and scientific reviews have now confirmed that such an association is weak, if it exists at all. In the CDC (2008) analysis, oral cancer accounted for 1.2% of smoking-related deaths annually in the US. Uncertainty about the possible relationship with snus remains for two other health outcomes presented in this section, notably esophageal cancer and stomach cancer, which account for 2.2% and 0.6% of annual smoking-related deaths, respectively.

The adverse health outcomes causally related to smoking were first confirmed in the 1960s, and have been well studied since that time (USDHHS 2010). These include lung and other cancers, noncancer pulmonary outcomes, such as emphysema and chronic obstructive pulmonary disease (COPD), cardiovascular diseases, and reproductive and developmental effects. The estimated disease mortality burden that smoking poses in the US has been quantified using relative risk estimates from the American Cancer Society's Cancer Prevention Study II (CPS-II), (See table 3-1) ranked by the highest number of deaths among smokers attributed to that health outcome (CDC 2008). More recently, the Food and Drug Administration revised the estimates of smoking-attributable mortality using updated relative risks based on National Health Interview Survey data (Rostron 2012). In the updated analysis, the estimated attributable fractions of smoking-related deaths were very similar to those presented in the CDC (2008) analysis (see Table 3-2). There were, however, fewer disease-specific categories; therefore, the original CDC (2008) estimates were used in the following analysis for all outcomes of interest except lung cancer, ischemic heart disease (IHD), other heart disease and stroke, for which the updated Rostron (2012) estimates were able to be used. AML, which accounts for 0.3% of

smoking-related deaths, was also included because of its known relationship with smoking (indicated in table 3-1).

Table 3-1: Estimated Number of Outcome-Specific Deaths and Attributable Fraction among All Smokers, 2000-2004

Rank (by # of deaths)	Outcome	Smoking Deaths	Attributable Fraction*
1	**Lung Cancer**	125,522	32.0%
2	**IHD**	80,005	20.4%
3	COPD	78,988	20.1%
4	**Other heart disease**	21,004	5.3%
5	**Stroke**	15,922	4.1%
6	Bronchitis, Emphysema	13,927	3.5%
7	Pneumonia, influenza	10,423	2.7%
8	**Esophageal Cancer**	8,592	2.2%
9	Aortic Aneurysm	8,419	2.1%
10	**Pancreatic Cancer**	6,683	1.7%
11	Urinary Bladder Cancer	4,983	1.3%
12	**Oral Cancer**	4,893	1.2%
13	Kidney Cancer	3,043	0.8%
14	Laryngeal Cancer	3,009	0.8%
15	**Stomach Cancer**	2,484	0.6%
16	Atherosclerosis	1,893	0.5%
17	Other circulatory disease	1,254	0.3%
18	**AML**	1,192	0.3%
19	Cervical Cancer	447	0.1%

*Among a total estimate of 392,683 smoking-related deaths (males and females combined)
Bolded outcomes were those analyzed in this section
Reference: CDC 2008 (Based on CPS-II data)

Table 3-2: Estimated Number of Outcome-Specific Deaths and Attributable Fraction (AF) among All Smokers, 2004

Rank (by # of deaths)	Outcome	Smoking Deaths	Attributable Fraction*
1	Lung Cancer	118,950	31.5%
2	COPD	91,045	24.1%
3	IHD	88,525	23.4%
4	Other heart disease	16,113	4.3%
5	Stroke	14,692	3.9%
6	Pneumonia, influenza	10,444	2.8%

*Among a total estimate of 377,521 smoking-related deaths (males and females combined)
Reference: Rostron (FDA) 2012 (Based on NHIS data)

3.2 Methods

Studies identified in the systematic search were evaluated for inclusion of effect estimates for dual users or switchers. These effect estimates were extracted and compared to within study effect estimates for smokers. Results for switchers were additionally compared to results for former smokers. The endpoints for which this data existed included oral and pharyngeal cancer, oral cancer, esophageal cancer and subtypes, pancreatic cancer, stomach cancer and subtypes, lung cancer, overall cardiovascular disease, incident and fatal ischemic heart disease and MI, nonfatal MI, incident and fatal stroke, sudden cardiac death, metabolic syndrome, diabetes prevalence and incidence, acute myeloid leukemia, and all-cause mortality.

No new studies since the 2013 ENVIRON report were identified for the majority of endpoints, and no outcome except for cardiovascular disease had sufficient studies to conduct meta-analyses. However, meta-analyses and comparisons between switchers or dual users with smokers have been performed previously (Lee 2013; Lee 2014). Additionally, these meta-analyses typically perform tests of multiplicative interaction or statistically compare risks in switchers or dual users to smokers. These prior results were referenced in this evaluation in lieu of new meta-analyses and comparisons.

The prior meta-analyses do a standard comparison between relevant exposure groups to compare risks statistically or derive estimates not reported explicitly in the study. For example, Lee (2014) notably derives RR/OR estimates from covariate-adjusted cross-tables to obtain the relevant effect measures to assess interaction. In cases when covariate-adjusted RRs were not provided, unadjusted estimates were calculated directly from numbers of cases and controls. In some cases, Lee (2014) derived estimates from estimates of ever snus among never smokers and an estimate of ever snus among the whole population. Interaction tests in Lee (2014) examined whether the proportional increase in risk associated with snus is greater in smokers than in non-smokers. Specifically, Lee (2014) assessed "whether the proportional increase in risk associated with snus is greater in smokers than in non-smokers (or equivalently whether the proportional increase in risk associated with smokers is greater in snus users than that associated with smoking in non-users of snus), i.e. whether there is any special hazard associated with dual use."

3.3 Oral and Pharyngeal Cancer

3.3.1 Overview of evidence compared to previous report

The previous report identified only Schildt et al. (1998b) as related to oral cancer risk for dual users and switchers. No new studies reported oral and pharyngeal cancer effect estimates in dual users or switchers since the 2013 ENVIRON report. Schildt et al. (1998b) is represented in comparative meta-analyses for dual users and switchers published by Lee (2013; 2014). Notably, Lee (2014) reported dual user effect estimates derived from Roosaar et al. (2008) that they did not report explicitly. The discussion of results from Lee (2013; 2014) was integrated with a more comprehensive discussion of Schildt et al. (1998b).

3.3.2 Outcome comparability

The two studies (Schildt et al. 1998b; Roosaar et al. 2008) identified in the systematic search differed in outcome specificity. Roosaar et al. (2008) included outcomes reported as ICD7: 140-148 that corresponds to "oral and pharyngeal cancer", while Schildt et al. (1998b) included outcomes reported as ICD7: 140, 141, 143, 144, 145 that correspond to the subset of "oral cancer". Consequently, these studies and study results were assessed separately.

3.3.3 Results for oral and pharyngeal cancer incidence in dual users

Reference	Effect measures for Exposures of interest (95% CI)	Effect measures for snus users, smokers, and former smokers (95% CI)	Interaction tests (95% CI)
Lee et al. (2014) *unadjusted* estimates from Roosaar et al. (2008)	Reference: Ever-exclusive smoker Ever dual user: 3.66 (1.45-9.24)	Reference: Never smoker/snuff Ever snus users: 2.30 (0.70-8.30)	*Interaction term for ever dual users* 1.59 (0.34-7.46)

3.3.4 Discussion/Conclusion of oral and pharyngeal cancer incidence

The one study (Roosaar et al. 2008) that considered oral and pharyngeal cancer incidence did not report effect measures for dual users or switchers in their paper. However, Lee (2014) estimated the risk for dual users compared to exclusive smokers using the reported results in the Roosaar et al. (2008) study. Lee (2014) found a statistically significant 3.66 (95% CI: 1.45-9.24) relative risk of oral and pharyngeal cancer compared to ever-exclusive smokers. Lee (2014) reported no evidence of multiplication interaction based on an interaction term of 1.59 (0.34-7.46). In other words, the change in risk associated with dual use is not statistically significantly different from risk observed in snus users.

The secondary analyses of results reported in Roosaar et al. (2008) provide some evidence indicating an increased risk in ever dual users compared to smokers. Lee (2014) also notes that statistically non-significant multiplicative interaction term indicating the reported relative risk in dual users was not statistically significantly different from the relative risk in ever snus users. The wide confidence intervals suggest a lack of statistical power and a need for more studies intended to gauge interaction between these exposures.

3.4 Oral cancer

3.4.1 Results for oral cancer incidence

Reference	Effect measures for Exposures of interest (95% CI)	Effect measures for snus users, smokers, and former smokers	Interaction tests (95% CI)

		(95% CI)	
Schildt et al. (1998b)	Reference: Never smoker/snuff Current dual users: 1.2 (0.6-2.4) Low consumption: 1.0 (0.4-2.1) High consumption: 2.3 (0.9-5.6) Switchers: 0.6 (0.3-1.3)	Reference: Never smoker/snuff Active exclusive snus user: 0.7 (0.4-1.2) Low consumption: 0.8 (0.4-1.6) High consumption: 1.3 (0.6-2.6) Active exclusive smokers: 1.7 (1.1-2.6) Low consumption: 1.2 (0.7-1.9) High consumption: 1.8 (1.1-2.9) Former exclusive smokers: 0.9 (0.6-1.4)	
Lee (2013; 2014) *unadjusted* estimates from Schildt et al. (1998b)	Reference: Current exclusive smoker Current dual user: 0.40 (0.17-0.93) Reference: Ever-exclusive smoker Ever dual user: 0.73 (0.45-1.19) Reference: Never tobacco Switchers: 0.77 (0.34-1.79)	Reference: Non-current smoker/snuff Current snus users: 0.86 (0.51-1.44) Reference: Never smoker/snuff Ever snus users: 1.20 (0.67-2.15) Reference: Never tobacco Current smokers: 1.78 (1.22-2.62) Former smokers: 0.94 (0.61-1.44)	*Interaction term for current dual users* 0.47 (0.17-1.26) *Interaction term for ever dual users* 0.61 (0.29-1.30) *Switchers vs. smokers:* 0.43 (0.18-1.02) *Switchers vs. former smokers*: 0.83 (0.34-1.99)

3.4.2 Discussion

Effects in dual users and comparisons to smokers

Based on one study (Schildt et al. 1998b) the risk of incident oral cancer for dual users was statistically non-significant compared to individuals that have never smoked or used snus. They also found statistically non-significant results for "high consumption" and "low consumption" dual users. High consumption refers to greater than 156.0 kg of life consumption for oral snuff and greater than 124.8 kg for smoking tobacco.

In contrast, the risk for smokers in the same study was a statistically significant 1.7 (95% CI: 1.1-2.6) compared to never compared to individuals that have never smoked or used snus. Based on the additional analysis by Lee (2014) of results in Schildt et al. (1998b), risks for dual users were also statistically non-significant compared to either ever exclusive smokers or current exclusive smokers. Additionally, Lee (2014) reported no statistically change in relative risk of dual users compared to the relative risks in smokers indicating no evidence of multiplicative interaction.

Effects in switchers and comparisons to smokers

Based on one study (Schildt et al. 1998b) the risk of incident oral cancer for switchers was statistically non-significant compared to individuals that have never smoked or used snus. Similarly, the risk for former smokers was statistically non-significant.

In contrast, the risk for smokers in the same study was a statistically significant 1.7 (95% CI: 1.1-2.6) compared to never compared to individuals that have never smoked or used snus. Additional analyses by Lee (2013) found statistically non-significant results for switchers compared to smokers and for switchers compared to former smokers.

Conclusion

No study reported statistically significant results for dual users compared to current smokers, ever smokers, or individuals that have never smokers or used snus. There was also no evidence of multiplicative interaction between smoking and snus use.

No study reported statistically significant results for switchers compared to current smokers, former smokers, never tobacco users, or individuals that have never smoked or used snus.

3.5 Esophageal Cancer

3.5.1 Overview of evidence compared to previous report

The previous report identified only Zendehdel et al. (2008) as related to esophageal cancer risk for dual users. No new studies that reported esophageal cancer effect estimates for dual users or switchers were published since the 2013 ENVIRON report. However, Zendehdel et al. (2008) was represented in a comparative meta-analysis for dual users published by Lee (2014). Notably, Lee (2014) reported dual user effect estimates derived from Zendehdel et al. (2008) that they did not report explicitly. The discussion of results from Lee (2014) was integrated with a more comprehensive discussion of Zendehdel et al. (2008).

3.5.2 Outcome considerations

Zendehdel et al. (2008) reported effect measures for adenocarcinoma and squamous cell carcinoma subtypes of esophageal cancer. "Esophageal cancer" refers to the overall range of disease outcomes represented by ICD7,8,9-150. In Zendehdel et al. (2008), identification of the outcome is defined by ICD-150 before division into esophageal subtypes based on histological code. These subtypes were combined through a fixed-effect meta-analysis to obtain an effect estimate for dual users of overall esophageal cancer.

3.5.3 Results for Esophageal cancer

Reference	Effect measures for Exposures of interest (95% CI)	Effect measures for snus users, smokers, and former smokers (95% CI)	Interaction tests (95% CI)
Zendehdel et al. (2008)	*Adenocarcinoma among ever-smokers:* Reference: Non-user of snus User of snus (Dual user): 1.3 (0.8-2.0) *Squamous cell carcinoma among ever-smokers:* Reference: Non-user of snus User of snus (Dual user): 1.2 (0.8-1.7) *Esophageal cancer among ever-*	*Adenocarcinoma among never-smokers* Reference: Never users of any tobacco User of snus only: 0.2 (0.0-1.9) *Squamous cell carcinoma among never smokers*: Reference: Never users of any tobacco User of snus only: 3.5 (1.6-7.6)	

	smokers:* Reference: Non-user of snus User of snus (Dual user): 1.24 (0.93-1.66)	*Adenocarcinoma:* Reference: Never-users of any tobacco Exclusive ever smokers: 2.3 (1.4–3.7) Exclusive Current smokers: 2.9 (1.8–4.8) Previous exclusive smoker: 1.2 (0.6-2.4) *Squamous cell carcinoma:* Reference: Never-users of any tobacco Exclusive Ever smokers: 5.2 (3.1-8.6) Exclusive Current smokers: 7.6 (4.5-12.7) Previous exclusive smoker: 0.9 (0.4-2.0)	
Lee (2014) *age-standardized* estimates from Zendehdel et al. (2008)	*Adenocarcinoma* Reference: Ever-exclusive smoker Ever dual user: 1.00 (0.60-1.50) *Squamous cell carcinoma* Reference: Ever-exclusive smoker Ever dual user: 0.80 (0.60-1.20)	*Adenocarcinoma* Reference: Never users of any tobacco Ever snus users: 0.20 (0.02-1.90) *Squamous cell carcinoma* Reference: Never users of any tobacco Ever snus users: 3.50 (1.60-7.60)	*Adenocarcinoma* Interaction term for ever dual users 5.00 (0.50-49.74) *Squamous cell carcinoma* Interaction term for ever dual users: 0.23 (0.10-0.54)
* Estimated through fixed-effect meta-analysis of both estimates			

3.5.4 Discussion of esophageal cancer

Effects in dual users compared to smokers

Based on Zendehdel et al. (2008) the risk of incident esophageal cancer and its subtypes were statistically non-significant in ever dual users compared to non-users of snus among ever smokers. In contrast, the risk for exclusive ever and current smokers compared to never tobacco users were statistically significant within the same study. Additionally, Lee (2014) compared ever dual users to ever exclusive smokers in Zendehdel et al. (2008) and found statistically non-significant results for esophageal cancer subtypes. In an interaction test, Lee (2014) found statistically non-significant results for adenocarcinoma, but statistically significant lower risk of squamous cell carcinoma for dual users compared to risk in smokers. There was a statistically significant change in the relative risk of 0.23 (95% CI: 0.10-0.54) for ever dual users compared to the relative risk in smokers. As prior knowledge links smoking to esophageal cancer, it is unclear why results for dual users would be significantly lower. Others have suggested that dual users may consume less smoking tobacco than exclusive smokers, however no evidence of lower smoking tobacco consumption was presented in the selected study.

Conclusion

No study reported statistically significant results for ever dual users compared to non-users of snus among ever smokers or compared to exclusive ever smokers. There was also no evidence of multiplicative interaction between smoking and snus use for risk of adenocarcinoma, however there was evidence of multiplicative interaction for risk of squamous cell carcinoma. This latter result provides possible support of lower consumption of smoking tobacco by dual users, however no evidence regarding consumption was presented in the selected study.

3.6 Pancreatic Cancer

3.6.1 Overview of evidence compared to previous report

The previous report identified only Boffetta et al. (2005) as related to pancreatic cancer risk for dual users. No new studies that reported pancreatic cancer effect estimates for dual users or switchers were published since the 2013 ENVIRON report. Unlike other endpoints, Boffetta et al. (2005) is not represented in a comparative meta-analysis for dual users published by Lee (2014). This may be due to the lack of effect measures for exclusive smokers that prevents statistical comparison, as well as a lack of reported incidence rates and person years for the exposures of interest that prevents derivation of missing effect measures. The results from Boffetta et al. (2005) were assessed in a more comprehensive manner than previously.

3.6.2 Study considerations

Boffetta et al. (2005) reported risk of pancreatic cancer incidence in ever dual users compared to never or occasional snus users.

3.6.3 Results for Pancreatic cancer

Reference	Effect measures for Exposures of interest (95% CI)	Effect measures for snus users, smokers, and former smokers (95% CI)
Boffetta et al. (2005)	Reference: Never or occasional user of snus Ever regular snus/former smoker: 1.37 (0.59-3.17) Ever regular snus/current smoker: 1.86 (1.13-3.05)	Reference: Never or occasional user of snus Ever regular snus/never smoker: 0.85 (0.24-3.07)

3.6.4 Discussion of pancreatic cancer incidence

Effects in dual users compared to snus users

Based on Boffetta et al. (2005), the relative risk of incident pancreatic cancer for ever dual users was a statistically significant 1.86 (95% CI: 1.13-3.05) compared to never regular users of snus. Boffetta et al. (2005) did not report relative risks in exclusive smokers but does report a statistically non-significant 0.85 (95% CI: 0.24-3.07) relative risk for exclusive snus users compared to never regular snus users. The statistically significant risk in dual users may be driven by smokers as the results for exclusive snus users indicate no increase in risk. Additionally, the effect measure for dual users overlaps the confidence interval for exclusive snus users. This suggests a statistically significant difference in relative risks between the two groups is unlikely.

The previous 2013 ENVIRON report also discussed results from Bertuccio et al. (2011). Bertuccio et al. (2011) is a pooled analysis of 11 international case-control studies and of cigarette and western population smokeless tobacco users. In this study, dual users and exclusive smokeless tobacco users did not face a significantly increased risk of pancreatic cancer, whereas the risk of pancreatic cancer was significantly increased among smokers. Given that the smokeless tobacco used by participants in these studies likely contained higher levels of TSNAs compared to Swedish snus, the principal component of tobacco thought to be associated with the development of pancreatic cancer (Boffetta et al. 2008), it is unlikely that Swedish snus poses a risk for pancreatic cancer. However, this study does not meet our criteria for Swedish snus use in this report.

Conclusion

One study reported statistically significant increased risk for ever dual users compared to never regular snus users. No comparisons with smokers was possible due to lack of reported effect measures. The effect measure for dual users overlaps the confidence interval for snus users suggesting the relative risk in ever dual users may not statistically differ multiplicatively from the relative risk in exclusive snus users.

3.7 Stomach Cancer

3.7.1 Overview of evidence compared to previous report

The previous report identified two studies (Ye et al. 1999; Zendehdel et al. 2008) that reported stomach cancer effect measures for dual users. No new studies that reported stomach cancer effect estimates for dual users or switchers were published since the 2013 ENVIRON report. Each of these studies were represented in a comparative meta-analysis for dual users published by Lee (2014). Notably, Lee (2014) derived additional estimates from studies to assess dual use, as well as compare them to within study estimates of relevant comparison groups. Additionally, Lee (2013) reports an estimate for "switchers" from Ye et al. (1999), however this does not meet the definition for switchers in this report as it evaluates former smokers who ever used snus rather than current snus users who formerly smoked. The discussion of results from Lee (2014) was integrated with a more comprehensive discussion of Zendehdel et al. (2008) and Ye et al. (1999).

3.7.2 Outcome considerations

In this report, "stomach cancer" refers to the overall range of disease outcomes represented by ICD7,8,9: 151 and ICD10: C16. This encompasses studies of cardia and non-cardia stomach cancer. Studies differed in reporting on specific subtypes of stomach cancer and overall stomach cancer. Ye et al. (1999) reported dual user effect measures of overall stomach cancer only, while Zendehdel et al. (2008) reported dual user effect measures of stomach cancer subtypes only. In Zendehdel et al. (2008), identification of the outcome is defined by ICD-151 before division into stomach cancer subtypes. These subtypes were combined through a fixed-effect meta-analysis to obtain an effect estimate for overall stomach cancer.

3.7.3 Results for Stomach cancer and its subtypes

Reference	Effect measures for Exposures of interest (95% CI)	Effect measures for snus users, smokers, and former smokers (95% CI)	Interaction tests (95% CI)
Zendehdel	*Cardia stomach cancer among*	*Cardia stomach cancer among*	

et al. (2008)	*ever-smokers:* Reference: Non-user of snus User of snus (Dual user): 1.1 (0.8-1.6) *Non-cardia stomach cancer among ever-smokers:* Reference: Non-user of snus User of snus (Dual user): 1.0 (0.9-1.2) *Stomach cancer among ever-smokers*:* Reference: Non-user of snus User of snus (Dual user): 1.01 (0.89- 1.16)	*never-smokers* Reference: Never users of any tobacco User of snus only: 0.9 (0.4-2.0) *Non-cardia stomach cancer among never smokers*: Reference: Never users of any tobacco User of snus only: 1.4 (1.1-1.9) *Cardia stomach cancer among full cohort:* Reference: Never-users of any tobacco Exclusive ever smokers: 2.1 (1.5-3.0) Exclusive Current smokers: 2.3 (1.6-3.3) Previous exclusive smoker: 1.8 (1.2-2.7) *Non-cardia stomach cancer among full cohort:* Reference: Never-users of any tobacco Exclusive Ever smokers: 1.3 (1.2-1.6) Exclusive Current smokers: 1.4 (1.2-1.6) Previous exclusive smoker: 1.3 (1.1-1.5)	
Lee (2014) *age-standardized* estimates from Zendehdel et al. (1998)	*Cardia stomach cancer* Reference: Ever-exclusive smoker Ever dual user: 0.90 (0.70-1.30) *Non-cardia stomach cancer* Reference: Ever-exclusive smoker Ever dual user: 1.00 (0.90-1.20)	*Cardia stomach cancer* Reference: Never users of any tobacco Ever exclusive snus: 0.9 (0.4-2.0) *Non-cardia stomach cancer* Reference: Never users of any tobacco Ever exclusive snus: 1.4 (1.1-1.9)	*Cardia stomach cancer* Interaction term for ever dual users 1.00 (0.42-1.37) *Non-cardia stomach cancer* Interaction term for ever dual users: 0.71 (0.52-0.97)
Ye et al. (1999)	*Stomach cancer among full cohort:* Reference: Never smoker/never snuff Ever snuff user/Current smoker: 1.0 (0.5-1.8)	*Stomach cancer among full cohort:* Reference: Never smoker/never snuff Current exclusive smoker: 2.0 (1.3-2.9) Previous exclusive smoker: 1.2 (0.8-1.9) Exclusive ever snuff user: 0.5 (0.2-1.2)	

Lee (2014) *unadjusted* estimates from Ye et al. (1999)	*Stomach cancer among full cohort:* Reference: Ever-exclusive smoker Ever snuff user/Ever smoker: 0.80 (0.57-1.13)[#]	*Stomach cancer among full cohort:* Reference: Never snuff/smoker Ever exclusive snus: 0.50 (0.20-1.22)	*Stomach cancer* Interaction term for ever dual users: 1.60 (0.61-4.18)
* Estimated through fixed-effect meta-analysis of both estimates # Calculated based on Table VII using cases and controls			

3.7.4 Discussion of stomach cancer

Effects in dual users compared to smokers

The results from three studies (Ye et al. 1999; Zendehdel et al. 2008; Lee 2014) did not indicate an increased risk of stomach cancer or its subtypes for dual users compared to non-users of snus, ever exclusive smokers, or individuals that have never smoked or used snus. In contrast, the risk in ever and current exclusive smokers within these studies was statistically significantly elevate. Additionally, interaction tests by Lee (2014) do not indicate a statistically significant change in the relative risk of stomach cancer or cardia stomach cancer for dual users compared to the relative risks in smokers. However, Lee (2014) reported a statistically significant 0.71 (95% CI: 0.52-0.97) change in the relative risk of non-cardia stomach cancer for dual users compared to the relative risk in smokers. This provides some evidence for multiplicative interaction in risk of non-cardia stomach cancer

Conclusion

No study reported statistically significant results for ever dual users compared to non-users of snus, ever exclusive smokers, or individuals that have never smoked or used snus. There was some evidence of multiplicative interaction between smoking and snus use for risk of non-cardia stomach cancer. As prior knowledge links smoking to stomach cancer, it is unclear why risk in dual users would be significantly lower than the risk in exclusive smokers. Others have suggested that dual users consume less smoking tobacco than exclusive smokers, however no evidence of lower smoking tobacco consumption was presented in the selected study.

3.8 Lung Cancer

3.8.1 Overview of evidence compared to previous report

The previous report identified only Boffetta et al. (2005) as related to lung cancer risk for dual users. No new studies that reported lung cancer effect estimates for dual users or switchers were published since the 2013 ENVIRON report. Unlike other endpoints, Boffetta et al. (2005) was not represented in a comparative meta-analysis for dual users published by Lee (2014). This may be due to the lack of reported effect measures for exclusive smokers that prevents statistical comparison. As well as a lack of reported incidence rates and person years for the exposures of interest that prevents derivation of missing effect measures. The results from Boffetta et al. (2005) are assessed in a more comprehensive manner than previously.

3.8.2 Study considerations

Boffetta et al. (2005) reported risk of lung cancer incidence in ever dual users compared to never or occasional snus users.

3.8.3 Results for Lung cancer

Reference	Effect measures for Exposures of interest (95% CI)	Effect measures for snus users, smokers, and former smokers (95% CI)
Boffetta et al. (2005)	Reference: Never or occasional user of snus Ever regular snus/former smoker: 0.64 (0.24-1.68) Ever regular snus/current smoker: 0.68 (0.51-0.90)	Reference: Never or occasional user of snus Ever regular snus/never smoker: 0.96 (0.26-3.56)

3.8.4 Discussion of Lung cancer

Effects in dual users compared to snus users

Based on Boffetta et al. (2005), the relative risk of incident pancreatic cancer for ever dual users was a statistically significant 0.68 (95% CI: 0.51-0.90) compared to never regular users of snus. Boffetta et al. (2005) did not report relative risks in exclusive smokers but does report a statistically non-significant 0.85 (95% CI: 0.96-3.56) relative risk for exclusive snus users compared to never regular snus users. The available estimates suggest that ever regular snus users who currently smoke have a lower risk of lung cancer compared to never regular snus users. The lower and significant effect in dual users is not consistent with knowledge on the risks of smoking. Notably, Boffetta et al. (2005) control for amount of tobacco smoking but the study could be underestimating risk due to a lack of consideration of other confounders. Additionally, the effect estimates for ever dual users overlapped the confidence interval for exclusive ever snus users suggesting that differences in relative risk between these two groups may not be statistically significant.

Conclusion

One study reported a statistically significant *decreased* risk for dual users compared to never regular snus users. No comparisons with smokers was possible due to lack of reported effect measures. The effect measure for dual users overlaps the confidence interval for snus users suggesting the relative risk in ever dual users may not statistically differ multiplicatively from the relative risk in exclusive snus users.

3.9 Chronic cardiovascular disease

3.9.1 Overview of evidence compared to previous report

The previous report identified four studies (Hansson et al. 2009; Hergens et al. 2005; Johansson et al. 2005; Wennberg et al. 2007) that reported risk estimates related to cardiovascular disease for switchers and six studies (Haglund et al. 2007; Hansson et al. 2009; Hergens et al. 2005; Huhtasaari et al. 1999; Johansson et al. 2005; Wennberg et al. 2007) that reported risk estimates for dual users. No new studies that reported cardiovascular disease related outcomes with corresponding risk estimates for dual users or switchers were published since the 2013 ENVIRON report. Each of these studies were represented in comparative meta-analyses by Lee (2013; 2014). Lee (2013) included a risk comparison estimate that compared switchers to current smokers. Lee (2014) compared dual users to smokers and assessed interaction between smoking and snus use. Notably, Lee (2014) reported dual user effect estimates derived from Huhtasaari et al. (1992) that they did not report explicitly. The discussion of results from Lee (2013; 2014) was integrated with a discussion of the results.

3.9.2 Outcome considerations

The four studies (Hansson et al. 2009; Hergens et al. 2005; Johansson et al. 2005; Wennberg et al. 2007) that reported risk estimates for switchers differed in outcome specificity. Only Hansson et al. (2009) reported incidence of overall cardiovascular disease. All four studies (Hansson et al. 2009; Hergens et al. 2005; Johansson et al. 2005; Wennberg et al. 2007) reported incidence of ischemic heart disease and myocardial infarction. Two studies (Hergens et al. 2005; Wennberg et al. 2007) additionally reported IHD and MI mortality.

The seven studies (Haglund et al. 2007; Hansson et al. 2009; Hergens et al. 2005; Huhtasaari et al. 1992; Huhtasaari et al. 1999; Johansson et al. 2005; Wennberg et al. 2007) that reported risk estimates for dual users differed in outcome specificity. All seven studies evaluated IHD incidence, however, only three studies (Haglund et al. 2008; Hergens et al. 2005; Wennberg et al. 2007) evaluated IHD mortality in dual users.

One study (Wennberg et al. 2007) assessed sudden cardiac death (SCD) in less than 24 hours and in less than an hour in dual users and switchers.

3.9.3 Results for cardiovascular disease related outcomes

3.9.3.1 Overall cardiovascular disease

Reference	Effect measures for Exposures of interest (95% CI)	Effect measures for snus users, smokers, and former smokers (95% CI)	Interaction tests or comparison (95% CI)
Hansson et al. (2009)	Reference: Never snus and never smoking Current Dual users: 1.51 (0.86-2.65)	Reference: Never snus and never smoking Exclusive current smokers: 1.86 (1.56-2.22)	

	Switchers: 1.04 (0.78-1.39)	Exclusive former smokers: 1.17 (1.00-1.38) Exclusive current snus: 1.00 (0.69-1.46)	
Lee (2014) estimates from Hansson et al. (2009)	Reference: Exclusive current smokers Current dual users 0.81 (0.46-1.43) Reference: Exclusive ever smokers Ever dual users: 0.91 (0.75-1.11) Reference: Never snus and never smoking Switchers: 1.04 (0.78-1.39)	Reference: Neither current snus or current smoker Exclusive current snus: 0.93 (0.74-1.17) Reference: Neither ever snus or ever smoker Exclusive ever snus: 1.07 (0.79-1.45)	Interaction term for current dual users: 0.87 (0.47-1.60) Interaction term for ever dual users: 0.85 (0.59-1.22) Switchers vs. current smokers: 0.56 (0.41-0.75) Switchers vs. former smokers: 0.89 (0.67-1.19)

3.9.3.2 Incidence of Ischemic Heart Disease and Myocardial Infarction

Reference	**Effect measures for Exposures of interest (95% CI)**	**Effect measures for snus users, smokers, and former smokers (95% CI)**	**Interaction tests or comparison (95% CI)**

Hansson et al. (2009)	Reference: Never snus and never smoking Current Dual users: 1.50 (0.73-3.08) Switchers: 1.22 (0.82-1.74)	Reference: Never snus and never smoking Exclusive current smokers: 1.99 (1.59-2.50) Exclusive former smokers: 1.34 (1.10-1.64) Exclusive current snus: 0.85 (0.51-1.41)	
Haglund et (al. 2007)	Reference: No tobacco Current Dual user: 1.64 (0.96-2.79)	Reference: No tobacco Current exclusive smoker: 1.74 (1.41-2.14) Current exclusive snuff: 0.77 (0.51-1.15)	
Hergens et al. (2005)	Reference: Never snus and never smoker Switchers: 1.60 (1.10-2.20) Current dual users: 2.30 (1.6-3.4)	Reference: Never snus and never smoker Exclusive current smokers: 2.8 (2.3-3.4) Exclusive former smokers 1.31 (1.1-1.6) Exclusive current snus: 0.73 (0.35-1.5)	
Huhtasaari et al. (1999) (unadjusted)	Reference: Never tobacco Current dual users: 2.66 (1.24-5.71)	Reference: never tobacco: Current smoker, no current snuff use: 3.65 (2.67-4.99) Former smoker, never used snuff: 1.05 (0.77-1.43) Current snuff user, no current smoking: 0.96 (0.65-1.41)	
Johansson et al. (2005)	Reference: Never-smoker	Reference: Never-smoker	

	Switcher: 1.18 (0.67-2.06) Current dual user: 2.73 (1.35-5.53)	Daily smoker: 2.30 (1.66-3.19) Daily snuffer: 1.41 (0.61-3.28)	
Wennberg et al. (2007)	Reference: Never used tobacco Switchers**:** 1.25 (0.80-1.96) Current Dual Users: 2.14 (1.28-3.60)	Reference: Never used tobacco Exclusive current smokers: 2.60 (1.91-3.54) Exclusive former smokers: 1.18 (0.82-1.70) Exclusive current snuff:0.82 (0.46-1.43)	
Lee (2014) estimates from Haglund et al. (2007)	Reference: Exclusive current smokers Current dual users 0.94 (0.56–1.59)	Reference: Neither current snus or current smoker Exclusive current snus: 0.77 (0.51–1.15)	Interaction term for current dual users: 1.22 (0.63–2.37)
Lee (2014) estimates from Hansson et al. (2009)	Reference: Exclusive current smokers Current dual users 0.75 (0.36-1.55) Reference: Exclusive ever smokers Ever dual users: 0.95 (0.74-1.22) Reference: Never snus and never smoker Switcher: 1.22 (0.82-1.74)	Reference: Neither current snus or current smoker Exclusive current snus: 0.90 (0.67-1.21) Reference: Neither ever snus or ever smoker Exclusive ever snus: 0.92 (0.61-1.39)	Interaction term for current dual users: 0.83 (0.38-1.82) Interaction term for ever dual users: 1.03 (0.64-1.67) Switchers vs. current smokers: 0.61 (0.42-0.90)

			Switchers vs. former smokers: 0.91 (0.63-1.32)
Lee (2013; 2014) estimates from Hergens et al. (2005)	Reference: Exclusive current smokers Current dual users 0.80 (0.55-1.16) Reference: Exclusive ever smokers Ever dual users: 0.99 (0.80-1.22) Reference: Never snus and never smoker Switcher: 1.60 (1.10-2.20)	Reference: Neither current snus or current smoker Exclusive current snus: 1.21 (0.89-1.63) Reference: Neither ever snus or ever smoker Exclusive ever snus:0.87 (0.48-1.55) Reference: Never snus and never smoker Exclusive current smokers: 2.8 (2.3-3.4)	Interaction term for current dual users: 0.66 (0.41-1.07) Interaction term for ever dual users: 1.14 (0.62-2.13) Switchers vs current smokers: 0.57 (0.40-0.81) Switchers vs former smokers: 1.23 (0.87-1.73)
Lee (2014) estimates from Huhtasaari	Reference: Exclusive current smokers Current dual users 0.68 (0.40-	Reference: Neither current snus or current smoker Exclusive current snus: 0.79	Interaction term for current dual

et al. (1992)	1.17)	(0.54-1.13)	users: 0.87 (0.45-1.67)
Lee (2014) estimates from Huhtasaari et al. (1999)	Reference: Exclusive current smokers Current dual users 0.73 (0.34-1.57)	Reference: Neither current snus or current smoker Exclusive current snus: 0.96 (0.65-1.41)	Interaction term for current dual users: 0.76 (0.32-1.80)
Lee (2013; 2014) estimates from Johansson et al. (2005)	Reference: Exclusive current smokers Current dual users 1.19 (0.60-2.37) Reference: Never snus and never smoker Switcher: 1.18 (0.67-2.06)	Reference: Neither current snus or current smoker Exclusive current snus: 0.99 (0.63-1.56) Reference: Never snus and never smoker Exclusive current smokers: 2.3 (1.66-3.19)	Interaction term for current dual users: 1.20 (0.52-2.73) Switchers vs current smokers: 0.51 (0.30-0.88) Switchers vs former smokers: 0.80 (0.47-1.38)
Lee (2013; 2014) estimates from Wennberg et al. (2007)	Reference: Exclusive current smokers Current dual users 0.82 (0.48–1.40) Reference: Never snus and	Reference: Neither current snus or current smoker Exclusive current snus: 1.00 (0.71–1.43) Reference: Never snus and never	Interaction term for current dual users: 0.82 (0.43–1.55)

	never smoker Switcher: 1.25 (0.80-1.96)	smoker Exclusive current smokers: 2.60 (1.91-3.54)	Switchers vs current smokers: 0.48 (0.30-0.76) Switchers vs former smokers: 1.06 (0.64-1.75)
Lee (2014) meta-analyses of IHD/CHD/AMI estimate of change in relative risk in dual users compared to smokers.			0.85 (0.68-1.05)
Lee (2013) meta-analyses of IHD/CHD/AMI in switchers vs. current smokers based on Hansson et al. (2009), Hergens et al. (2005), Johansson et al. (2005), Wennberg et al. (2007)			Switchers vs current smokers: 0.55 (0.45-0.68)
Lee (2013) meta-analyses of IHD/CHD/AMI in switchers vs. former smokers based on Hansson et al. (2009), Hergens et al. (2005), Johansson et al. (2005), Wennberg et al. (2007)			Switchers vs former smokers: 1.02 (0.83-1.26)

3.9.3.3 Mortality related to Ischemic Heart Disease and Myocardial Infarction

Reference	**Effect measures for Exposures of interest (95% CI)**	**Effect measures for snus users, smokers, and former smokers (95% CI)**	**Interaction tests or comparison (95% CI)**
Haglund et (2007)	Reference: No tobacco Current Dual user: 1.69 (0.52-5.46)	Reference: No tobacco Current exclusive smoker: 1.98 (1.35-2.91) Current exclusive snuff: 1.15 (0.54-2.41)	

Hergens et al. (2005)	Reference: Never snus and never smoker Switchers: 1.50 (0.69-3.20) Current dual users: 3.80 (1.9-7.5)	Reference: Never snus and never smoker Exclusive current smokers: 3.6 (2.4-5.2) Exclusive former smokers: 1.7 (1.6-2.6) Exclusive current snus: 1.7 (0.49-5.5)	
Wennberg et al. (2007)	Reference: Never used tobacco Switchers: 1.24 (0.44–3.53) Current Dual Users: 1.11 (0.34–3.69)	Reference: Never used tobacco Exclusive current smokers: 3.53 (1.83-6.84) Exclusive former smokers: 1.02 (0.45-2.31) Exclusive current snuff: 1.12 (0.38-3.29)	
Lee (2014) estimates from Haglund et al. (2007)	Not provided	Not provided	Interaction term for current dual users: 0.74 (0.19-2.97)
Lee (2013; 2014) estimates from Hergens et al. (2005)	Mortality estimates not provided Reference: Never snus and never smoker Switcher: 1.50 (0.69-3.20)	Mortality estimates not provided Reference: Never snus and never smoker Exclusive current smokers: 3.60 (2.40-5.20)	Interaction term for current dual users: 0.89 (0.36-2.18) Interaction term for ever dual users: 0.50 (0.16-

			1.58) Switchers vs current smokers: 0.42 (0.20-0.86) Switchers vs former smokers: 0.88 (0.42-1.87)
Lee (2013; 2014) estimates from Wennberg et al. (2007)	Mortality estimates not provided Reference: Never snus and never smoker Switcher: 1.24 (0.44-3.53)	Mortality estimates not provided Reference: Never snus and never smoker Exclusive current smokers: 3.53 (1.83-6.84)	Interaction term for current dual users: 0.25 (0.06-1.03) Switchers vs current smokers: 0.35 (0.12-1.02) Switchers vs former smokers: 1.22 (0.38-3.90)

3.9.3.4 Other cardiovascular disease outcomes

Reference	Outcome	Effect measures for Exposures of interest (95% CI)	Effect measures for snus users, smokers, and former smokers (95% CI)	Interaction tests or comparison (95% CI)
Hergens et al. (2005)	Non-fatal AMI	Reference: Never smoke and never snus Switchers: 1.60 (1.10-2.20) Current dual user: 2.1 (1.4-3.1)	Reference: Never tobacco Current smokers: 2.70 (2.20-3.30) Former smokers: 1.20 (0.98-1.50)	
Wennberg et al. (2007)	SCD with survival <24 hr	Reference: Never tobacco Switchers: 1.39 (0.44-4.42) Current dual user: 0.75 (0.17-3.28)	Reference: Never tobacco Current smokers: 3.12 (1.53-6.33) Former smokers: 0.74 (0.28-1.97)	
	SCD with survival <1 hr	Reference: Never tobacco Switchers: 2.67 (0.52-13.80) Current dual user: 0.13 (0.01-2.10)	Reference: Never tobacco Current smokers: 4.54 (1.55-13.25) Former smokers: 0.35 (0.07-1.78)	
Lee (2013) estimates from Hergens et al. (2005)	Non-fatal AMI	Reference: Never tobacco Switchers: 1.60 (1.10-2.20)	Reference: Never tobacco Current smokers: 2.70 (2.20-3.30) Former smokers: 1.20 (0.98-1.50)	Switchers vs. current smokers: 0.59 (0.42-0.83) Switchers vs. former smokers: 1.33 (0.94-1.88)
Lee (2013;)	SCD with survival	Reference: Never tobacco	Reference: Never tobacco	Switchers vs. current smokers:

estimates from Wennberg et al. (2007)	<24 hr	Switchers: 1.39 (0.44-4.42)	Current smokers: 3.12 (1.53-6.33) Former smokers: 0.74 (0.28-1.97)	0.45 (0.14-1.45) Switchers vs. former smokers: 1.88 (0.48-7.27)
	SCD with survival <1 hr	Reference: Never tobacco Switchers: 2.67 (0.52-13.80)	Reference: Never tobacco Current smokers: 4.54 (1.55-13.25) Former smokers: 0.35 (0.07-1.78)	Switchers vs. current smokers: 0.59 (0.10-3.53) Switchers vs. former smokers: 7.63 (0.42-137.8)

3.9.4 Discussion

Effects in dual users and comparisons to smokers

Based on one study (Hansson et al. 2009), the risk of overall cardiovascular disease for dual users was a statistically non-significant 1.51 (95% CI: 0.86-2.65) compared to never users of snus and smoking tobacco. In contrast, exclusive current smokers in the same study had a statistically significant elevated risk of 1.86 (95% CI: 1.56-2.22) compared to never users of snus and smoking tobacco. Additionally, Lee (2014) reported no statistically significant change in relative risk for current or ever dual users compared to the relative risks in smokers indicating no evidence of multiplicative interaction in the study population from Hansson et al. (2009).

The incident risk of ischemic heart disease and myocardial infarction in dual users was assessed in seven studies (Haglund et al. 2007; Hansson et al. 2009; Hergens et al. 2005; Huhtasaari et al. 1992; Huhtasaari et al. 1999; Johansson et al. 2005; Wennberg et al. 2007). Two studies (Hansson et al. 2009; Haglund et al. 2007) reported statistically non-significant results for current dual users compared to never snus/smoker or no tobacco users. Additionally, Lee (2013) reported statistically non-significant results of current dual users compared to current smokers in the study population from Huhtasaari et al. (1992). The remaining four studies all had statistically significant results above a relative risk of two for current dual users compared to never-smokers, never/no tobacco, or never snus/smoker reference groups. All of these studies reported statistically significant results for exclusive smokers and statistically non-significant results for exclusive snus users. Importantly, Lee (2014) calculated relative risks for current dual users compared to current smokers in each study and found statistically non-significant results for each study. Lee (2014), also reported no statistically significant change in relative risk for current or ever dual users compared to relative risks in smokers indicating no evidence of multiplicative interaction in any of these study populations. The summary

estimate for interaction reported by Lee (2014) was a statistically non-significant 0.85 (95% CI: 0.68-1.05). Overall, these results indicate a possible increase in risk of IHD and MI incidence in dual users compared to never tobacco users, but consistent evidence of no difference in risk between dual users and smokers.

The risk of fatal ischemic heart disease and myocardial infarction in dual users was assessed in three studies (Haglund et al. 2008; Hergens et al. 2005; Wennberg et al. 2007). Only Hergens et al. (2005) had a statistically significant increased risk in current dual users compared to never snus/smoker. For comparison, each of these studies reported statistically significant results for exclusive smokers and statistically non-significant results for exclusive snus users. Importantly, Lee (2014) reported no statistically significant change in the relative risk for current or ever dual users compared to the relative risks in smokers indicating no evidence of multiplicative interaction in any of these study populations. Overall, these results indicate a mixed evidence of an increase in risk of IHD and MI mortality in dual users compared to never tobacco users, but consistent evidence of no difference in risk between dual users and smokers.

Effects in switchers and comparisons to smokers

Based on one study (Hansson et al. 2009), the risk of overall cardiovascular disease for switchers was a statistically non-significant 1.04 (95% CI: 0.78-1.39) compared to never users of snus and smoking tobacco. In contrast, exclusive current smokers in the same study had a statistically significant elevated risk of 1.86 (95% CI: 1.56-2.22) compared to never users of snus and smoking tobacco. Former smokers had a statistically non-significant risk of 1.17 (95% CI: 0.69-1.46). Additionally, Lee (2013) reported a statistically significant relative risk of 0.56 (95% CI: 0.41-0.75) for switchers compared to current smokers in the study population from Hansson et al. (2009). Lee (2013) reported a statistically non-significant relative risk of 0.89 (95% CI: 0.67-1.19) for switchers compared to former smokers in the study population from Hansson et al. (2009). These results suggest evidence of a significant decline in risk of incident cardiovascular disease for switchers compared to current smokers.

The incident risk of ischemic heart disease and myocardial infarction in switchers was assessed in four studies (Hansson et al. 2009; Hergens et al. 2005; Johansson et al. 2005; Wennberg et al. 2007). Only Hergens et al. (2005) reported statistically significant increased results for switchers compared to never snus/smokers. For comparison, each of these studies reported statistically significant results for exclusive smokers. Two out of the four studies (Hansson et al. 2009; Hergens et al. 2005; Huhtasaari et al. 1999; Wennberg et al. 2007) that reported effect measures for former smokers had statistically significant increased risk. Importantly, Lee (2013) calculated relative risks for switchers compared to current smokers and found statistically significant results lower risks in switchers for each study. The summary estimate of switchers compared to current smokers reported by Lee (2013) was a statistically significant 0.55 (95% CI: 0.45-0.68). Lee (2013) also calculated relative risks for switchers compared to former smokers and found statistically non-significant risks for each study. The summary estimate of switchers compared to former smokers reported by Lee (2013) was a statistically non-significant 1.02 (95% CI: 0.83-1.26). Overall, these results provide mixed evidence of an increase in risk of IHD and MI incidence in switchers compared to never tobacco users. The studies provide consistent evidence of a significant decline in risk of incident ischemic heart disease and myocardial infarction in switchers compared to current smokers, as well as a consistently non-significant risk for switchers compared to former smokers.

The risk of fatal ischemic heart disease and myocardial infarction in switchers was assessed in two studies (Hergens et al. 2005; Wennberg et al. 2007). No studies reported statistically significant results for switchers compared to never snus/smokers. In contrast, each of these studies reported statistically significant results for exclusive smokers and one study (Hergens et al. 2005) reported statistically significant increased risk for former smokers. Importantly, Lee (2013) calculated relative risks for switchers compared to exclusive smokers and found statistically significant lower risks in switchers compared to current smokers for each study. Lee (2013) found statistically non-significant risks in switchers compared to former smokers. No summary estimate was calculated for risk of fatal ischemic heart disease and myocardial infarction in switchers. Overall these results provide consistent evidence of no association between switchers and fatal IHD/MI, consistent evidence of significant decline in risk in switchers compared to current smokers, and consistent evidence of no risk in switchers compared to former smokers.

Other cardiovascular disease outcomes

One study (Wennberg et al. 2007) assessed sudden cardiac death in less than 24 and in less than an hour in current dual users and switchers. Wennberg et al. (2007) reported statistically non-significant risk of these outcomes in switchers, current dual users, and former smokers compared to never tobacco users. In contrast, smokers had statistically significant elevated risk of both outcomes. Additionally, Lee (2013) reported statistically non-significant risk of both outcomes in switchers compared to current smokers or former smokers using the results from Wennberg et al. (2007). Notably, the confidence intervals of each effect measure discussed above is fairly wide suggesting a need for a larger sample size.

One study (Hergens et al. 2005) assessed nonfatal myocardial infarction in current dual users and switchers. They found a statistically significant elevated risk of nonfatal myocardial infarction in dual users and switchers compared to individuals who have never smoked or used snus. They reported a 1.60 (95% CI: 1.10-2.20) relative risk for switchers and a 2.1 (95% CI: 1.4-3.1) for current dual users. For comparison, they reported a statistically significant relative risk of 2.70 (95% CI: 2.20-3.30) in current smokers and a statistically non-significant relative risk of 1.20 (95% CI: 0.98-1.50) in former smokers compared to individuals who have never smoked or used snus. Using these effect estimates from Hergens et al. (2005), Lee (2013) compared switchers to current smokers and found a statistically significant lower relative risk of 0.59 (95% CI: 0.42-0.83). Lee (2013) reported a statistically non-significant risk in switchers compared to former smokers. No statistical comparison between current smokers and dual users was performed by Lee (2014). The effect estimate for smokers overlaps the confidence interval for dual users. This suggests no statistically significant change in the relative risk of dual users compared to smokers.

Conclusion

Overall cardiovascular disease

One study reported a statistically nonsignificant risk of overall cardiovascular disease for ever dual users compared to non-users of snus among ever smokers or compared to never users of snus and smoking tobacco. There was also no evidence of multiplicative interaction between smoking and snus

use. The same study suggests evidence of a significant decline in risk of incident cardiovascular disease for switchers compared to current smokers.

Incident IHD and MI

The results of seven studies provide mixed evidence of a possible increase in risk of IHD and MI incidence in dual users compared to never tobacco users but provide consistent evidence of no difference in relative risk between dual users and smokers.

The results of four studies provide mixed evidence of an increase in risk of IHD and MI incidence in switchers compared to never tobacco users. The studies provide consistent evidence of a significant decline in risk of incident ischemic heart disease and myocardial infarction in switchers compared to current smokers, as well as a consistently non-significant risk for switchers compared to former smokers.

Fatal IHD and MI

The results of three studies provide mixed evidence of an increase in risk of IHD and MI mortality in dual users compared to never tobacco users, but consistent evidence of no difference in relative risk between dual users and smokers.

The results of two studies provide consistent evidence of no association between switchers and fatal IHD/MI, consistent evidence of significant decline in risk in switchers compared to current smokers, and consistent evidence of no risk in switchers compared to former smokers.

Other cardiovascular disease outcomes

Based on one study (Wennberg et al. 2007), there is no evidence for risk of SCD < 24 hr or SCD <1 hr in switchers and current dual users compared to never tobacco users or current smokers.

Based on one study (Hergens et al. 2005), there is evidence of increased risk of nonfatal myocardial infarction in switchers and current dual users compared to individuals who have never smoked or used snus. However, there is also evidence of a significant lower risk in switchers compared to current smokers. There is no evidence of an increased risk in switchers compared to former smokers or in dual users compared to current smokers.

3.10 Incident stroke and mortality

3.10.1 Overview of evidence compared to previous report

The 2013 ENVIRON report identified only one study (Hansson et al. 2009) that reported risk estimates of stroke for switchers and two studies (Haglund et al. 2007; Hansson et al. 2009) that reported risk estimates for dual users. No new studies that reported stroke risk estimates for dual users or switchers were published since the 2013 ENVIRON report. Each of these studies were represented in comparative meta-analyses by Lee (2013; 2014). Lee (2013) included a risk comparison estimate for Hansson et al. (2009) that compared switchers to continuers (continued smokers). Lee (2014) similarly assesses whether any statistically significant interaction occurs for dual users compared to smokers. The discussion of results from Lee (2013; 2014) was integrated with a discussion of the results.

3.10.2 Outcome considerations

Haglund et al. (2007) had a broad outcome definition of any stroke corresponding to ICD9: 430-438, while Hansson et al. (2009) had a more restricted outcome definition corresponding to ICD9: 430-431, 434-436. Additionally, Haglund et al. (2007) was the only study to report effect measures for fatal stroke. Both studies reported measures for incident stroke.

3.10.3 Results for Stroke

Reference	**Effect measures for Exposures of interest (95% CI)**	**Effect measures for snus users, smokers, and former smokers (95% CI)**	**Interaction tests or comparison (95% CI)**
Hansson et al. (2009)	Reference: Never snus and never smoking Current Dual users: 1.45 (0.58-3.62) Switchers: 0.77 (0.46-1.29)	Reference: Never snus and never smoking Exclusive current smokers: 1.61 (1.22-2.13) Exclusive former smokers: 1.01 (0.78-1.30) Exclusive current snus: 1.18 (0.67-2.08)	
Haglund et al. (2007)	*Incidence* Reference: No tobacco Current dual users: 1.98 (1.00-3.95) *Mortality* Reference: No tobacco Current dual users: 4.30 (1.22-15.1)	*Incidence* Reference: No tobacco Current exclusive smokers: 1.40 (1.03-1.91) Current exclusive snuff users: 1.07 (0.65-1.77) *Mortality* Reference: No tobacco Current exclusive smokers: 1.02 (0.50-2.05) Current exclusive snuff users: 1.01 (0.35-2.92)	

Lee (2013) reported risk estimates from Hansson et al. (2009)	Reference: Never snus and never smoker Switcher: 0.77 (0.46-1.29)	Reference: Never snus and never smoker Current exclusive smoker: 1.61 (1.22-2.13)	Switchers vs current smokers: 0.48 (0.28-0.82) Switchers vs former smokers: 0.76 (0.45-1.28)
Lee (2014) reported risk estimates from Hansson et al. (2009)	Reference: Exclusive smokers Current dual users: 0.90 (0.36-2.27) Ever dual users: 0.83 (0.59-1.16)	Reference: Never snus and never smoker Current exclusive snus user: 0.89 (0.61-1.31) Ever exclusive snus user: 1.24 (0.78-1.97)	Interaction term for current dual users: 1.01 (0.37-2.73) Interaction term for ever dual users: 0.67 (0.38-1.19)
Lee (2014) reported risk estimates from Haglund et al. (2007)	*Incidence* Reference: Exclusive smokers Current dual users: 1.41 (0.71-2.83)	*Incidence* Reference: No tobacco Current snus user: 1.07 (0.65-1.77)	*Incidence* Interaction term for current dual users: 1.32 (0.56-3.11) *Mortality* Interaction term for current dual users 4.17 (0.78-22.36)

3.10.4 Discussion of Stroke

Effects in dual users and comparisons

Based on two studies (Haglund et al. 2007; Hansson et al. 2009), the risk of incident stroke for dual users was statistically non-significant compared to smokers or never-users of snus and smoking tobacco. The risk for current smokers within the same studies, however were statistically significantly elevated. Additionally, Lee (2014) reported no statistically significant change in relative risk for dual users compared to relative risks in smokers indicating no evidence of multiplicative interaction.

The one study (Haglund et al. 2007) that considered fatal stroke in dual users reported a statistically significant relative risk of 4.30 (1.22-15.1) compared to non-tobacco users. In contrast with prior knowledge, Haglund et al. (2007) reported a statistically non-significant 1.02 (0.50-2.05) relative risk in current smokers compared to non-tobacco users. However, Lee (2014) found no statistically significant change in relative risk for dual users compared to relative risks in smokers indicating no evidence of multiplicative interaction. The three fatal stroke cases in Haglund et al. (2007) likely contribute to the wide confidence intervals for risk of fatal stroke as the risk of fatal stroke in smokers within this study were not significantly elevated.

Effects in switchers and comparisons

In the one study (Hansson et al. 2009) that considered switchers, the risk of incident stroke in switchers was statistically non-significant compared to never-users of snus and smoking tobacco. The risk for current smokers were statistically significantly elevated. Additionally, Lee (2013) compared switchers in Hansson et al. (2009) to current smokers in the same study and found a statistically significant lower risk of 0.48 (95% CI: 0.28-0.82) in switchers compared to current smokers. Lee (2013) also found a statistically non-significant risk of 0.76 (95% CI: 0.45-1.28) in switchers compared to former smokers

Conclusion

Except for statistically significant results for fatal stroke in dual users, no study reported statistically significant results for dual users or switchers compared to non-users. There were also no statistically significant differences in either incident or fatal stroke risk in dual users when compared to smokers. There was a statistically significant lower risk of incident stroke in switchers compared to current smokers within the same study, but statistically non-significant results for switchers compared to former smokers.

3.11 Metabolic Effects: Diabetes and Metabolic syndrome

3.11.1 Overview of evidence compared to previous report

The previous report discussed only Wandell et al. (2008) as related to risk of diabetes and metabolic syndrome for dual users and switchers. The 2013 ENVIRON report also identified Eliasson et al. (2004) as related to diabetes but did not discuss the results for switchers reported in the study. Only one related new study (Rasouli et al. 2017) that reported risk of diabetes in dual users has been published since the 2013 ENVIRON report. This study however evaluates two distinct study populations. No new studies related to metabolic syndrome risk in dual users or switchers was identified. Wikstrom et al. (2010b) is represented in a comparative meta-analysis for dual users published by Lee (2014). Notably, Lee (2014) report dual user effect estimates derived from Wikstrom et al. (2010b) that they did not report explicitly. The discussion of results from Lee (2014) was integrated with the other relevant studies

3.11.2 Metabolic Syndrome

3.11.2.1 Metabolic syndrome study considerations

The one study that reported risk of metabolic syndrome in dual users considered three definitions of metabolic syndrome, however in this report "metabolic syndrome" refers to the International Diabetes Federation (IDF) definition. Only results for IDF-defined metabolic syndrome were considered here.

Reference	Effect measures for Exposures of interest (95% CI)	Effect measures for snus users, smokers, and former smokers (95% CI)
Wandell et al. (2008)	Reference: Never smoke or snuff Switcher: 1.18 (0.76-1.83) Current snuffer/smoker: 0.85 (0.36-2.02)	Reference: Never smoke or snuff Current exclusive snuffer: 1.81 (0.65-5.02) Exclusive Ex-smoker: 1.44 (1.14-1.83) Current exclusive smoker: 1.00 (0.74-1.35)

3.11.2.2 Results and Discussion for Metabolic Syndrome

In a cross-sectional study of 60-year old Swedish men, Wandell et al. (2008) found no statistically significant results for current dual users, switchers, current exclusive snuffers, or current exclusive smokers compared to never smokers/snuffers. The only statistically significant result reported is for exclusive ex-smokers who have a prevalence odds ratio of 1.44 (95% CI: 1.14-1.83). This effect estimate overlaps the confidence interval for switchers and dual users suggesting no statistically significant risk difference between these groups. The generalizability of results is greatly limited as the study is only of 60-year old Swedish men.

Conclusion

The evidence for metabolic syndrome is limited to one prevalence study that indicates no increased risk in switchers, dual users, current smokers, or current snus users compared to never smokers/snuffers among 60-year old Swedish men. Comparison of confidence intervals suggests no statistically significant risk of switchers compared to former smokers.

3.11.3 Diabetes

3.11.3.1 Diabetes' study consideration

Three studies (Eliasson et al. 2004; Rasouli et al. 2017; Wandell et al. 2008) assessed Type II diabetes as defined previously in this report. Two studies (Wandell et al. 2008; Rasouli et al. 2017) assessed diabetes prevalence, and two studies (Rasouli et al. 2017; Eliasson et al. 2017; Lee 2014) assessed incident diabetes. Lee (2014) derives estimates of risk for current dual users from Wikstrom et al. (2010b).

The results for diabetes prevalence and incidence are presented separately.

3.11.3.2 Results for Diabetes

Reference	Effect measures for Exposures of interest (95% CI)	Effect measures for snus users, smokers, and former smokers (95% CI)	Interaction tests (95% CI)

Wandell et al. (2008)	*Prevalence:* Reference: Never smoke or snuff Switcher: 1.71 (0.67-4.35) Current snuffer/smoker: 2.48 (0.52-11.82)	*Prevalence:* Reference: Never smoke or snuff Current exclusive snuffer: 2.12 (0.25-17.71) Exclusive Ex-smoker: 1.41 (0.76-2.60) Current exclusive smoker: 1.40 (0.68-2.89)	
Rasouli et al. (2017) *ESTRID matched case-control*	*Among ever smokers:* Reference: Never snus Current snus/ever smoker: 0.91 (0.39-1.01)	*Among never smokers:* Reference: Never snus Exclusive current snus: 1.17 (0.58-2.37)	
Rasouli et al. (2017) *HUNT cross-sectional*	*Prevalence:* *Among ever smokers:* Reference: Never snus Ever dual user: 0.86 (0.70-1.07)	*Prevalence:* *Among never smokers:* Reference: Never snus Exclusive ever snus: 1.12 (0.72-1.72)	
Eliasson et al. (2004)	Reference: Consistent no tobacco Smokers who switched to snus: 3.25 (0.78-13.6)	Reference: Consistent no tobacco Consistent exclusive snus users: 0 cases Consistent exclusive smokers: 4.61 (1.37-15.5) Ex-smokers: 3.13 (1.13-8.67)	

Lee (2014) estimates from Wikstrom et al (2010b)	Reference: Current Smoker Current Dual user: 0.88 (0.42-0.84)	Reference: No tobacco Current Snuff: 0.93 (0.76-1.14)	Interaction term for current dual users: 0.95 (0.44-2.04)

3.11.3.3 Discussion of Diabetes

Diabetes Prevalence

Based on two studies (Wandell et al. 2008; Rasouli et al. 2017) the prevalence of diabetes in ever or current dual users was statistically non-significant compared to individuals that have never smoked or used snus. Similarly, Wandell et al. (2008) reported statistically non-significant prevalence in current smokers compared to individuals that have never smoked or used snus. No studies reported evidence of increased prevalence of diabetes in ever or current dual users.

Based on one study (Wandell et al. 2008) the prevalence of diabetes in switchers was statistically non-significant compared to individuals that have never smoked or used snus. Similarly, neither current or former smokers had statistically significant results. No studies reported evidence of increased prevalence of diabetes in switchers.

Diabetes Incidence

Based on one study (Rasouli et al. 2017), the risk of diabetes in ever dual users was a statistically non-significant 2.48 (95% CI: 0.52-11.82) compared to ever smokers that have never used snus. Additionally, Lee (2014) used the results from Wikstrom et al. (2010b) to derive effect measures for current dual users. Lee (2014) found current dual users have a statistically significant lower risk of diabetes (0.88 95% CI: 0.42-0.84) compared to current smokers. The interaction test by Lee (2014) showed no statistically significant change in relative risk for dual users compared to the relative risk in snus users indicating no multiplicative interaction. The two studies provided mixed evidence of risk of diabetes in ever or current dual users compared to ever or current smokers. One study presented statistically non-significant results, while the other study presented a statistically significant lower risk of diabetes in dual users. As prior knowledge links smoking to diabetes, it is unclear why results for dual users would be significantly lower. Others have suggested that dual users consume less smoking tobacco than exclusive smokers, however no evidence of lower smoking tobacco consumption was presented in the selected study.

Based on one study (Eliasson et al. 2004), the risk of diabetes in switchers is statistically non-significant compared to consistent non-tobacco users. In contrast, the same study reported statistically significant risk in current smokers and former smokers compared to non-tobacco users. The effect measures for each exposure group overlap each other's confidence intervals suggesting no statistically significant multiplicative difference in risk between the groups.

Conclusion

No studies reported evidence of increased prevalence or risk of diabetes in ever or current dual users compared to ever smokers, current smokers, non-tobacco users, or individuals that have never smoked or used snuff. One study (Lee 2014) provided evidence for a lower risk in current dual users compared to current smokers. There was no evidence of multiplicative interaction in the same study. Others have suggested that dual users consume less smoking tobacco than exclusive smokers, however no evidence of lower smoking tobacco consumption was presented in the selected study. There was no evidence of multiplicative interaction in the same study.

No studies reported evidence of increased prevalence or risk of diabetes in switchers compared to non-tobacco users or individuals that have never smoked or used snuff.

3.12 Acute Myeloid Leukemia

3.12.1 Overview of evidence

Out of the other outcomes described in the 2013 ENVIRON report, only acute myeloid leukemia (AML) is on the list of smoking-related outcomes. Only Fernberg et al. (2007) assessed AML in dual users, while no studies assessed AML in switchers. No AML studies have been published since the 2013 ENVIRON report.

3.12.2 Study considerations

Fernberg et al. (2007) did not report a "mixed user" effect measure defined as "users of at least two tobacco products, either snuff and smoking tobacco or more than one type of smoking tobacco". Results for only snus users and smokers was not available.

3.12.3 Results for AML

Reference	Effect measures for Exposures of interest (95% CI)	Effect measures for snus users, smokers, and former smokers (95% CI)
Fernberg et al. (2007)	Reference: Never tobacco use Mixed user: 1.38 (95% CI: 0.96-1.98)	Reference: Never tobacco user Pure cigarette smoker: 1.29 (0.89-1.86) Pure pipe smoker: 1.38 (0.85-2.24) Pure snuff dippers: 0.81 (0.41-1.60)

3.12.4 Discussion

One study (Fernberg et al. 2007) reported a statistically non-significant 1.38 (95% CI: 0.96-1.98) relative risk for mixed users compared to never tobacco users. This study similarly reported statistically non-significant results for pure snuff dippers, pure pipe smokers, and pure cigarette

smokers. It was not possible to separate the effects in only concurrent snus users and smokers. However, it is not likely dual users of snus and smoking tobacco had a statistically significant elevated risk as every exposure group is statistically non-significant and the magnitude of risk for exclusive snus users is below one.

Conclusion

There is limited evidence suggesting no statistically significant increased risk for "mixed users" compared to never tobacco users.

3.13 All-cause mortality

3.13.1 Overview of evidence compared to previous report

The 2013 ENVIRON report did not identify any study that reported all-cause mortality. No new studies related to these outcomes for dual users or switchers were published since the 2013 ENVIRON report. However, Roosaar et al. (2008) was represented in a comparative meta-analysis for dual users published by Lee (2014). Notably, Lee (2014) reported dual user effect estimates derived from Roosaar et al. (2008) that they did not report explicitly. The results from Lee (2014) are discussed.

3.13.2 Results for Endpoints

Reference	**Endpoints**	**Effect measures for Exposures of interest (95% CI)**	**Effect measures for snus users, smokers, and former smokers (95% CI)**	**Interaction tests (95% CI)**
Lee (2014) *unadjusted* estimates from Roosaar et al. (2008)	Smoking-related cancer-incidence[a]	Dual Users vs. exclusive smokers: 0.79 (0.54-1.16)	Exclusive snus vs neither: 1.60 (1.10-2.50)	0.50 (0.28-0.87)
	Any cancer-incidence	Dual Users vs. exclusive smokers: 0.94 (0.78-1.12)	Exclusive snus vs neither: 1.10 (0.90-1.40)	0.85 (0.64-1.13)
	Any cancer-mortality	Dual Users vs. exclusive smokers: 0.80 (0.62-1.04)	Exclusive snus vs neither: 1.28 (0.96-1.69)	0.63 (0.74-0.91)
	All-cause mortality	Dual Users vs. exclusive smokers: 0.97 (0.85-1.11)	Exclusive snus vs neither: 1.23 (1.09-1.40)	0.79 (0.66-0.95)

[a] It includes oral, pharyngeal, esophageal, gastric, pancreatic, laryngeal and pulmonary cancer, as well as cancer

of the kidney, bladder and other urinary organs

3.13.3 Discussion of total mortality, cancer-related mortality, incidence of any cancer, and smoking-related cancer incidence.

Effects in dual users and comparison to snus users

Lee (2014) calculated relative risks for current dual users compared to current smokers in Roosaar et al. (2008) and found statistically non-significant results for smoking-related cancer incidence, any-cancer incidence, any-cancer mortality, and all-cause mortality. Lee (2014), also reported statistically significant change in relative risk for dual users compared to the relative risk in snus users. This indicated evidence of multiplicative interaction in the Roosaar et al. (2008) study population for each outcome reported. It is unclear why there would be a statistically significant decrease in the relative risk for dual users compared to the relative risk in snus users considering that prior knowledge links smoking to smoking-related cancer incidence, any-cancer incidence, any-cancer mortality, and all-cause mortality. Others have suggested that dual users consume less smoking tobacco than exclusive smokers, however no evidence of lower smoking tobacco consumption was presented in the selected study.

Conclusion

Overall, these results indicate a statistically non-significant risk of smoking-related cancer incidence, any-cancer incidence, any-cancer mortality, and all-cause mortality in dual users compared to current smokers. There was also evidence of multiplicative interaction between smoking and snus use.

3.14 Summary of Results

This report assessed the following outcomes: oral and pharyngeal cancer, oral cancer, esophageal cancer and subtypes, pancreatic cancer, stomach cancer and subtypes, lung cancer, overall cardiovascular disease, incident and fatal ischemic heart disease and MI, nonfatal MI, incident and fatal stroke, sudden cardiac death, metabolic syndrome, diabetes prevalence and incidence, acute myeloid leukemia, and total mortality related-outcomes.

3.14.1 Dual users compared to never tobacco or never snus/smoke

The majority of endpoints had statistically non-significant results for the comparison of dual users to never tobacco or never snus/smoke, however eight endpoints varied in evidence. Results did not exist for oral and pharyngeal cancer. Lung cancer had evidence of a lower risk in dual users, while four endpoints (non-fatal MI, fatal stroke, total mortality-related outcomes, and pancreatic cancer) had evidence of an increased risk. Two endpoints (IHD/MI incidence and mortality) had mixed evidence of increased risk and statistically non-significant results. The remaining ten outcomes have statistically non-significant results only. Notably endpoints with statistically significant increased, decreased, or mixed evidence of risk in dual users did not have evidence for significant risk compared to smokers and/or no evidence of statistical interaction.

3.14.2 Dual users compared to smokers

Except for three endpoints (oral and pharyngeal cancer, lung cancer, and pancreatic cancer), all studies present some evidence of statistical non-significance either through statistical comparison,

tests of interaction, or effect measures that overlap confidence intervals. Dual users compared to smokers was not assessed in two endpoints (lung cancer, pancreatic cancer) due to a lack of smoking effect estimates. Oral and pharyngeal cancer was the only study to report increased risk in dual users, although with evidence of statistically non-significant interaction. Two endpoints (fatal stroke and fatal IHD/MI) did not have a statistical comparison reported but had evidence of a statistically non-significant interaction between smoking and snus use. Two endpoints (diabetes incidence and total mortality related outcomes) had mixed evidence of lower risk and statistical non-significance. Five endpoints (non-fatal MI, SCD, MetSy, Diabetes prevalence, AML) had neither a statistical comparison between dual users and smokers or an assessment of interaction, however all of these had dual user effect measures that overlapped the confidence interval for the smoker effect measure suggesting no statistically significant difference in relative risks. The remaining six endpoints (IHD/MI incidence, oral, esophageal, stomach, overall cardiovascular disease, and incident stroke) had statistically non-significant results assessed through a statistical test.

3.14.3 Effects in switchers and comparison to smokers

Only ten endpoints presented results for switchers in this report: non-fatal MI, incident and fatal IHD/MI, diabetes incidence and prevalence, oral cancer, overall cardiovascular disease, stroke incidence, sudden cardiac death, and metabolic syndrome.

3.14.3.1 Switchers compared to never tobacco or never smoke/snus

Only evidence for non-fatal MI suggests an increased risk for switchers. Evidence for IHD/MI incidence is mixed with studies suggesting increased risk and statistical non-significance. Notably, these two endpoints (IHD/MI incidence and non-fatal MI) have evidence suggesting a significant lower risk in dual users compared to smokers. The remaining eight endpoints have evidence of statistical non-significance through a statistical test.

3.14.3.2 Switchers compared to current smokers

In the comparison of switchers to current smokers, evidence for all endpoints suggested either lower risk, mixed evidence of lower or non-significant risk, or statistical non-significance. Four endpoints (non-fatal MI, IHD/MI incidence, overall cardiovascular disease, and incident stroke) had lower risk, while one endpoint (Fatal IHD/MI) had mixed evidence of lower or non-significant risk. The remaining five endpoints had evidence that suggested statistical non-significance due to effect measures overlapping confidence intervals or a statistical test.

3.14.3.3 Switchers compared to former smokers

All studies had evidence suggesting statistical non-significance either due to a statistical test or effect measures overlapping confidence intervals.

3.15 Discussion

Some studies provided evidence for an increased or decreased risk in dual users compared to never tobacco users, however most studies also provided evidence for statistical non-significant risks in dual users compared to smokers. Similarly, studies of switchers provide some evidence for increased risk compared to never tobacco users, however all studies provide evidence of decreased or statistically non-significant risk in switchers compared to smokers.

These conclusions regarding switchers differ from those reported by Henley and colleagues (2007) who investigated the potential health effects of switching from cigarettes to smokeless tobacco in the US American Cancer Society Cancer Prevention Study II cohort. The authors reported that men who switched from smoking cigarettes to using smokeless tobacco (using data that was collected at baseline only) had a higher rate of death from all causes, lung cancer, coronary heart disease, and stroke than those who had never used tobacco or those who were former cigarette smokers and quit using tobacco entirely following adjustment for several relevant potential confounders. The authors noted that switchers, compared to those who quit tobacco entirely, were less educated, more often employed in blue-collar occupations, and had a less healthy diet. Because information on tobacco use was collected only at baseline and not updated during follow-up, it is possible that men who quit smoking before enrollment, but resumed during the follow-up period, and those who initiated or discontinued using spit tobacco after enrolment, could have been misclassified, in fact, a subset of the cohort whose smoking status was updated after 10 years, had low overall rate of recidivism, but was statistically significantly higher among switchers (3.0%) than among those who quit using tobacco entirely (1.4%). Additional limitations of the study include lack of information on intensity of smoking, and the possibility that addiction may have influenced both smoking behavior and use of smokeless tobacco. Former smokers who switched may have been more addicted on average and may have smoked differently than those who quit tobacco entirely.

A limitation of these studies is that most of the studies of dual users did not provide qualitative or quantitative information on consumption of individual tobacco types among dual users with the exception of two of the studies (Hergens et al. 2005; Ye et al. 1999). In both of these studies, the authors reported that dual users smoked slightly less compared to exclusive smokers, and in the Ye et al. (1999) study, smoked for a shorter duration. Though dual users smoked less in these two studies, the authors of at least one US study have reported that dual users smoked more than exclusive smokers in that particular study population (Accortt et al. 2002). Among the studies where the amount of tobacco consumption by type is not provided, it is not known how smoking intensity may affect the interpretation of the reported risk estimates.

Additionally, though most of the studies reported relative risk estimates among concurrent users of snus and cigarettes (those who used both tobacco types at the same time, typically daily), four of the studies reported relative risk estimates among dual users who were either ever users of snus, cigarettes, or both (Bertuccio et al. 2011; Boffetta et al. 2005; Ye et al. 1999; Zendehdel et al. 2008). Thus, it is likely that not all of the participants were concurrent users of both tobacco types, or were concurrent users for different time frames, before they developed a disease.

It is also possible that the lifestyles, especially unhealthy habits known to affect disease risk, may differ significantly among the various tobacco groups, and may not be accounted for in the studies. Several individual studies have found that unhealthy lifestyle habits to be more prevalent among dual users of tobacco compared to exclusive tobacco user groups, and nontobacco users. Engstrom and colleagues (2010) reported that unhealthy lifestyle was strongly associated with dual use among Swedish men and women. This included risky alcohol consumption, binge drinking, low fruit and vegetable consumption, and a sedentary lifestyle. Bombard and colleagues (2009) reported that lifetime polytobacco users in Canada were more likely to use drugs and alcohol. Klesges and colleagues (2011) reported that US Air Force recruits, who were dual users, had a higher prevalence of heavier alcohol consumption, more risk-taking behaviors, and were more likely to be surrounded by

smokers. Johansson and colleagues (2005) reported that the highest percentage of "no physical activity" was observed among daily smokers and dual users in a Swedish population. The highest percentage of overweight and obesity was also found among dual users in this study. Aro and colleagues (2010) found that the high alcohol consumption (>100 g/week) was highest among dual users in a Northern Swedish study population.

Dual use of cigarettes and nicotine replacement therapy (NRT) products has also been reported. Hughes and colleagues (2005) investigated the potential off-label use of a nicotine inhaler that had recently been prescribed to US smokers in a prospective study. Off-label use included using the inhaler and cigarettes concurrently or using the inhaler for non-cessation reasons. The authors reported that many smokers used the inhaler and cigarettes concurrently on the same day (43-55%) at some time during the six-month follow-up period but found that this behavior did not persist in most individuals. Repeated concurrent use (weekly concurrent use for at least a month) was reported by only 7-12% of participants. The participants did not appear to become dependent on the inhaler (only 1.4% self-reported the DSM-IV or ICD-10 criteria for dependence, but a clinician who interviewed them did not believe any were dependent). The authors concluded that although concurrent use of NRT and cigarettes occurs in some users, harm from and dependence on NRT is rare.

Despite the potential limitations of the studies of dual users of Swedish snus and cigarettes, the evidence from several different cohorts suggests that dual users do not face a higher disease risk than exclusive smokers, and that generally, the health risks among dual users appear to be similar to those observed among exclusive smokers. A number of smoking-related diseases were examined, including various cardiovascular outcomes, smoking-related cancers and other non-smoking-related diseases. Thus, no unique or multiplicative health risks were identified among dual users of tobacco. These conclusions are consistent with that reached by Frost-Pineda and colleague (2010), who reviewed the available literature on the health effects of dual use from US and European epidemiology studies. Those authors concluded that "the evidence is sufficient and clear that there are no unique health risks (either qualitative or quantitative) associated with dual use of cigarettes and smokeless tobacco products, which are not anticipated or observed from single use of these products for the major health effects associated with smoking and smokeless tobacco. Some data indicate that the risks of dual use are lower than those of exclusive smoking." In this current review, the health risks among those who switch to snus from cigarettes were lower than those observed among individuals who continued to smoke cigarettes, and were generally comparable to, or had lower point estimates than the risks estimates observed among those who quit tobacco entirely. These conclusions are also consistent with those reached by Lee (2013), who reviewed the health effects of switching among the same studies of smoking-related outcomes included in this analysis. With respect to incident IHD or MI, Lee (2013) compared risk estimates of switchers with quitters and continuing smokers quantitatively, and where appropriate, provided combined summary estimates of switching vs. continued smoking (0.55; 95% CI: 0.45-0.68) and quitting (1.02; 95% CI: 0.83-1.26). Lee (2013) concluded that "the findings consistently demonstrate that switching from cigarettes to snus is associated with a clearly lower risk of CVD and cancer than is continuing to smoke. The risk in switchers is no different than that in smokers who quit smoking."

4. NON-CLINICAL TOXICOLOGICAL STUDIES WITH SNUS

Nine potentially relevant non-clinical toxicological and *in vitro* studies were identified in the July 28, 2017 literature search. Of the nine, five were identified as relevant, with four excluded for reasons including nonuse of Swedish Match snus product(s), or previous inclusion in the 2013 ENVIRON report.

4.1 *In Vitro* Studies of Swedish Snus

4.1.1 Cardiovascular

Ljungberg et al. (2013) conducted an experiment in which the effects of nicotine and its metabolites on platelet function (platelet adhesion, aggregation and P-selectin expression), and Ettan moist snuff (Swedish Match) extract, Copenhagen snuff fine cut extract, tobacco free snuff extract (Choice apple), and Camel cigarette smoke extract on platelet adhesion were evaluated *in vitro*. The effects of tobacco extracts were evaluated both alone and with known platelet activators (ADP and adrenaline). Blood was collected from healthy human donors. A weak, but significant effect of nicotine at 10 µM only on platelet aggregation was observed, while none of the four metabolites evaluated at 0.1 to 10 µM affected ADP-induced platelet aggregation. Nicotine had no effect on platelet adhesion and only two of the four metabolites caused a weak inhibition: trans-3´-hydroxycotinine exclusively at 0.1 µM (but not at higher concentrations), and nicotine-1´-N-oxide at 1 and 10 µM.

With respect to the effects of tobacco extracts, a reduction in platelet adhesion to fibrinogen and collagen was observed for 10% Ettan snuff extract, while 10% Copenhagen moist extract reduced platelet adhesion to collagen, and reduced adhesion to fibrinogen at 3% and 10%. Camel cigarette smoke extract induced a significant decrease in adhesion to albumin and fibrinogen at all concentrations (0.001 to 10%), with adhesion to collagen decreased at 3% and 10%. 10% Choice apple extract reduced platelet adhesion to collagen, and 3% and 10% to fibrinogen. When platelets were pretreated with a nicotine-receptor inhibitor, or drugs that interfere with the nitric oxide system, the inhibitory effect of the tobacco extracts on platelet adhesion persisted. The authors concluded that because "only limited effects of nicotine and nicotine metabolites were seen, the tobacco-induced platelet inhibition are likely induced by other compounds present in tobacco and tobacco free snuff." The potential clinical significance of these results are unclear, as previous smoking studies, noted by the authors, have indicated increased platelet activity and increased risk for thrombosis. This contradicts the results of the current study. Furthermore, the authors noted that the direct effects of nicotine or tobacco products on platelet activity can be difficult to elucidate from *in vivo* studies.

4.1.2 Genotoxicity, Mutagenicity, and Cytotoxicity

Merne et al. (2014) conducted an *in vitro* study in which human HPV-positive and HPV-negative oral keratinocytes and oral HPV-negative fibroblasts were exposed to Ettan snus (Swedish Match) (STE1), and US-type reference snuff extract (STE2) to investigate the potential genotoxic effects on the cells, specifically, aneuploidy (abnormal number of chromosomes). The results were as follows:

- The HPV-positive keratinocytes exposed to STE2 showed a statistically significant increase in the number of aneuploid cells from 27.4% to 80.5%, while the changes following STE1 exposure were much less (27.4% to 30.8%).

- In oral spontaneously transformed HPV-negative keratinocytes, the number of aneuploid cells at G2-M stage increased after STE1 and STE2 exposure from 3.4% to 8.5% and 7.2%, respectively.
- In HPV-negative oral fibroblasts, the number of aneuploid cells at G2-M phase increased from 11% to 21% after STE1 and 29% after STE2 exposure.
- Neither STE1 or STE2 exposure had an effect on HPV16 E6 and E7 oncogene expression.

The authors concluded that the effects of the STEs varied by cell line, but that they both increased the aneuploidy of HPV16 E6/E7-transformed oral epithelial cells. However, only STE2 led to statistically significant increases in aneuploidy cells. The authors further noted that their "*in vitro* results are in line with the epidemiological reports showing greater risk of oropharyngeal cancer with STE2, the North American snuff, than STE1, the Scandinavian type of snuff."

Song et al. (2016) evaluated and compared the chemical composition and *in vitro* toxicity of seven conventional and 12 low-TSNA moist snuff products (including Swedish Match products: Ettan Lossnus and General Mini Portion). The products were extracted with dimethyl sulfoxide (DMSO). The assays included the Ames Salmonella reverse mutation assay, the Neutral Red Uptake (NRU) Cytotoxicity assay, and the micronucleus (MN) assay. A limitation of the study, however, was that the results reported by the authors included the combined effects of Swedish products, including the two Swedish Match product(s) with a non-Swedish Match product called Skruf Stark Portion. The results of experiments on mutagenicity, cytotoxicity, and genotoxicity were as follows:

- The authors reported that "the largest increase (average 22%) in mutagenicity was observed in Swedish low-TSNA moist snuff products with the highest addition of the extracted products (1.1 mg/mL) compared to its absence ($p=0.049$)."
- Loss of cell viability was observed with exposure of 2.2 mg/mL of extracts in all products, with Swedish low-TSNA products showing similar low cytotoxicity to conventional moist snuff products. Statistically significantly higher cytotoxicity was observed in South Africa and US low-TSNA moist snuff products compared to conventional products ($p=0.04$), with mean proportions of cell death of 56.6%, 50% and 34.8%, respectively.
- The MN genotoxicity test showed that the mean proportion of micronuclei was statistically significantly increased (122%-127%) ($p=1.47\times10-7$) with treatment of all products compared to controls, but no differences were observed among the products.

A major limitation of *in vitro* studies such as this one, as acknowledged by the authors, is that "it is difficult to apply these data to human risk because the cell culture conditions do not exist in humans."

4.2 Studies of Swedish snus in Experimental Animals (*In Vivo*)

4.2.1 Cardiovascular & Developmental

Folkesson et al. (2016) conducted an *in vivo* study to investigate the potential differences in developmental and cardiovascular toxicities associated with cigarette and snuff extracts (Göteborgs Rapé snuff, Swedish Match) in a zebrafish model (embryos). The authors reported that exposure to the tobacco extracts led to a variety of toxic effects including early embryonic mortality, developmental delay, cerebral hemorrhages, defects in lymphatics development and ventricular

function, and aneurysm development, with both extracts more toxic than nicotine alone. Developmental delay and aneurysm development were specifically observed in the snuff extract group, while cerebral hemorrhages were found only in the group exposed to cigarette extracts. It is important to note, however, that the differences in the route of exposure, and use (e.g., combustion) could present differences in toxicity when comparing snuff use and cigarette smoking in humans. Furthermore, aside from the potential differences between human and zebrafish embryos, the conditions for which the embryos were exposed (injection) is not necessarily representative of real-world tobacco use in humans.

4.2.2 Non-Cancer Soft Tissue Changes

Nilsson et al. (2016) conducted an *in vivo* study in which Wistar rats consumed a tobacco slurry in which 10 g of Ettan brand snus from Swedish Match was homogenized in 100 ml of water alone, as well as in conjunction with additives including blueberries and an extract from milk thistle that might exert protective effects against soft tissue changes in the rat forestomach. The rat forestomach was used as a model in the study of "undesirable keratotic lesions and associated epithelial abnormalities in the oral cavity" among snus users. The authors noted the reversibility of snus-induced oral lesions in humans, and that "the cancer risk from snus is extremely low."

Following 4 weeks of treatment with Ettan snus, observed effects included dilation of blood vessels in the submucosa, and a thickening of the basal region of squamous epithelium forestomach due to a proliferation of cells in the basal layer, compared with controls. In comparison with treatment of Ettan snus only, combined administration with blueberries or extract from milk thistle decreased the number of proliferating cells significantly by 36-44%. The authors concluded that "in spite of a relatively short time of exposure, the marked inhibition by blueberries and milk thistle extract on cellular proliferation induced by Swedish snus in the rate forestomach epithelium indicates a possible approach for achieving protection against the soft tissue changes in the human oral cavity caused by smokeless tobacco."

With respect to the effects of Ettan snus alone on the rat forestomach in this study, the results are consistent with snus's effects on the oral mucosa in humans, and those reported in a study of Ettan snus placed in the rat lip canal described in the 2013 ENVIRON report (Schwartz et al. 2010).

4.3 Summary and Conclusions

Five new studies were identified since publication of the 2013 ENVIRON report. Similar to the 2013 report, some of the new studies included genotoxicity, mutagenicity, and cytotoxicity endpoints investigated *in vitro*, as well as an *in vivo* study of rats. New endpoints included *in vitro* effects on platelet function (adhesion) and aneuploidy (abnormal number of chromosomes), and an *in vivo* study of potential cardiovascular and developmental effects of Swedish snus on zebrafish embryos.

Consistent with previous findings, one study of the combined effect of three Swedish snus products (one of which was not Swedish Match brand) indicated that Swedish snus may be mutagenic (increased mutation revertants), genotoxic (increased micronuclei), and cytotoxic (lower cell viability) *in vitro*. Another *in vitro* study of the potential genotoxicity of Swedish snus did not report a statistically significant increase in aneuploid HPV-positive keratinocytes. A third *in vitro* study reported a reduction in platelet adhesion to fibrinogen and collagen for 10% Ettan snuff extract. The potential

clinical significance of these results is unclear, and it remains unknown to what extent any of the *in vitro* effects from these studies may be relevant to humans *in vivo*.

In an *in vivo* study of rats that consumed a tobacco slurry of Swedish snus, consistent with previous findings in animals as well as oral changes in humans, non-cancerous soft tissue changes in the forestomach were observed including cell proliferation, and a thickening of the basal region of squamous epithelium. In a new study of the potential cardiovascular and developmental effects of Swedish snus on zebrafish embryos, a variety of toxic effects including early embryonic mortality, developmental delay, defects in lymphatics development and ventricular function, and aneurysm development were observed following injection with Swedish snus extracts. Aside from the potential differences between human and zebrafish embryos, the conditions for which the embryos were exposed in this study (injection) is not necessarily representative of potential real-world exposure of human embryos as a result of the mother using snus.

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Appendix A: The PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	23
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.	Not applicable
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	12-13
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	12-13
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.	13-22
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.	13-14
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.	14
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	14, Appendix B
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).	14-16
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.	14-18
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendix E

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.	18-22
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.	20-22
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).	18-22
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.	16-18, Appendix C, Appendix D
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.	Appendix F
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).	Within each respective endpoint section
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.	Appendix F, Within each respective endpoint section
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).	Within each respective endpoint section
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).	Within each respective endpoint section
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of	Within each respective

		identified research, reporting bias).	endpoint section
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Within each respective endpoint section
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.	12

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.

For more information, visit: **www.prisma-statement.org**.

Appendix B: Search Results Tracking Table

The following search terms seek to be as inclusive as possible, and consequently focus on the exposure of interest for the updated literature search (Table B1). Table B2 presents the search terms and results that were used in the retrospective literature search of the health effects studies on Swedish snus through December 1, 2012.

Table B1: Update Literature Searches

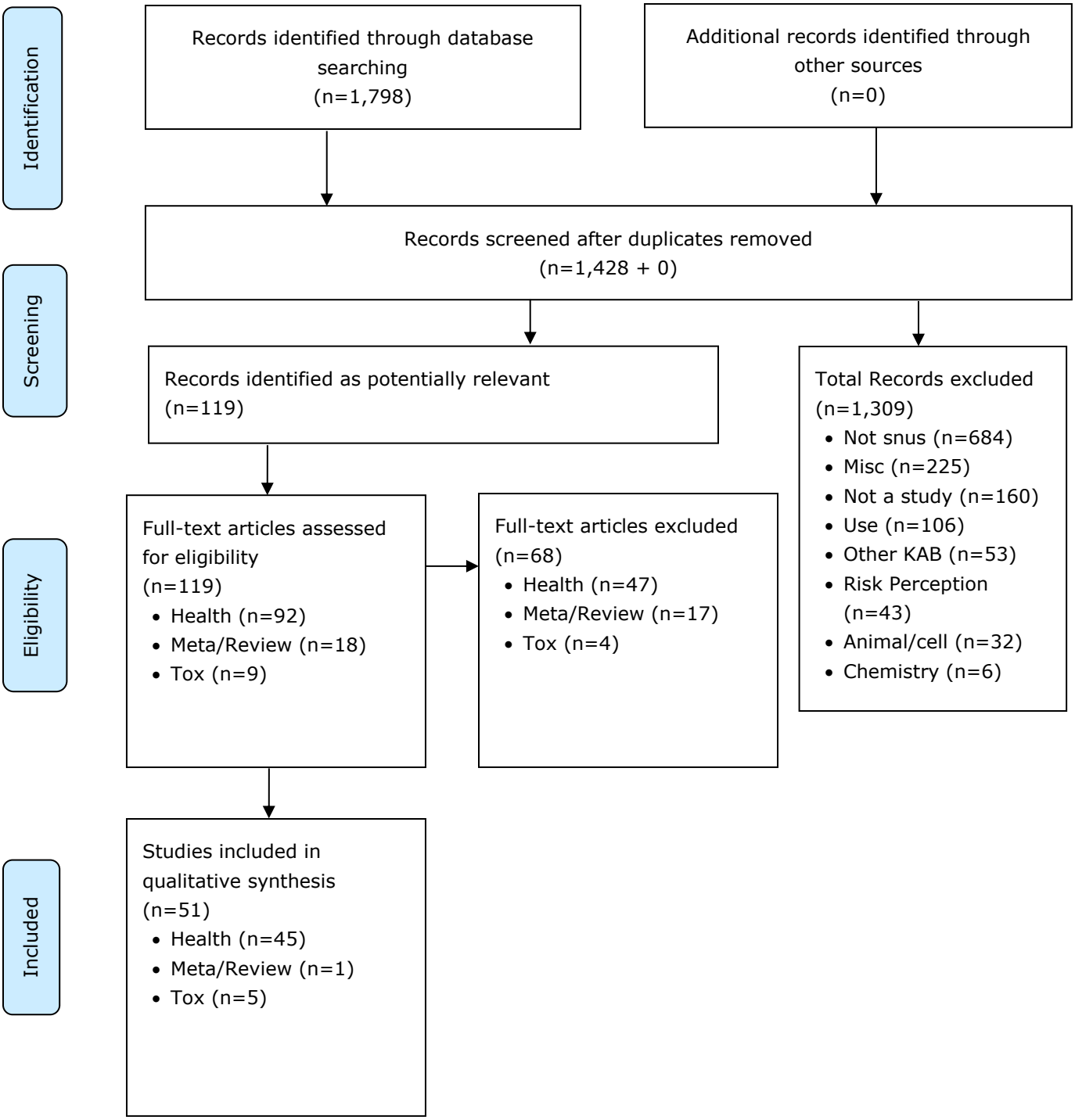
Search No.	Source	Date	Search terms	Results (#)
1	PubMed	7/28/2017	snus OR snuff Filter: December 1, 2012 to present	1,194
2	Scopus	7/28/2017	TITLE-ABS-KEY(snus OR snuff) AND PUBYEAR > 2011 Filter: January 1, 2012 to Present	578
4	Clinicaltrials.gov	7/28/2017	snus OR snuff Filter: Limited to studies that have been "completed" and "with results." Terms entered into the "other terms" field. No year limits available.	26 total results (includes studies from all years) 0 relevant studies conducted after 2012.
5	http://www.scb.se/	7/28/2017	snus, snuff, tobacco	**Snus:** 249 "pages and documents," 1 "statistical database" **Snuff:** 17 "pages and documents," 2 "statistical databases" **Tobacco:** 548 "pages and documents," 2 "statistical databases"
6	www.socialstyrelsen.se	7/28/2017	snus, snuff, tobacco	**Snus:** 8 **Snuff:** 3 **Tobacco:** 28
7	www.folkhalsomyndigheten.se	7/28/2017	snus, snuff, tobacco	**Snus:** 103 **Snuff:** 18 **Tobacco:** 122
8	www.helsedirektoratet.no	7/28/2017	snus, snuff, tobacco	**Snus:** 70 **Snuff:** 1 **Tobacco:** 40

9	www.fhi.no	7/28/2017	snus, snuff, tobacco	**Snus:** 78 **Snuff:** 4 **Tobacco:** 30

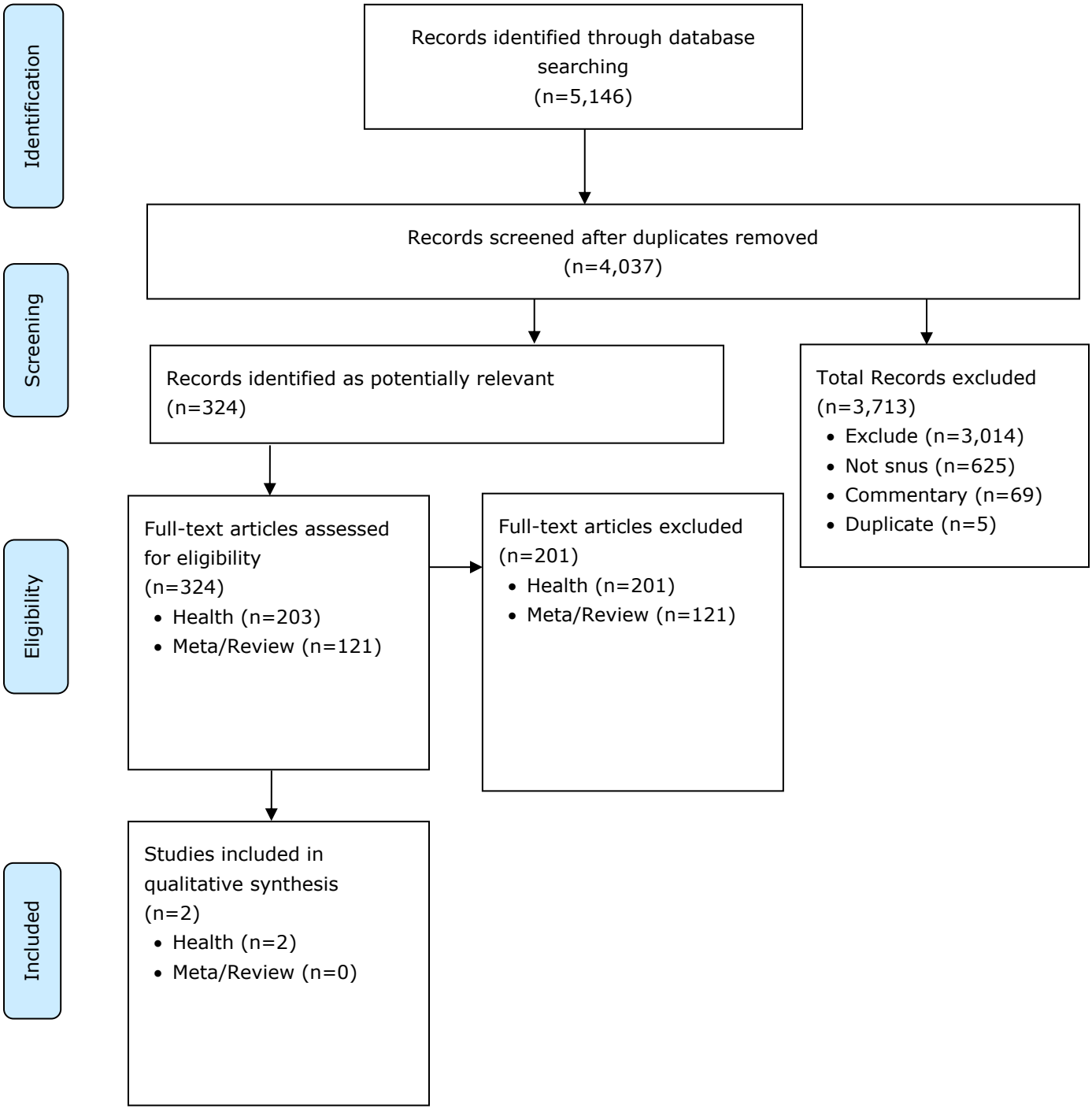
Table B2: Retrospective literature search on the health effects of Swedish snus through December 1, 2012

	Source	Date	Search terms	Results (#)
1	PubMed	7/28/2017	snus OR snuff Filter: All time to December 1, 2012	3,541
2	Scopus	7/28/2017	TITLE-ABS-KEY(snus OR snuff) AND PUBYEAR < 2013 Filter: All time to December 31, 2012	1,579
3	Clinicaltrials.gov	7/28/2017	snus OR snuff Filter: Limited to studies that have been "completed" and "with results." Terms entered into the "other terms" field. No year limits available.	26 total results (includes studies from all years) 3 potentially relevant studies conducted prior to 2012: 1 was a duplicate, 1 wasn't Swedish snus, and the last was previously reviewed and determined to be non-relevant

Appendix C: Adapted PRISMA Literature Inclusion/Exclusion Diagram for the Updated Search



Appendix D: Adapted PRISMA Literature Inclusion/Exclusion Diagram for Retrospective Health Effects Literature Search Prior to December 1, 2012



Appendix E: Literature Abstraction Templates

Health-Related Literature (Update to Section 5 of the 2013 ENVIRON Report)

Note: If a study provides information for multiple endpoints, the results for each endpoint will be recorded as separate line items.

TABLE HEADER	**DETAILS**
First Author	Last name of first author
Year	Year of publication
Overall Evidence Quality	Overall quality determination for this line of evidence: Strong, Moderate, Weak
Limitations and Potential Biases	Study limitations potentially influencing the reported findings.
Product Description	Brand and type of snus, as applicable, author description
Study Design	Examples: cohort, case-control, clinical trial, focus group, etc.
Population (total)	Population/cohort description and total number of participants, prior to any screening/exclusion
No. case/controls or equivalent	Numbers used in specific analysis, and number of exposed cases
Study Period	--
Endpoint Category	Non-cancer Oral, Dental, Cancer, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, Repro, Other
Endpoint	Health endpoint evaluated (as described in the study)
Covariates	Examples: age, sex, race, education status, etc.
Exposed Group	Description of tobacco use (e.g. exclusive, duration, intensity, etc.)
Referent Group	Examples: never-users of tobacco, non-users of tobacco
Risk Estimate Description	Examples: Odds ratio, relative risk, etc.
Risk Estimate	--
LCL	Lower confidence limit
UCL	Upper confidence limit
p-value (if applicable)	--
Statistically Significant?	Yes/No
Funding Source	--
Author Conclusion + Comments	Author conclusion in quotes, and any additional comments regarding the study.

Appendix F: Literature Abstraction Table: Health-Related Literature (Update to Section 5 of the 2013 ENVIRON Report)

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
Andersson MLE, Bergman S and Söderlin MK. 2013. The effect of snuff (smokeless tobacco) on disease activity and function in rheumatoid arthritis: Experiences from the better anti-rheumatic farmacotherapy, a longitudinal multicenter study on early rheumatoid arthritis. Journal of Clinical Rheumatology, 19(1): 14–18.	Weak	Snuff use assessed retrospectively (potential misclassification and recall bias), snuff users may have smoked previously, small sample size	Swedish "Snuff (moist smokeless tobacco)"	Cohort	2,800 patients older than 18 years enrolled in the BARFOTstudy, which included patients with early rheumatoid arthritis (RA) in southern Sweden	51 snuff users / 49 never-smoking controls	Enrolled in 1992-2005, followed through September 2010	Other	Rheumatoid Arthritis disease activity: Disease Activity Score 28 joints (DAS28)	socioeconomic class, disease duration, number of previous disease-modifying antirheumatic drugs and biologics (grouped together)	Snuff users (prior to start of, and after inclusion into the BARFOT study)	Never-smokers	Difference in mean DAS28 score				0.001	Yes (for 3 months and 6 months, but not 1, 2, and 5 years)	Swedish Society of Medicine, the Swedish Rheumatism Association, the Research Department of the County Council of Halland, the Gothenburg District Rheumatology Foundation, and the Crafoord Foundation	"No significant differences in DAS28 values at inclusion, at 3, 6, and 12 months, and at 1, 2, and 5 years of follow-up between snuff users and never smokers (P = 0.35, P = 0.81, P = 0.17, P = 0.89, P = 0.77, and P = 0.74, respectively)." Following adjustments, "snuff users had significantly lower DAS28 scores at 3 months of follow-up (mean DAS28, 2.0 in snuff users vs. 3.7 in never smokers; P = 0.001) and at 6 months (mean DAS28, 2.1 in snuff users vs. 3.2 in never smokers, P = 0.003)." "patients with RA using snuff generally had lower DAS28 values than those who had never smoked at up to 6 months of follow-up, and as compared with previous smokers at up to 2 years of follow-up, but no effect of snuff use was seen on HAQ or EULAR response."
Araghi M, Rosaria Galanti M, Lundberg M, Lager A, Engström G, Alfredsson L, Knutsson A, Norberg M, Sund M, Wennberg P, Trolle Lagerros Y, Bellocco R, Pedersen NL, Östergren P-O and Magnusson C. 2017. Use of moist oral snuff (snus) and pancreatic cancer: Pooled analysis of nine prospective observational studies. International Journal of Cancer, 141(4): 687–693.	Strong	Possible misclassification of exposure with long follow up	Swedish "moist oral snuff (snus)"	Pooled cohort	418,448 male participants from nine cohort studies. Data came from the Swedish Collaboration on Health Effects of Snus Use, and participants were followed up through linkage to health registries.	30% of participants had ever used snus at time of entry. 321 exposed cases	1978-2013	Cancer	Pancreatic cancer	attained age, smoking (never, former, current), and BMI	Ever users	Never users of snus	HR (95% CI)	0.93	0.82	1.06		No	Not stated	Cohorts included: Construction Worker Cohort, Malmo diet and Cancer Study, Multinational Monitoring of Trends and Determinants in Cardiovascular disease (MONICA), National March Cohort, Scania Public Health Cohort, Stockholm Public Health Cohort, Vasterbotten Intervention Programme (VIP), Work Lipids, and Fibrinogen Study. "Our findings, from the largest sample to date, do not support a role of snus use in the development of pancreatic cancer in men. They, furthermore, point to tobacco smoke constituents other than nicotine or its metabolites, i.e. carcinogens associated with combustion, as the causal agent explaining the increased risk of pancreatic cancer in smokers." "We had the opportunity to control for alcohol consumption, the level of physical activity as well as diabetes, and again the main findings did not change." Sensitivity analyses (Table 3) for cases from cancer register only, excluding the Construction Worker Cohort,
	Strong					30% of participants had ever used snus at time of entry. 93 exposed cases		Cancer	Pancreatic cancer	attained age, smoking (never, former, current), and BMI	Former users	Never users of snus	HR (95% CI)	0.88	0.71	1.1		No		
	Strong					30% of participants had ever used snus at time of entry. 227 exposed cases		Cancer	Pancreatic cancer	attained age, smoking (never, former, current), and BMI	Current users	Never users of snus	HR (95% CI)	0.96	0.83	1.11		No		
	Strong					30% of participants had ever used snus at time of entry. 91 exposed cases		Cancer	Pancreatic cancer	attained age, smoking (never, former, current), and BMI	<4 cans/week	Never users of snus	HR (95% CI)	0.87	0.7	1.08		No		
	Strong					30% of participants had ever		Cancer	Pancreatic cancer	attained age, smoking	4-6 cans/week	Never users of snus	HR (95% CI)	1.16	0.93	1.46		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						used snus at time of entry.				(never, former, current), and BMI										and excluding cohorts with no information on former snus use were all nonsignificant.
	Strong					83 exposed cases 30% of participants had ever used snus at time of entry.		Cancer	Pancreatic cancer	attained age, smoking (never, former, current), and BMI	≥ 7 cans/week	Never users of snus	HR (95% CI)	0.87	0.65	1.17		No		
	Strong					48 exposed cases 30% of participants had ever used snus at time of entry.		Cancer	Pancreatic cancer	attained age, smoking (never, former, current), and BMI	<5 years	Never users of snus	HR (95% CI)	0.82	0.56	1.21		No		
	Strong					27 exposed cases 30% of participants had ever used snus at time of entry.		Cancer	Pancreatic cancer	attained age, smoking (never, former, current), and BMI	5-<10 years	Never users of snus	HR (95% CI)	1	0.72	1.39		No		
	Strong					38 exposed cases 30% of participants had ever used snus at time of entry.		Cancer	Pancreatic cancer	attained age, smoking (never, former, current), and BMI	10-<15 years	Never users of snus	HR (95% CI)	0.99	0.72	1.36		No		
	Strong					41 exposed cases 30% of participants had ever used snus at time of entry.		Cancer	Pancreatic cancer	attained age, smoking (never, former, current), and BMI	15-<20 years	Never users of snus	HR (95% CI)	0.98	0.67	1.44		No		
	Strong					27 exposed cases 30% of participants had ever used snus at time of entry.		Cancer	Pancreatic cancer	attained age, smoking (never, former, current), and BMI	≥ 20 years	Never users of snus	HR (95% CI)	0.95	0.75	1.19		No		
	Strong					78 exposed cases 30% of participants had ever used snus at time of entry. 92 exposed cases		Cancer	Pancreatic cancer	attained age, smoking (never, former, current), BMI, alcohol consumption, physical activity, and interaction between alcohol consumption and smoking among	Ever users	Never users of snus	HR (95% CI)	1.12	0.76	1.63		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
										studies where info was available										
	Strong					30% of participants had ever used snus at time of entry. 33 exposed cases		Cancer	Pancreatic cancer	attained age, smoking (never, former, current), BMI, alcohol consumption, physical activity, and interaction between alcohol consumption and smoking among studies where info was available	Former users	Never users of snus	HR (95% CI)	0.9	0.51	1.59		No		
	Strong					30% of participants had ever used snus at time of entry. 59 exposed cases		Cancer	Pancreatic cancer	attained age, smoking (never, former, current), BMI, alcohol consumption, physical activity, and interaction between alcohol consumption and smoking among studies where info was available	Current users	Never users of snus	HR (95% CI)	1.32	0.84	2.08		No		
	Strong					30% of participants had ever used snus at time of entry. 50 exposed cases		Cancer	Pancreatic cancer	attained age, smoking (never, former, current), and BMI	Exclusive ever snus users (never-smokers)	Never users of snus	HR (95% CI)	1.04	0.77	1.42		No		
	Strong					30% of participants had ever used snus at time of entry. 9 exposed cases		Cancer	Pancreatic cancer	attained age, smoking (never, former, current), and BMI	Exclusive former snus users (never-smokers)	Never users of snus	HR (95% CI)	0.92	0.47	1.8		No		
	Strong					30% of participants had ever used snus at time of entry. 41 exposed cases		Cancer	Pancreatic cancer	attained age, smoking (never, former, current), and BMI	Exclusive current snus users (never-smokers)	Never users of snus	HR (95% CI)	1.07	0.77	1.5		No		
Arefalk G, Hambraeus K,	Moderate	Limited number of	Swedish "Snus"	Cohort	20,911 patients with MI who	1,799 post-MI snus	2005-2009,	Other	Mortality	Model D: age, sex,	Post-MI snus	Post-MI snus	HR (95% CI)	0.55	0.31	0.99		Yes	Swedish Heart-Lung	"In this prospective cohort study, discontinuation of snus

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
Lind L, Michaëlsson K, Lindahl B and Sundström J. 2014. Discontinuation of smokeless tobacco and mortality risk after myocardial infarction. Circulation, 130(4): 325–332.		neversmoking snus users (no analysis among exclusive users). No comparison with neverusers of snus.			were admitted to a coronary care unit in Sweden between 2005-2009, then followed using a secondary prevention database (SEPHIA).	users / 675 post-MI snus quitters	followed until death or December 31, 2009			smoking exposure, diabetes mellitus, hypertension, blood pressure, BMI, waist circumference, LDL/HDL ratio, type of MI, occupation status, physical activity (4 levels), participation in cardiac rehabilitation program, treatment with aspirin, treatment with any other platelet inhibitor (primarily clopidogrel), β-blockers, statins, and renin-angiotensin-aldosterone system inhibitors (angiotensin-converting enzyme inhibitor or angiotensin 2 receptor blocker)	quitters	users							Foundation, the Swedish Research Council, and the Swedish Geriatric Fund	use after an MI was associated with a nearly halved mortality risk, similar to that associated with smoking cessation. These observations suggest that the use of snus after an MI should be discouraged."
	Moderate					1,799 post-MI snus users / 675 post-MI snus quitters		Other	Mortality	Model C: age, sex, past and present smoking and sun exposure, respectively, occupation status, participation in cardiac rehabilitation program	Post-MI snus quitters	Post-MI snus users	HR (95% CI)	0.57	0.32	1.02		No		
	Moderate					1,799 post-MI snus users / 675 post-MI snus quitters		Other	Noncardiovascular mortality	Model C: age, sex, past and present smoking and sun exposure, respectively, occupation status, participation in cardiac rehabilitation program	Post-MI snus quitters	Post-MI snus users	HR (95% CI)	0.43	0.15	1.27		No		

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	Moderate					1,799 post-MI snus users / 675 post-MI snus quitters		Heart/IHD	CV events	Model C: age, sex, past and present smoking and sun exposure, respectively, occupation status, participation in cardiac rehabilitation program	Post-MI snus quitters	Post-MI snus users	HR (95% CI)	0.38	0.11	1.32		No		
	Moderate					1,799 post-MI snus users / 675 post-MI snus quitters		Heart/IHD	Mortality from CV events	Model C: age, sex, past and present smoking and sun exposure, respectively, occupation status, participation in cardiac rehabilitation program	Post-MI snus quitters	Post-MI snus users	HR (95% CI)	0.56	0.16	2		No		
Baba S, Wikstrom A-K, Stephansson O and Cnattingius S. 2014. Influence of snuff and smoking habits in early pregnancy on risks for stillbirth and early neonatal mortality. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco, 16(1): 78–83.	Strong	Limitations: small number of exposed cases; self-reported tobacco use during pregnancy might lead to underreporting	"Swedish snuff"	Cohort	948,137 women born in Sweden, Denmark, Norway, Iceland, or Finland who were in the Swedish Medical Birth Register with single births during 1999-2010	9,198 current snuff users; 14,162 former snuff users; 667,301 nonusers of tobacco 27 stillbirths and 15 early neonatal deaths among former snuff users; 37 stillbirths and 7 early neonatal deaths among current snuff users	1999-2010	Reproductive	Stillbirths (in pregnancies with gestational age ≥28 weeks)	crude (no covariates)	Current snuff user	Nonusers of snuff and cigarettes	OR (95% CI)	1.56	1.12	2.17	NA	Yes	Swedish Council for Working Life and Social Research; Karolinska Institutet; Uehara Memorial Foundation Scholarship for Overseas Postdoctoral Researcher	The authors concluded that there was no effect of current snuff use or snuff cessation on early neonatal mortality, though the findings on early neonatal mortality had low statistical power due to a small number of cases. Snuff use in early pregnancy was associated with stillbirth, but cessation of snuff use before pregnancy or in early pregnancy reduced risk. Definition of "former" use: former snuff users reported using snuff 3 months before pregnancy, but had stopped using snuff at their first prenatal care visit.
	Strong					9,198 current snuff users; 14,162 former snuff users; 667,301 nonusers of tobacco 27 stillbirths and 15 early neonatal deaths among former snuff users; 37 stillbirths and 7 early neonatal deaths		Reproductive	Stillbirths (in pregnancies with gestational age ≥28 weeks)	maternal age, parity, early pregnancy BMI, education	Current snuff user	Nonusers of snuff and cigarettes	OR (95% CI)	1.43	1.02	1.99	NA	Yes		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						among current snuff users														
	Strong					9,198 current snuff users; 14,162 former snuff users; 667,301 nonusers of tobacco 27 stillbirths and 15 early neonatal deaths among former snuff users; 37 stillbirths and 7 early neonatal deaths among current snuff users		Reproductive	Stillbirths (in pregnancies with gestational age ≥28 weeks)	crude (no covariates)	Former snuff user	Nonusers of snuff and cigarettes	OR (95% CI)	0.76	0.52	1.1	NA	No		
	Strong					9,198 current snuff users; 14,162 former snuff users; 667,301 nonusers of tobacco 27 stillbirths and 15 early neonatal deaths among former snuff users; 37 stillbirths and 7 early neonatal deaths among current snuff users		Reproductive	Stillbirths (in pregnancies with gestational age ≥28 weeks)	maternal age, parity, early pregnancy BMI, education	Former snuff user	Nonusers of snuff and cigarettes	OR (95% CI)	0.73	0.5	1.06	NA	No		
	Strong					9,198 current snuff users; 14,162 former snuff users; 667,301 nonusers of tobacco 27 stillbirths and 15 early neonatal deaths among former snuff users; 37 stillbirths and 7 early neonatal deaths among		Reproductive	Early neonatal deaths (among live born infants at ≥22 weeks)	crude (no covariates)	Current snuff user	Nonusers of snuff and cigarettes	OR (95% CI)	0.8	0.38	1.7	NA	No		

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						current snuff users														
	Strong					9,198 current snuff users; 14,162 former snuff users; 667,301 nonusers of tobacco 27 stillbirths and 15 early neonatal deaths among former snuff users; 37 stillbirths and 7 early neonatal deaths among current snuff users		Reproductive	Early neonatal deaths (among live born infants at ≥22 weeks)	maternal age, parity, early pregnancy BMI, education	Current snuff user	Nonusers of snuff and cigarettes	OR (95% CI)	0.75	0.35	1.58	NA	No		
	Strong					9,198 current snuff users; 14,162 former snuff users; 667,301 nonusers of tobacco 27 stillbirths and 15 early neonatal deaths among former snuff users; 37 stillbirths and 7 early neonatal deaths among current snuff users		Reproductive	Early neonatal deaths (among live born infants at ≥22 weeks)	maternal age, parity, early pregnancy BMI, education, gestational age	Current snuff user	Nonusers of snuff and cigarettes	OR (95% CI)	0.64	0.3	1.37	NA	No		
	Strong					9,198 current snuff users; 14,162 former snuff users; 667,301 nonusers of tobacco 27 stillbirths and 15 early neonatal deaths among former snuff users; 37 stillbirths and 7 early neonatal deaths among current		Reproductive	Early neonatal deaths (among live born infants at ≥22 weeks)	crude (no covariates)	Former snuff user	Nonusers of snuff and cigarettes	OR (95% CI)	1.12	0.67	1.86	NA	No		

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						snuff users														
	Strong					9,198 current snuff users; 14,162 former snuff users; 667,301 nonusers of tobacco 27 stillbirths and 15 early neonatal deaths among former snuff users; 37 stillbirths and 7 early neonatal deaths among current snuff users		Reproductive	Early neonatal deaths (among live born infants at ≥22 weeks)	maternal age, parity, early pregnancy BMI, education	Former snuff user	Nonusers of snuff and cigarettes	OR (95% CI)	1.06	0.64	1.78	NA	No		
	Strong					9,198 current snuff users; 14,162 former snuff users; 667,301 nonusers of tobacco 27 stillbirths and 15 early neonatal deaths among former snuff users; 37 stillbirths and 7 early neonatal deaths among current snuff users		Reproductive	Early neonatal deaths (among live born infants at ≥22 weeks)	maternal age, parity, early pregnancy BMI, education, gestational age	Former snuff user	Nonusers of snuff and cigarettes	OR (95% CI)	1.15	0.68	1.93	NA	No		
Bjorkman F, Edin F, Mattsson CM, Larsen F, Ekblom B, Björkman F, Edin F, Mattsson CM, Larsen F and Ekblom B. 2017. Regular moist snuff dipping does not affect endurance exercise performance. PLoS ONE, 12(7): e0181228.	Strong	Participants may have modified other behaviors during follow-up; cotinine test for snuff abstinence done only at the end of cessation, not during cessation period	"Swedish snuff (i.e. oral moist snuff, 'snus')"	Clinical trial	24 regular snuff users (>2 years daily use), no illnesses or medications, regular exercise >3 times/week	24 participants who stopped using snuff for >6 weeks; 11 snuff users who continued their usual daily use	Not stated	CV Effects	Resting systolic BP (mmHg) Resting diastolic BP (mmHg) Resting mean BP Resting heart rate (beats min-1) blood lactate (mM L-1) total cholesterol (mM L-1)	NA	Snuff cessation group	Usual snuff use group	arithmatic mean ± SD	NA	NA	NA	Not reported no significant difference between groups in any of these measures	No	The Public Health Agency of Sweden; the Swedish School of Sport and Health Sciences	Regular daily snuff use does not affect endurance exercise performance. Effects of snuff on cardiovascular risk factors are mixed; heart rate and blood pressure improved after cessation, but total cholesterol, LDL, and body mass showed negative effects after cessation.

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									LDL (mM L-1) HDL (mM L-1) free fatty acids (FFA) (mM L-1) C-reactive protein (mg L-1)											
	Strong					24 participants who stopped using snuff for >6 weeks; 11 snuff users who continued their usual daily use		CV Effects	Peak values during maximal running tests: VO2 max (L min-1) Time to exhaustion (sec) HR peak (beats min-1) VE (L min-1) RER blood lactate (mM L-1) RPE (breathing) RPE (legs)	NA	Snuff cessation group	Usual snuff use group	arithmatic mean ± SD	NA	NA	NA	<0.000 (time to exhaustion) 0.02 (blood lactate) no significant difference between groups in any of these measures except time to exhaustion (p<0.000) and blood lactate (p=0.02)	No		
	Strong				42 regular snuff users (>2 years daily use), no illnesses or medications, regular exercise >3 times/week	24 participants who stopped using snuff for >6 weeks; 11 snuff users who continued their usual daily use		Diabetes/MetSy	Resting blood glucose (mM L-1) Resting insulin (mU L-1)	NA	Snuff cessation group (for insulin, n=11)	Usual snuff use group (for insulin, n=10)	arithmatic mean ± SD	NA	NA	NA	0.093 no significant difference for blood glucose insulin group effect p=0.093	No		
	Strong					24 participants who stopped using snuff for >6 weeks; 11 snuff users who continued their usual daily use		Diabetes/MetSy	Peak values during maximal running tests: Blood glucose (mM L-1)	NA	Snuff cessation group	Usual snuff use group	arithmatic mean ± SD	NA	NA	NA	0.02 group effect is significantly different, p=0.02	No		
	Strong					24		Body Weight	Body	NA	Snuff	Usual	arithmati	NA	NA	NA	Not	No		

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						participants who stopped using snuff for >6 weeks; 11 snuff users who continued their usual daily use			mass BMI		cessation group	snuff use group	c mean ± SD				reported no significant differences between groups for these measures			
Byhamre ML, Gustafsson PE, Jansson J-H, Wennberg M, Hammarstrom A and Wennberg P. 2017. Snus use during the life-course and risk of the metabolic syndrome and its components. Scandinavian journal of public health, 14034948177 06631.	Moderate	Small numbers, especially of exclusive snus users; participants only followed until age 43, and metabolic risk factors may take longer to develop; possible residual confounding from changes in other variables (like SES) over time; cumulative snus analysis included smokers	Swedish Snus	Cohort	All students in Swedish municipality of Lulea who attained 9th grade in 1981 (n=1083); at follow-up in 2008, the 94% of baseline still alive participated (n=1001)	Never tobacco users, age 43: n=308; current snus users who never smoked, age 43: n=37 (smokers and dual users are also evaluated)	1981-2008	Diabetes/MetSy	Metabolic syndrome age 16 (n=81) Metabolic syndrome age 21 (n=53) Metabolic syndrome age 30 (n=57) Metabolic syndrome age 43 (n=37)	in adjusted models: sex, cumulative smoking, BMI at 16 years, SES at 16 years, family history of diabetes, alcohol consumption at 43 years, physical activity at 43 years	Snus users who never smoked, at different ages	Never-users of tobacco	OR (95% CI)	0.95 1.15 1.01 1.15	0.54 0.60 0.52 0.52	1.65 2.21 1.99 2.51		No	County Council of Vasterbotten, County Council of Vasternorrland, Swedish Society of Medicine, VISARE NORR Fund (Northern County Councils Regional Federation)	Snus exposure in different life periods and cumulative snus exposure from age 16 to 43 were not associated with developing metabolic syndrome or its components at age 43. Note that models in Table 2 among never-smokers were adjusted for cumulative smoking.
	Moderate					Never tobacco users, age 43: n=308; current snus users who never smoked, age 43: n=37 (smokers and dual users are also evaluated)		Body Weight	central obesity age 16 (n=81) central obesity age 21 (n=53) central obesity age 30 (n=57) central obesity age 43 (n=37)	in adjusted models: sex, cumulative smoking, BMI at 16 years, SES at 16 years, family history of diabetes, alcohol consumption at 43 years, physical activity at 43 years	Snus users who never smoked, at different ages	Never-users of tobacco	OR (95% CI)	1.40 1.24 1.15 1.65	0.83 0.65 0.61 0.76	2.35 2.34 2.15 3.58		No		
	Moderate					Never tobacco users, age 43: n=308; current snus users who never smoked, age 43: n=37 (smokers and dual users are also evaluated)		CV Effects	Raised triglycerides age 16 (n=81) Raised triglycerides age 21 (n=53) Raised triglycerides age 30 (n=57) Raised triglycerides age 43 (n=37)	in adjusted models: sex, cumulative smoking, BMI at 16 years, SES at 16 years, family history of diabetes, alcohol consumption at 43 years, physical activity at 43 years	Snus users who never smoked, at different ages	Never-users of tobacco	OR (95% CI)	1.38 1.27 1.37 1.10	0.81 0.66 0.71 0.49	2.37 2.45 2.63 2.45		No		
	Moderate					Never tobacco users, age 43: n=308; current snus users who never		CV Effects	Low HDL-C age16 (n=81) Low HDL-C age 21 (n=53)	in adjusted models: sex, cumulative smoking, BMI at 16 years, SES	Snus users who never smoked, at different ages	Never-users of tobacco	OR (95% CI)	1.23 0.84 0.53 0.69	0.72 0.41 0.25 0.29	2.12 1.70 1.12 1.66		No		

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						smoked, age 43: n=37 (smokers and dual users are also evaluated)			Low HDL-C age 30 (n=57) Low HDL-C age 43 (n=37)	at 16 years, family history of diabetes, alcohol consumption at 43 years, physical activity at 43 years									
	Moderate					Never tobacco users, age 43: n=308; current snus users who never smoked, age 43: n=37 (smokers and dual users are also evaluated)		Diabetes/MetSy	Impaired fasting glucose or T2DM age 16 (n=81) Impaired fasting glucose or T2DM age 21 (n=53) Impaired fasting glucose or T2DM 30 (n=57) Impaired fasting glucose or T2DM 43 (n=37)	in adjusted models: sex, cumulative smoking, BMI at 16 years, SES at 16 years, family history of diabetes, alcohol consumption at 43 years, physical activity at 43 years	Snus users who never smoked, at different ages	Never-users of tobacco	OR (95% CI)	1.08 1.28 1.01 0.38	0.59 0.63 0.48 0.12	1.97 2.62 2.11 1.16		No		
	Moderate					Never tobacco users, age 43: n=308; current snus users who never smoked, age 43: n=37 (smokers and dual users are also evaluated)		CV Effects	High blood pressure age 16 (n=81) High blood pressure age 21 (n=53) High blood pressure age 30 (n=57) High blood pressure age 43 (n=37)	in adjusted models: sex, cumulative smoking, BMI at 16 years, SES at 16 years, family history of diabetes, alcohol consumption at 43 years, physical activity at 43 years	Snus users who never smoked, at different ages	Never-users of tobacco	OR (95% CI)	1.08 1.31 1.61 1.41	0.66 0.71 0.88 0.69	1.77 2.42 2.96 2.89		No		
	Moderate					Never tobacco users, age 43: n=308; current snus users who never smoked, age 43: n=37 (smokers and dual users are also evaluated)		Diabetes/MetSy	Metabolic syndrome	in adjusted models: sex, smoking, BMI at 16 years, SES at 16 years, family history of diabetes, alcohol consumption at 43 years, physical activity at 43 years	Snus use 1 period (n=122) Snus use 2 periods (n=97) Snus use 3 periods (n=64) Snus use 4 periods (n=47) (period= time between follow-up ages 16, 21, 30, and 43 years; includes smokers)	Never-users of tobacco	OR (95% CI)	1.08 1.11 1.01 0.91	0.59 0.57 0.50 0.40	1.96 2.17 2.06 2.05	p for trend= 0.660	No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
Carlsson S, Andersson T, Araghi M, Galanti R, Lager A, Lundberg M, Nilsson P, Norberg M, Pedersen NL, Trolle-Lagerros Y and Magnusson C. 2017. Smokeless tobacco (snus) is associated with an increased risk of type 2 diabetes: results from five pooled cohorts. Journal of Internal Medicine, 281(4): 398–406.	Strong	Incidence of diabetes was not assessed uniformly across the pooled studies, with some cases being self-reported. This might lead to underreporting and undiagnosed cases.	Swedish Snus	pooled Cohort	Male never smokers from 5 Swedish cohorts: the Vasterbotten Intervention Programme, the Stockholm Public Health Cohort, the Malmo Diet and Cancer Study, the National March Cohort, and the SALT study (n=54,531).	248 cases among current snus users; 118 cases among former users. Number of unexposed was reported as percentage of each cohort and number of person-years, not number of participants.	1991-2013	Diabetes/MetSy	Incident type 2 diabetes ICD-10, E11 type 2, E14 unspecified ICD-9, 250	age, calendar time, BMI, physical activity, education, alcohol consumption	Current snus users Former snus users	Never smoking, never snus users	HR (95% CI)	1.15 0.86	1.00 0.71	1.32 1.05		No	Not stated	The authors concluded that high snus consumption increases the risk of developing type 2 diabetes.
	Strong					248 cases among current snus users; 118 cases among former users. Number of unexposed was reported as percentage of each cohort and number of person-years, not number of participants.		Diabetes/MetSy	Incident type 2 diabetes ICD-10, E11 type 2, E14 unspecified ICD-9, 250	age, calendar time, BMI, physical activity, education, alcohol consumption	Number of boxes/week (current) 1-2 (n=54 exposed case) 3-4 (n=83 exposed case) 5-6 (n=54 exposed case) 7+ (n=31 exposed case) 1-4 (n=137 exposed case) 4+ (n=85 exposed case)	Never smoking, never snus users	HR (95% CI)	1.14 1.03 1.42 1.68 1.08 1.43	0.86 0.82 1.07 1.17 0.90 1.15	1.50 1.29 1.87 2.41 1.29 1.79		Yes, at 5-6, 7+ boxes/week, and 4+ boxes/week	
	Strong					248 cases among current snus users; 118 cases among former users. Number of unexposed was reported as percentage of each cohort and number of person-years, not number of participants.		Diabetes/MetSy	Incident type 2 diabetes ICD-10, E11 type 2, E14 unspecified ICD-9, 250	age, calendar time, BMI, physical activity, education, alcohol consumption	Duration of snus use (current users) <30 years (n=66 exposed case) 30+ years (n=152 exposed case)	Never smoking, never snus users	HR (95% CI)	1.34 1.17	1.03 0.98	1.73 1.39		Yes, for <30 years		
Dafar A, Çevik-Aras H, Robledo-Sierra J, Mattsson U and Jontell M. 2016. Factors associated	Weak	Methods/study design unclear (referent group is unclear in model); authors do	Swedish snus	Case-control (authors describe as "retrospective	6448 patients examined by dentists in Boras, Sweden from 2004-2006	Nonreferred GT patients (n=130) and FT patients (n=62), referred GT patients	2004-2006	Non-cancer oral	Geographic tongue or fissured tongue	age, gender	Answered "yes" to snus use (may include smokers--not stated)	Referent group is unclear, but is described as a random sample of	OR (95% CI)	2.1	1.1	4.35	0.025	Yes	Saudi Arabian Ministry of Higher Education; Cultural Bureau, Berlin,	"In conclusion, the present study demonstrates that hypertension or hypertensive medications and the use of snus are factors associated with GT." Snus use was significantly

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
with geographic tongue and fissured tongue. Acta Odontologica Scandinavica, 74(3): 210–216.		not state whether snus users are also smokers, and don't control for smoking in the analysis		cross-sectional)		(n=166) and FT patients (n=15), and 1029 controls with no oral mucosal lesions						patients with no oral mucosal lesions						Germany	more prevalent among those with geographic tongue vs. controls (10.1% vs. 3.8%, P<0.01). No significant difference was observed in prevalence of use among those with fissured tongue.
Dahlin S, Gunnerbeck A, Wikström A-K, Cnattingius S and Edstedt Bonamy A-K. 2016. Maternal tobacco use and extremely premature birth – a population-based cohort study. BJOG: An International Journal of Obstetrics and Gynaecology, 123(12): 1938–1946.	Strong	Tobacco use was self-reported (possible misclassification); more than 20% of women who had extremely preterm deliveries had missing tobacco information (information bias)	Swedish snuff	Cohort	All live singleton births in the Swedish Medical Birth Register 1999-2012	14,671 snuff users 1,117,464 nonusers of tobacco 37 extremely preterm births among snuff users 72 very preterm births among snuff users 712 moderately preterm births among snuff users	1999-2012	Reproductive	Extremely preterm births (<28 weeks gestation)	maternal age, parity, cohabitant with father, country of birth, education, BMI	Snuff user in early pregnancy	Non-tobacco users	OR (95% CI)	1.58	1.14	2.21		Yes	Swedish Research Council for Health, Working Life, and Welfare	The authors concluded that the use of Swedish snuff in pregnancy was associated with risk of extremely preterm birth, and that the risk was similar to that observed in women who smoked during pregnancy. Cessation of snuff or smoking reduced risks. Further results are available (Table 4) which break down the three categories of preterm births by spontaneous vs. medically indicated.
	Strong					14,671 snuff users 1,117,464 nonusers of tobacco 37 extremely preterm births among snuff users 72 very preterm births among snuff users 712 moderately preterm births among snuff users		Reproductive	Very preterm (28-31 weeks)	maternal age, parity, cohabitant with father, country of birth, education, BMI	Snuff user in early pregnancy	Non-tobacco users	OR (95% CI)	1.25	0.98	1.59		No		
	Strong					14,671 snuff users 1,117,464 nonusers of tobacco 37 extremely preterm births among snuff users 72 very preterm births among snuff users 712 moderately preterm births among snuff users		Reproductive	Moderately preterm (32-36 weeks)	maternal age, parity, cohabitant with father, country of birth, education, BMI	Snuff user in early pregnancy	Non-tobacco users	OR (95% CI)	1.21	1.11	1.31		Yes		
	Strong					14,671 snuff users 1,117,464 nonusers of		Reproductive	Extremely preterm births (<28	maternal age, parity, cohabitant with father,	Kept using snuff in pregnancy	Non-tobacco users	OR (95% CI)	1.69 0.78	1.17 0.52	2.45 1.16		Yes for kept using snuff		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						tobacco 37 extremely preterm births among snuff users 72 very preterm births among snuff users 712 moderately preterm births among snuff users			weeks gestation)	country of birth, education, BMI	Ceased snuff before early pregnancy									
	Strong					14,671 snuff users 1,117,464 nonusers of tobacco 37 extremely preterm births among snuff users 72 very preterm births among snuff users 712 moderately preterm births among snuff users		Reproductive	Very preterm (28-31 weeks)	maternal age, parity, cohabitant with father, country of birth, education, BMI	Kept using snuff in pregnancy Ceased snuff before early pregnancy	Non-tobacco users	OR (95% CI)	1.26 0.90	0.95 0.71	1.66 1.15		No		
	Strong					14,671 snuff users 1,117,464 nonusers of tobacco 37 extremely preterm births among snuff users 72 very preterm births among snuff users 712 moderately preterm births among snuff users		Reproductive	Moderately preterm (32-36 weeks)	maternal age, parity, cohabitant with father, country of birth, education, BMI	Kept using snuff in pregnancy Ceased snuff before early pregnancy	Non-tobacco users	OR (95% CI)	1.26 0.95	1.15 0.88	1.38 1.02		Yes for kept using snuff		
Eriksson M and Ng N. 2015. Changes in access to structural social capital and its influence on self-rated health over time for middle-aged men and women: A longitudinal study from	Weak	Snuff was included as a covariate, not as an exposure. Results not shown for association of snuff with self-reported health, and reported association is based on a cross-sectional analysis.	Swedish "snuff"	Cohort (analysis of snuff use is cross sectional)	96,475 men and women aged 40, 50, and 60 at baseline who participated in the Vasterbotten Intervention Program (VIP) study. This study included 21,139 people who were 40 or 50 at baseline, who had complete data at follow-	Men: 8611 never snuff users 2679 former users 4137 current users Women: 16,129 never snuff users 499 former users 705 current	1990-2013	Other	Self-reported health	not reported for snuff analysis	Current snuff users	People who did not smoke or use snuff at baseline	Data not shown	Data not shown	Data not shown	Data not shown	Data not shown	Data not shown	FORTE, the Swedish Research Council for Health, Working Life, and Welfare	"Men and women who were current snuff users and only women who were current smokers had higher odds of reporting poor SRH than those who did not smoke or use snuff at baseline. However, these associations were not observed in the follow-up data (data not shown)." Associations were only observed at baseline.

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
northern Sweden. Social Science and Medicine, 130: 250–258.					up.	users (snuff was a covariate, so there is no # of exposed cases given)														
Gudnadottir AY, Olafsdottir IS, Middelveld R, Ekerljung L, Forsberg B, Franklin K, Lindberg E, Janson C, Gudnadóttir AÝ, Ólafsdóttir IS, Middelveld R, Ekerljung L, Forsberg B, Franklin K, Lindberg E and Janson C. 2017. An investigation on the use of snus and its association with respiratory and sleep-related symptoms: A cross-sectional population study. BMJ Open, 7(5): e015486.	Weak	Sample size is large, but study is limited by cross-sectional design. Tobacco-free comparison group for some analyses includes nearly 27% former smokers, and so is not truly tobacco-free.	Swedish "Snus"	Cross-sectional	45,000 subjects randomly selected for a postal questionnaire in the Global Allergy and Asthma European Network survey in 2008 In this study, 26,697 respondents from four Swedish cities, aged 16-75 years	20,699 tobacco free 2265 exclusive snus users (current) 597 snus/smoker dual users (current) # of exposed cases not given, but percentages are in Table 1	2008	Other	Asthma	gender, age, BMI, study center, educational level, physical activity	Nonsmoking current snus users who have used snus every day for 6+ months	Currently tobacco-free (includes former smokers)	OR (95% CI)	1.51	1.28	1.77	<0.05	Yes	EU Sixth Framework Programme for Research, Swedish Heart and Lung Foundation, Swedish Asthma and Allergy Foundation, Swedish Association against Heart and Lung Diseases, Centre for Allergy Research at the Karolinska Institutet, Karolinska Institutet and AstraZeneca Translational Science Centre Collaboration Research Program, Science for Life Laboratory Stockholm and AstraZeneca Collaboration Research Program, VBG Group Centre for Asthma and Allergy Research	The authors reported an association between risk of asthma and current snus use; no increased risk was observed among smokers or dual users. Snus users, smokers, and dual users all showed increased risk of asthmatic and other respiratory symptoms. Snus users had an increased risk of some sleep problems (snoring, difficulty initiating sleep, excessive daytime sleepiness) but decreased risk of difficulty maintaining sleep. Table 4 has results for former and current snus users among never smokers, but does not report the referent group (see Table 4 for these results, which are not abstracted here).
	Weak					20,699 tobacco free 2265 exclusive snus users (current) 597 snus/smoker dual users (current) # of exposed cases not given, but percentages are in Table 1		Other	Asthma	gender, age, BMI, study center, educational level, physical activity	Dual users (current snus users who have used snus every day for 6+ months who have also smoked in the past month, and have smoked at least one cigarette a day for at least 1 year)	Currently tobacco-free (includes former smokers)	OR (95% CI)	0.93	0.65	1.33	>0.05	No		
	Weak					20,699 tobacco free 2265 exclusive snus users (current) 597 snus/smoker dual users (current) # of exposed cases not given, but percentages are in Table 1		Other	Asthmatic symptoms: Wheezing Wheezing and breathlessness Wheezing without having a cold Night-time chest tightness Night-time attacks of breathlessness Night-time coughing	gender, age, BMI, study center, educational level, physical activity	Nonsmoking current snus users who have used snus every day for 6+ months	Currently tobacco-free (includes former smokers)	OR (95% CI)	1.50 1.42 1.50 1.21 1.02 1.10	1.33 1.23 1.30 1.05 0.83 0.99	1.69 1.65 1.73 1.40 1.24 1.23	All but night-time attacks of breathlessness and night-time coughing <0.05	Yes, all but night-time attacks of breathlessness and night-time coughing		
	Weak					20,699 tobacco		Other	Asthmatic symptoms	gender, age, BMI,	Dual users	Currently tobacco-	OR (95% CI)				<0.05	Yes		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						free 2265 exclusive snus users (current) 597 snus/smoker dual users (current) # of exposed cases not given, but percentages are in Table 1			: Wheezing Wheezing and breathlessness Wheezing without having a cold Night-time chest tightness Night-time attacks of breathlessness Night-time coughing	study center, educational level, physical activity	(current snus users who have used snus every day for 6+ months who have also smoked in the past month, and have smoked at least one cigarette a day for at least 1 year)	free (includes former smokers)		2.09 1.46 2.17 1.43 1.58 1.79	1.71 1.12 1.73 1.12 1.16 1.49	2.55 1.90 2.73 1.82 2.13 2.15				
	Weak					20,699 tobacco free 2265 exclusive snus users (current) 597 snus/smoker dual users (current) # of exposed cases not given, but percentages are in Table 1		Other	Chronic bronchitis	gender, age, BMI, study center, educational level, physical activity	Nonsmoking current snus users who have used snus every day for 6+ months	Currently tobacco-free (includes former smokers)	OR (95% CI)	1.19	1.03	1.37	<0.05	Yes		
	Weak					20,699 tobacco free 2265 exclusive snus users (current) 597 snus/smoker dual users (current) # of exposed cases not given, but percentages are in Table 1		Other	Chronic bronchitis	gender, age, BMI, study center, educational level, physical activity	Dual users (current snus users who have used snus every day for 6+ months who have also smoked in the past month, and have smoked at least one cigarette a day for at least 1 year)	Currently tobacco-free (includes former smokers)	OR (95% CI)	1.85	1.48	2.31	<0.05	Yes		
	Weak					20,699 tobacco free 2265 exclusive snus users (current) 597 snus/smoker dual users (current) # of		Other	Allergic rhinitis	gender, age, BMI, study center, educational level, physical activity	Nonsmoking current snus users who have used snus every day for 6+ months	Currently tobacco-free (includes former smokers)	OR (95% CI)	1.17	1.05	1.3	<0.05	Yes		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						exposed cases not given, but percentages are in Table 1														
	Weak					20,699 tobacco free 2265 exclusive snus users (current) 597 snus/smoker dual users (current) # of exposed cases not given, but percentages are in Table 1		Other	Allergic rhinitis	gender, age, BMI, study center, educational level, physical activity	Dual users (current snus users who have used snus every day for 6+ months who have also smoked in the past month, and have smoked at least one cigarette a day for at least 1 year)	Currently tobacco-free (includes former smokers)	OR (95% CI)	0.92	0.75	1.13	>0.05	No		
	Weak					20,699 tobacco free 2265 exclusive snus users (current) 597 snus/smoker dual users (current) # of exposed cases not given, but percentages are in Table 1		Other	Chronic rhinosinusitis	gender, age, BMI, study center, educational level, physical activity	Nonsmoking current snus users who have used snus every day for 6+ months	Currently tobacco-free (includes former smokers)	OR (95% CI)	1.28	1.09	1.5	<0.05	Yes		
	Weak					20,699 tobacco free 2265 exclusive snus users (current) 597 snus/smoker dual users (current) # of exposed cases not given, but percentages are in Table 1		Other	Chronic rhinosinusitis	gender, age, BMI, study center, educational level, physical activity	Dual users (current snus users who have used snus every day for 6+ months who have also smoked in the past month, and have smoked at least one cigarette a day for at least 1 year)	Currently tobacco-free (includes former smokers)	OR (95% CI)	1.78	1.38	2.29	<0.05	Yes		
	Weak					20,699 tobacco free 2265 exclusive snus users (current) 597 snus/smoker dual users		Other	Sleeping problems: Snoring Difficulty initiating sleep Difficulty	gender, age, BMI, study center, educational level, physical activity	Nonsmoking current snus users who have used snus every day for 6+ months	Currently tobacco-free (includes former smokers)	OR (95% CI)	1.41 1.76 0.74 1.18	1.25 1.56 0.66 1.07	1.58 1.99 0.83 1.31	For all but early morning awakening, p<0.05	Yes, for all but early morning awakening		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						(current) # of exposed cases not given, but percentages are in Table 1			maintaining sleep Excessive daytime sleepiness Early morning awakening Use of medication for sleeping problems					0.87 1.33	0.76 1.07	1.00 1.65				
	Weak					20,699 tobacco free 2265 exclusive snus users (current) 597 snus/smoker dual users (current) # of exposed cases not given, but percentages are in Table 1		Other	Sleeping problems: Snoring Difficulty initiating sleep Difficulty maintaining sleep Excessive daytime sleepiness Early morning awakening Use of medication for sleeping problems	gender, age, BMI, study center, educational level, physical activity	Dual users (current snus users who have used snus every day for 6+ months who have also smoked in the past month, and have smoked at least one cigarette a day for at least 1 year)	Currently tobacco-free (includes former smokers)	OR (95% CI)	 2.16 2.95 0.91 1.38 0.91 2.77	 1.77 2.43 0.75 1.16 0.70 2.05	 2.63 3.58 1.12 1.65 1.17 3.74	For all but difficulty maintaining sleep and early morning awakening, p<0.05	Yes, for all but difficulty maintaining sleep and early morning awakening		
	Weak					14,914 tobacco free, never smoked 1168 exclusive snus users (current), never smoked # of exposed cases not given, but percentages are in Table 3		Other	Asthma	gender, age, BMI, study center, educational level, physical activity	Nonsmoking current snus users who have used snus every day for 6+ months, never smokers	Tobacco-free, never smoked	OR (95% CI)	1.49	1.2	1.85	<0.001	Yes		
	Weak					14,914 tobacco free, never smoked 1168 exclusive snus users (current), never smoked # of exposed cases not given, but percentages are in Table		Other	Asthma	gender, age, BMI, study center, educational level, physical activity	Ex-snus users, never smokers	Not stated	OR (95% CI)	1.06	0.79	1.4		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						3														
	Weak					14,914 tobacco free, never smoked 1168 exclusive snus users (current), never smoked # of exposed cases not given, but percentages are in Table 3		Other	Asthmatic symptoms: Wheezing Wheezing and breathlessness Wheezing without having a cold Night-time chest tightness Night-time attacks of breathlessness Night-time coughing	gender, age, BMI, study center, educational level, physical activity	Nonsmoking current snus users who have used snus every day for 6+ months, never smokers	Tobacco-free, never smoked	OR (95% CI)	1.56 1.38 1.48 1.41 1.39 1.27	1.32 1.12 1.21 1.16 1.07 1.09	1.84 1.69 1.80 1.71 1.82 1.47	<0.001 0.002 <0.001 0.004 0.045 0.987	Yes. Unclear why the p-value for night time coughing is 0.987 if the CI does not include 1.		
	Weak					14,914 tobacco free, never smoked 1168 exclusive snus users (current), never smoked # of exposed cases not given, but percentages are in Table 3		Other	Asthmatic symptoms: Wheezing Wheezing and breathlessness Wheezing without having a cold Night-time chest tightness Night-time attacks of breathlessness Night-time coughing	gender, age, BMI, study center, educational level, physical activity	Ex-snus users, never smokers	Not stated	OR (95% CI)	1.10 1.00 1.24 1.01 1.27 1.14	0.89 0.76 0.97 0.78 0.92 0.96	1.36 1.31 1.59 1.30 1.76 1.37		No		
	Weak					14,914 tobacco free, never smoked 1168 exclusive snus users (current), never smoked # of exposed cases not given, but percentages are in Table 3		Other	Chronic bronchitis	gender, age, BMI, study center, educational level, physical activity	Nonsmoking current snus users who have used snus every day for 6+ months, never smokers	Tobacco-free, never smoked	OR (95% CI)	1.47	1.21	1.78	<0.001	Yes		
	Weak					14,914 tobacco free, never smoked 1168		Other	Chronic bronchitis	gender, age, BMI, study center, educational	Ex-snus users, never smokers	Not stated	OR (95% CI)	0.91	0.7	1.19		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						exclusive snus users (current), never smoked				level, physical activity										
						# of exposed cases not given, but percentages are in Table 3														
	Weak					14,914 tobacco free, never smoked 1168 exclusive snus users (current), never smoked		Other	Allergic rhinitis	gender, age, BMI, study center, educational level, physical activity	Nonsmoking current snus users who have used snus every day for 6+ months, never smokers	Tobacco-free, never smoked	OR (95% CI)	1.14	0.99	1.31	0.012	No (again, unclear why p-value is so low if CI includes 1; the p-values might be for some measure other than the OR, but the table is unclear)		
						# of exposed cases not given, but percentages are in Table 3														
	Weak					14,914 tobacco free, never smoked 1168 exclusive snus users (current), never smoked		Other	Allergic rhinitis	gender, age, BMI, study center, educational level, physical activity	Ex-snus users, never smokers	Not stated	OR (95% CI)	0.95	0.8	1.12		No		
						# of exposed cases not given, but percentages are in Table 3														
	Weak					14,914 tobacco free, never smoked 1168 exclusive snus users (current), never smoked		Other	Chronic rhinosinusitis	gender, age, BMI, study center, educational level, physical activity	Nonsmoking current snus users who have used snus every day for 6+ months, never smokers	Tobacco-free, never smoked	OR (95% CI)	1.37	1.11	1.7	0.005	Yes		
						# of exposed cases not given, but percentages are in Table 3														
	Weak					14,914 tobacco free, never smoked 1168 exclusive snus users (current),		Other	Chronic rhinosinusitis	gender, age, BMI, study center, educational level, physical activity	Ex-snus users, never smokers	Not stated	OR (95% CI)	0.95	0.71	1.28		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						never smoked # of exposed cases not given, but percentages are in Table 3														
	Weak					14,914 tobacco free, never smoked 1168 exclusive snus users (current), never smoked # of exposed cases not given, but percentages are in Table 3		Other	Sleeping problems: Snoring Difficulty initiating sleep Difficulty maintaining sleep Excessive daytime sleepiness Early morning awakening Use of medication for sleeping problems	gender, age, BMI, study center, educational level, physical activity	Nonsmoking current snus users who have used snus every day for 6+ months, never smokers	Tobacco-free, never smoked	OR (95% CI)	1.53 1.71 0.71 1.08 0.83 1.24	1.29 1.44 0.59 0.94 0.67 0.85	1.82 2.03 0.84 1.24 1.04 1.80	<0.001 <0.001 <0.001 0.433 <0.001 0.143	First 3, Yes Second 3, No p-value does not always appear to correspond with CI		
	Weak					14,914 tobacco free, never smoked 1168 exclusive snus users (current), never smoked # of exposed cases not given, but percentages are in Table 3		Other	Sleeping problems: Snoring Difficulty initiating sleep Difficulty maintaining sleep Excessive daytime sleepiness Early morning awakening Use of medication for sleeping problems	gender, age, BMI, study center, educational level, physical activity	Ex-snus users, never smokers	Not stated	OR (95% CI)	1.37 0.81 1.20 1.00 1.28 1.32	1.12 0.62 1.01 0.85 1.03 0.87	1.68 1.05 1.42 1.18 1.59 2.01		Yes, for snoring, difficulty maintaining sleep, and excessive morning awakening		
Gunnerbeck A, Edstedt Bonamy A-K, Wikstrom A-K, Granath F, Wickstrom R and Cnattingius S. 2014. Maternal snuff use and smoking and the risk of oral cleft malformations--a	Moderate	Sample size is large, but results are not presented adequately--analyses of subsets of oral cleft malformations are not labelled in the table. Possible misclassification of	Swedish snuff	Cohort	1,086,213 live born infants recorded in the Swedish Medical Birth Register 1999-2009	Before pregnancy: 773,625 non-tobacco users, 21,994 snuff users, 2,895 dual users Early pregnancy (<15 weeks gestation): 917,900	1999-2009	Reproductive	Oral cleft malformations, ICD-10 codes Q35-Q37	maternal age, parity, education, living with father-to-be or not, hypertension, diabetes, preeclampsia, sex of newborn, birth (singleton or multiple), variation of	Current snuff user in pregnancy (n=25 exposed cases) Stopped using snuff before or in early pregnancy (n=17 exposed	Non-tobacco users	OR (95% CI)	1.48 0.71	1.00 0.44	2.21 1.14		No (borderline for current users)	Swedish Council for Working Life and Social Research; Karolinska Institutet; Stockholm County Council	The authors concluded that maternal snuff use in early pregnancy is associated with increased risk of oral clefts. Snuff users who stopped using snuff before their antenatal booking had no increased risk. Note that some of the tables in this article were difficult to interpret. Table 4 includes results for different kinds of oral cleft malformations (according to the text), but the results are not labelled.

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
population-based cohort study. PloS one, 9(1): e84715.		exposure due to self-report of tobacco use; also, no information on consumption patterns of snuff (duration, intensity of use). Exact timing of cessation of exposure among women who quit was also not available (whether it was during or before pregnancy).				non-tobacco users, 11,461 snuff users, 746 dual users Exposed cases: 31 cases among snuff users in early pregnancy, 2 among dual users in early pregnancy.				diagnosis frequency, mother's country of birth	cases)								
	Moderate					Before pregnancy: 773,625 non-tobacco users, 21,994 snuff users, 2,895 dual users Early pregnancy (<15 weeks gestation): 917,900 non-tobacco users, 11,461 snuff users, 746 dual users Exposed cases: 31 cases among snuff users in early pregnancy, 2 among dual users in early pregnancy.		Reproductive	Cleft lip, with or without cleft palate (ICD-10 codes Q36 & Q37)	maternal age, parity, education, living with father-to-be or not, hypertension, diabetes, preeclampsia, sex of newborn, birth (singleton or multiple), variation of diagnosis frequency, mother's country of birth	Current snuff user in pregnancy (n=17 exposed cases) Stopped using snuff before or in early pregnancy (n=12 exposed cases)	Non-tobacco users	OR (95% CI)	1.61 0.77	1.00 0.44	2.61 1.37		No (borderline for current users)		
	Moderate					Before pregnancy: 773,625 non-tobacco users, 21,994 snuff users, 2,895 dual users Early pregnancy (<15 weeks gestation): 917,900 non-tobacco users, 11,461 snuff users, 746 dual users Exposed		Reproductive	Isolated cleft palate	maternal age, parity, education, living with father-to-be or not, hypertension, diabetes, preeclampsia, sex of newborn, birth (singleton or multiple), variation of diagnosis frequency, mother's country of birth	Current snuff user in pregnancy (n=8 exposed cases) Stopped using snuff before or in early pregnancy (n=5 exposed cases)	Non-tobacco users	OR (95% CI)	1.26 0.59	0.63 0.24	2.55 1.43		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						cases: 31 cases among snuff users in early pregnancy, 2 among dual users in early pregnancy. Before pregnancy: 773,625 non-tobacco users, 21,994 snuff users, 2,895 dual users Early pregnancy (<15 weeks gestation): 917,900 non-tobacco users, 11,461 snuff users, 746 dual users Exposed cases: 31 cases among snuff users in early pregnancy, 2 among dual users in early pregnancy.													
	Moderate							Reproductive	Other malformations among infants with oral clefts	maternal age, parity, education, living with father-to-be or not, hypertension, diabetes, preeclampsia, sex of newborn, birth (singleton or multiple), variation of diagnosis frequency, mother's country of birth	Current snuff user in pregnancy	Non-tobacco users	Chi^2 (Difference between groups)				0.4	No		
Gustavsen MW, Page CM, Moen SM, Bjølgerud A, Berg-Hansen P, Nygaard GO, Sandvik L, Lie BA, Celius EG and Harbo HF. 2014. Environmental exposures and the risk of multiple sclerosis investigated in a Norwegian case-control study. BMC Neurology, 14(1): 196.	Moderate	Exposure assessment was limited to ever/never use, and snuff users included smokers (analysis adjusted for smoking). Possible selection bias, as controls selected from a bone marrow donor registry might be healthier than the general population.	Swedish "snuff"	Case-control	cases, 756 MS patients from the Oslo MS Registry controls, 1090 randomly selected healthy people from the Norwegian Bone Marrow Donor Registry	530 cases, 918 controls 60 exposed cases, 141 exposed controls	2011-2012	Other	Multiple sclerosis	age, gender, smoking status, mononucleosis	Ever snuff users, carrier of HLA-DRB1*15:01 gene Ever snuff users, NOT carrier of carrier of HLA-DRB1*15:01 gene	Not stated; likely never snuff users within gene carrier category	OR (95% CI)	0.60 0.88	0.27 0.39	1.32 2.0	0.20 0.76	No	The Research Council of Norway; Oslo MS Society; Odd Fellow Norway	A smaller percentage of MS patients (11.4%) reported ever using snuff than controls (15.6%). The authors reported a significant association (decreased risk) of MS among snuff users who were carriers of the HLA-DRB1*15:01 gene (OR, 95% CI 0.41, 0.22-0.77), but this association was only seen in the unadjusted analysis. (See Table 4 for complete stratified unadjusted and adjusted results.)
Hansson J, Galanti MR, Hergens MP, Fredlund P, Ahlbom A, Alfredsson L, Bellocco R, Engström G,	Strong	Large pooled analysis, restricted to never smokers. Possible misclassification of	Swedish Snus	pooled Cohort	291,309 participants in eight prospective cohort studies which have been pooled into the	130,485 men with no history of smoking or stroke included in analyses # of cases	Recruitment from 1978-2004, follow-up ranged from 5-29 years	Stroke	First ever stroke, all types: ICD-10: I60-I61, I63, I64 ICD-9: 430-431,	age, BMI	Current snus users (n=291 exposed cases) Former	Never tobacco users	HR (95% CI)	1.01 0.88	0.89 0.64	1.14 1.22		No	Stockholm County Council, Swedish Research Council, National Institute of	The authors reported no association between snus use and incident stroke. Snus users showed increased case fatality, especially in the first weeks after diagnosis, but the authors could not rule out confounding as an

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
Eriksson M, Hallqvist J, Hedblad B, Jansson JH, Pedersen NL, Trolle Lagerros Y, Ostergren PO and Magnusson C. 2014. Snus (Swedish smokeless tobacco) use and risk of stroke: pooled analyses of incidence and survival. Journal of internal medicine, 276(1): 87–95.		exposure, as snus exposure was measured at baseline and may have changed over time. Also, most analyses included former snus users in the referent group.			Swedish Collaboration on Health Effects of Snus Use	in all snus users= 2934 # of cases, former snus users = 2630 # of cases, current snus users = 304			434, 436 "corresponding codes in the 8th and 7th edition" Included main and secondary diagnoses and underlying cause of death		snus users (n=39 exposed cases)							Public Health, Swedish Council for Working Life and Social Research	explanation.
	Strong					130,485 men with no history of smoking or stroke included in analyses # of cases in all snus users= 2934 # of cases, former snus users = 2630 # of cases, current snus users = 304		Stroke	First ever stroke, all types: ICD-10: I60-I61, I63, I64 ICD-9: 430-431, 434, 436 "corresponding codes in the 8th and 7th edition" Included main and secondary diagnoses and underlying cause of death	age, BMI, education	Current snus users (exposed cases not provided)	Never tobacco users	HR (95% CI)	1.1	0.78	1.57		No		
	Moderate					130,485 men with no history of smoking or stroke included in analyses # of cases in all snus users= 2934 # of cases, former snus users = 2630 # of cases, current snus users = 304		Stroke	First ever stroke, all types, mortality: ICD-10: I60-I61, I63, I64 ICD-9: 430-431, 434, 436 "corresponding codes in the 8th and 7th edition" Included main and secondary diagnoses and underlying cause of death	age, BMI, year of diagnosis	Current snus users (n=115 exposed cases)	Never tobacco users	HR (95% CI)	1.32	1.08	1.61		Yes		
	Strong					130,485 men with no history of smoking or stroke included in analyses # of cases in all snus users= 2934 # of cases, former snus users = 2630 # of cases, current		Stroke	First ever stroke, all types: ICD-10: I60-I61, I63, I64 ICD-9: 430-431, 434, 436 "corresponding codes in the 8th and 7th edition" Included main and	age, BMI	Current snus users (exposed cases not provided)	"Noncurrent snus users"	HR (95% CI)	1.04	0.92	1.17		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						snus users = 304			secondary diagnoses and underlying cause of death											
	Strong					130,485 men with no history of smoking or stroke included in analyses # of cases in all snus users= 2934 # of cases, former snus users = 2630 # of cases, current snus users = 304		Stroke	Ischaemic stroke ICD-10 I63 ICD-9 434 "corresponding codes in the 8th and 7th edition" Included main and secondary diagnoses and underlying cause of death	age, BMI	Current snus users (exposed cases not provided)	"Noncurrent snus users"	HR (95% CI)	1.06	0.91	1.23		No		
	Moderate					130,485 men with no history of smoking or stroke included in analyses # of cases in all snus users= 2934 # of cases, former snus users = 2630 # of cases, current snus users = 304		Stroke	Ischaemic stroke mortality ICD-10 I63 ICD-9 434 "corresponding codes in the 8th and 7th edition" Included main and secondary diagnoses and underlying cause of death	age, BMI, year of diagnosis	Current snus users (exposed cases not provided)	"Noncurrent snus users"	HR (95% CI)	1.29	1	1.67		No		
	Strong					130,485 men with no history of smoking or stroke included in analyses # of cases in all snus users= 2934 # of cases, former snus users = 2630 # of cases, current snus users = 304		Stroke	Haemorrhagic stroke ICD-10 I60-I61 ICD-9 430-431 "corresponding codes in the 8th and 7th edition" Included main and secondary diagnoses and underlying cause of death	age, BMI	Current snus users (exposed cases not provided)	"Noncurrent snus users"	HR (95% CI)	0.94	0.73	1.22		No		
	Moderate					130,485 men with no history of smoking or stroke included in analyses # of cases in all snus users= 2934 # of cases, former snus		Stroke	Haemorrhagic stroke mortality ICD-10 I60-I61 ICD-9 430-431 "corresponding codes in the 8th and 7th	age, BMI, year of diagnosis	Current snus users (exposed cases not provided)	"Noncurrent snus users"	HR (95% CI)	1.76	1.16	2.67		Yes		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						users = 2630 # of cases, current snus users = 304			edition" Included main and secondary diagnoses and underlying cause of death											
	Strong					130,485 men with no history of smoking or stroke included in analyses # of cases in all snus users= 2934 # of cases, former snus users = 2630 # of cases, current snus users = 304		Stroke	Unspecified stroke ICD-10 I64 ICD-9 436 "corresponding codes in the 8th and 7th edition" Included main and secondary diagnoses and underlying cause of death	age, BMI	Current snus users (exposed cases not provided)	"Noncurrent snus users"	HR (95% CI)	1.1	0.78	1.54		No		
	Strong					130,485 men with no history of smoking or stroke included in analyses # of cases in all snus users= 2934 # of cases, former snus users = 2630 # of cases, current snus users = 304		Stroke	28-day case fatality for overall stroke	age, BMI, year of diagnosis	Current snus users (n=41 exposed cases)	Never tobacco users	HR (95% CI)	1.42	0.99	2.04		No		The authors reported no association between snus use and incident stroke. Snus users showed increased case fatality, especially in the first weeks after diagnosis, but the authors could not rule out confounding as an explanation. OR was much lower following exclusion of construction worker cohort (OR was 1.43 (95% CI 0.52–3.92)
	Strong					130,485 men with no history of smoking or stroke included in analyses # of cases in all snus users= 2934 # of cases, former snus users = 2630 # of cases, current snus users = 304		Stroke	First ever stroke, all types: ICD-10: I60-I61, I63, I64 ICD-9: 430-431, 434, 436 "corresponding codes in the 8th and 7th edition" Included main and secondary diagnoses and underlying cause of death	age, BMI	Snus use at baseline: <4 cans/week (235 cases) 4-6 cans/week (26 cases) 7+ cans/week (14 cases)	"Noncurrent snus users"	HR (95% CI)	 1.05 1.00 0.72	 0.92 0.67 0.42	 1.20 1.47 1.22		No		The authors reported no association between snus use and incident stroke. Snus users showed increased case fatality, especially in the first weeks after diagnosis, but the authors could not rule out confounding as an explanation.
	Strong					130,485 men with no history of smoking or stroke included in analyses # of cases in all snus		Stroke	Ischaemic stroke ICD-10 I63 ICD-9 434 "corresponding codes in the 8th	age, BMI	Snus use at baseline: <4 cans/week (151 cases)	"Noncurrent snus users"	HR (95% CI)	 1.06 1.02 0.54	 0.89 0.62 0.24	 1.26 1.68 1.26		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						users= 2934 # of cases, former snus users = 2630 # of cases, current snus users = 304			and 7th edition" Included main and secondary diagnoses and underlying cause of death		4-6 cans/week (16 cases) 7+ cans/week (6 cases)									
	Strong					130,485 men with no history of smoking or stroke included in analyses # of cases in all snus users= 2934 # of cases, former snus users = 2630 # of cases, current snus users = 304		Stroke	Haemorrhagic stroke ICD-10 I60-I61 ICD-9 430-431 "corresponding codes in the 8th and 7th edition" Included main and secondary diagnoses and underlying cause of death	age, BMI	Snus use at baseline: <4 cans/week (151 cases) 4-6 cans/week (16 cases) 7+ cans/week (6 cases)	"Noncurrent snus users"	HR (95% CI)	0.95 1.02 0.78	0.71 0.51 0.32	1.27 2.07 1.90		No		
	Strong					130,485 men with no history of smoking or stroke included in analyes # of cases in all snus users= 2934 # of cases, former snus users = 2630 # of cases, current snus users = 304		Stroke	Unspecified stroke ICD-10 I64 ICD-9 436 "corresponding codes in the 8th and 7th edition" Included main and secondary diagnoses and underlying cause of death	age, BMI	Snus use at baseline: <4 cans/week (151 cases) 4-6 cans/week (16 cases) 7+ cans/week (6 cases)	"Noncurrent snus users"	HR (95% CI)	1.16 0.75 1.52	0.81 0.19 0.49	1.68 3.01 4.79		No		
	Strong					130,485 men with no history of smoking or stroke included in analyses # of cases in all snus users= 2934 # of cases, former snus users = 2630 # of cases, current snus users = 304		Stroke	First ever stroke, all types: ICD-10: I60-I61, I63, I64 ICD-9: 430-431, 434, 436 "corresponding codes in the 8th and 7th edition" Included main and secondary diagnoses and underlying cause of death	age, BMI	Duration of snus use at baseline: <20 years 20+ years	"Noncurrent snus users"	HR (95% CI)	0.98 1.05	0.81 0.89	1.18 1.23		No		
	Strong					130,485 men with no history of smoking or stroke included in		Stroke	Ischaemic stroke ICD-10 I63 ICD-9 434 "correspo	age, BMI	Duration of snus use at baseline: <20 years	"Noncurrent snus users"	HR (95% CI)	1.01 1.05	0.79 0.85	1.29 1.28		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						analyses # of cases in all snus users= 2934 # of cases, former snus users = 2630 # of cases, current snus users = 304			nding codes in the 8th and 7th edition" Included main and secondary diagnoses and underlying cause of death		20+ years									
	Strong					130,485 men with no history of smoking or stroke included in analyses # of cases in all snus users= 2934 # of cases, former snus users = 2630 # of cases, current snus users = 304		Stroke	Haemorrhagic stroke ICD-10 I60-I61 ICD-9 430-431 "corresponding codes in the 8th and 7th edition" Included main and secondary diagnoses and underlying cause of death	age, BMI	Duration of snus use at baseline: <20 years 20+ years	"Noncurrent snus users"	HR (95% CI)	 0.99 0.89	0.71 0.59	1.38 1.35		No		
	Strong					130,485 men with no history of smoking or stroke included in analyses # of cases in all snus users= 2934 # of cases, former snus users = 2630 # of cases, current snus users = 304		Stroke	Unspecified stroke ICD-10 I64 ICD-9 436 "corresponding codes in the 8th and 7th edition" Included main and secondary diagnoses and underlying cause of death	age, BMI	Duration of snus use at baseline: <20 years 20+ years	"Noncurrent snus users"	HR (95% CI)	 0.79 1.26	0.41 0.83	1.51 1.89		No		
Hardell L, Eriksson M, Degerman A. 1994. Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma. Cancer research. 54(9):2386-9.	Weak	Small number of cases. No data on quantity or timing, and no control for potential confounders.	Oral snuff	Case-control	Men aged 25-85 years who were admitted to the Department of Oncology in Umea between 1974-1978 with histopathologically verified NHL, n=105 Controls n=335 Living controls were drawn from the National Population Registry Deceased controls were drawn from the National Registry for Causes of Death	# Cases exposed = 35 # Controls exposed = 84	1974-1978	Cancer	non-Hodgkin's lymphoma	None	Reported oral snuff use	Did not report snuff use	OR (95% CI)	1.5	0.9	2.5		No	Not stated	Neither smoking nor oral snuff use were associated with an increased risk for NHL.
Hedström AK, Hillert J,	Moderate	By authors' own	Swedish "moist	Pooled case-	17320 Swedish adults	7883 cases 9437	2005-2012	Other	Multiple Sclerosis	Age, gender,	<5 packet-	Snuff non-users	OR (95% CI)	0.85	0.75	0.97	0.02	Yes	Swedish Medical	Snuff-takers of both sexes have a decreased risk of

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
Olsson T, Alfredsson L, Hedstrom AK, Hillert J, Olsson T and Alfredsson L. 2013. Nicotine might have a protective effect in the etiology of multiple sclerosis. Multiple Sclerosis Journal, 19(8): 1009–1013.		admission: "Only the results from the unmatched analyses are presented in this report since these were significant and in close agreement with those from the matched analyses but had wider CIs (around 2000 more controls in unconditional analysis)." This suggests that the matched analysis produced statistically non-significant values, though it is somewhat mitigated by the fact that the estimates were "in close agreement" and the matched factors were controlled for in the presented analyses. Given the likely negative attitude toward snus use, it is unlikely that information bias, a typical weakness in case-control studies, led to an inverse association between snus use and decreased odds of MS.	snuff"	control		controls				residential area, educational level, ancestry, smoking	years								Research Council, Swedish Council for Working Life and Social Research, FP6 EU Program Neuropromise, Bibbi and Niels Jensens Foundation, Knut and Alice Wallenberg Foundation, Söderberg Foundation, and Swedish Association for Persons with Neurological Disabilities.	developing MS compared with those who have never used moist snuff, with an inverse dose-response correlation between cumulative dose of snuff use and the risk of developing the disease. Those who combined smoking and snuff use had a significantly lower risk for MS than smokers who had never used moist snuff.
	Moderate					7883 cases 9437 controls		Other	Multiple Sclerosis	Age, gender, residential area, educational level, ancestry, smoking	5-10 packet-years	Snuff non-users	OR (95% CI)	0.77	0.63	0.95	0.01	Yes		
	Moderate					7883 cases 9437 controls		Other	Multiple Sclerosis	Age, gender, residential area, educational level, ancestry, smoking	>10 packet-years	Snuff non-users	OR (95% CI)	0.57	0.44	0.74	<0.0001	Yes		
	Moderate					7883 cases 9437 controls		Other	Multiple Sclerosis	Age, gender, residential area, educational level, ancestry, smoking	<5 packet-years, females only	Snuff non-users, females only	OR (95% CI)	0.83	0.68	1.04	0.1	No		
	Moderate					7883 cases 9437 controls		Other	Multiple Sclerosis	Age, gender, residential area, educational level, ancestry, smoking	5-10 packet-years, females only	Snuff non-users, females only	OR (95% CI)	0.65	0.41	1.05	0.08	No		
	Moderate					7883 cases 9437 controls		Other	Multiple Sclerosis	Age, gender, residential area, educational level, ancestry, smoking	>10 packet-years, females only	Snuff non-users, females only	OR (95% CI)	0.35	0.13	0.96	0.04	Yes		
	Moderate					7883 cases 9437 controls		Other	Multiple Sclerosis	Age, gender, residential area, educational level, ancestry, smoking	<5 packet-years, males only	Snuff non-users, males only	OR (95% CI)	0.83	0.71	0.98	0.03	Yes		
	Moderate					7883 cases 9437 controls		Other	Multiple Sclerosis	Age, gender, residential area, educational level, ancestry, smoking	5-10 packet-years, males only	Snuff non-users, males only	OR (95% CI)	0.78	0.62	0.99	0.04	Yes		
	Moderate					7883 cases 9437 controls		Other	Multiple Sclerosis	Age, gender, residential area, educational level, ancestry, smoking	>10 packet-years, males only	Snuff non-users, males only	OR (95% CI)	0.59	0.45	0.78	0.0004	Yes		
	Moderate					7883 cases 9437 controls		Other	Multiple Sclerosis	Age, gender, residential area, educational level, ancestry	<5 packet-years, never smokers	Never smoking snuff non-users	OR (95% CI)	0.96	0.68	1.35	0.9	No		
	Moderate					7883 cases 9437		Other	Multiple Sclerosis	Age, gender,	5-10 packet-	Never smoking	OR (95% CI)	0.87	0.68	1.1	0.6	No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						controls				residential area, educational level, ancestry	years, never smokers	snuff non-users								
	Moderate					7883 cases 9437 controls		Other	Multiple Sclerosis	Age, gender, residential area, educational level, ancestry	>10 packet-years, never smokers	Never smoking snuff non-users	OR (95% CI)	0.45	0.28	0.68	0.001	Yes		
	Moderate					7883 cases 9437 controls		Other	Multiple Sclerosis	Age, gender, residential area, educational level, ancestry, smoking	Snus use and ever smoking	Never smoking snuff non-users	OR (95% CI)	1.19	1.06	1.34	<0.0001	Yes		
	Moderate					7883 cases 9437 controls		Other	Multiple Sclerosis	Age, gender, residential area, educational level, ancestry, smoking	Snus use and current smoking	Never smoking snuff non-users	OR (95% CI)	1.42	1.21	1.65	<0.0001	Yes		
	Moderate					7883 cases 9437 controls		Other	Multiple Sclerosis	Age, gender, residential area, educational level, ancestry, smoking	Snus use and past smoking	Never smoking snuff non-users	OR (95% CI)	1.03	0.88	1.2	0.7	No		
	Moderate					7883 cases 9437 controls		Other	Multiple Sclerosis	Age, gender, residential area, educational level, ancestry, smoking	Exclusive snus use	Never smoking snuff non-users	OR (95% CI)	0.75	0.63	0.9	0.002	Yes		
Hellqvist L, Boström A, Lingström P, Hugoson A, Rolandsson M and Birkhed D. 2012. Effect of nicotine-free and nicotine-Containing snus on plaque pH in vivo. Swedish Dental Journal, 36(4): 187–194.	Weak	The biological relevance of short-term snus-related changes in plaque pH to dental caries is unknown. Small number of participants.	Swedish Match - General Original Portion	Clinical trial (cross-over)	10 Swedish adults	NA	11 weeks, 45 minute sessions/ week	Dental	plaque pH	NA	Swedish Match - General Original Portion	Sucrose control	Increased				<0.001	Yes	Karlstad University	Intraoral pH for nicotine-containing products increased in contrast to three of the six nicotine-free products, which lowered the plaque pH considerably, though all 10 products induced statistically significant pH changes compared to sucrose control. Overall, there appears to be a relationship between the content of fermentable carbohydrates in the snus and the pH fall in dental plaque after the application of the product intraorally.
	Weak		FLsnus - Granit White			NA		Dental	plaque pH	NA	FLsnus - Granit White	Sucrose control	Increased				<0.001	Yes		
	Weak		Swedish-snus - Gustavus Original Portion			NA		Dental	plaque pH	NA	Swedish-snus - Gustavus Original Portion	Sucrose control	Increased				<0.001	Yes		
	Weak		Skruf Snus AB - Skruf Original Portion			NA		Dental	plaque pH	NA	Skruf Snus AB - Skruf Original Portion	Sucrose control	Increased				<0.001	Yes		
	Weak		Gotlandssnus - Jakobsson Classic			NA		Dental	plaque pH	NA	Gotlandssnus - Jakobsson Classic	Sucrose control	Decreased				<0.001	Yes		
	Weak		Nicofree AB - Choice Original Pepper			NA		Dental	plaque pH	NA	Nicofree AB - Choice Original Pepper	Sucrose control	Decreased				<0.001	Yes		
	Weak		Rebel Tobaccol AB - Energy			NA		Dental	plaque pH	NA	Rebel Tobaccol AB - Energy	Sucrose control	Decreased				<0.001	Yes		
	Weak		Swedish Match - Onico (old recipe)			NA		Dental	plaque pH	NA	Swedish Match - Onico (old recipe)	Sucrose control	Decreased				<0.001	Yes		

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	Weak		Swedish Match - Onico			NA		Dental	plaque pH	NA	Swedish Match - Onico	Sucrose control	Decreased				<0.001	Yes		
	Weak		Svenska XQ´s AB - XQ's			NA		Dental	plaque pH	NA	Svenska XQ´s AB - XQ's	Sucrose control	Decreased				<0.001	Yes		
Hellqvist L, Margot R, Hucoson A, Lingstrom P, Birkhed D, Hellqvist L, Rolandsson M, Hugoson A, Lingstrom P and Birkhed D. 2015. Dental caries and associated factors in a group of Swedish snus users. Swedish Dental Journal, 39(1): 47–54.	Weak	The results appear to have been from crude models. Cross-sectional study design.	"Swedish moist powder tobacco (snus)"	Cross-sectional	203 Swedish adults living in or near Karlstad	101 non-smoking daily snus users for >= 10 years 100 tobacco non-users for >= 10 years	2009-2011	Dental	Plaque Index	NA	Non-smoking daily snus users	Tobacco non-users	Mean Difference	0.042			0.084	No	Karlstad University, University of Gothenburg	There were no statistically significant difference in prevalence of dental caries between the snus users and non-users and there were only minor differences regarding carie-associated factors.
	Weak					101 non-smoking daily snus users for >= 10 years 100 tobacco non-users for >= 10 years		Dental	Gingival Index	NA	Non-smoking daily snus users	Tobacco non-users	Mean Difference	0.06			0.009	Yes		"There was no statistically significant difference between snus users and non-users regarding tooth-brushing habits and approximal cleaning with toothpicks and an interdental brush. In contrast, the use of dental floss was more frequent among non-users (p=0.001).
	Weak					101 non-smoking daily snus users for >= 10 years 100 tobacco non-users for >= 10 years		Dental	Enamel caries	NA	Non-smoking daily snus users	Tobacco non-users	Mean Difference	0.5			0.264	No		There was no significant difference in the intake of candy, sweets and soft drinks between the two groups (data not shown)." "poor oral hygiene was the main risk factor for caries development and that the main risk factor for poor oral hygiene was intellectual disability."
	Weak					101 non-smoking daily snus users for >= 10 years 100 tobacco non-users for >= 10 years		Dental	Number of decayed and filled tooth surfaces	NA	Non-smoking daily snus users	Tobacco non-users	Mean Difference	-1			0.648	No		
	Weak					101 non-smoking daily snus users for >= 10 years 100 tobacco non-users for >= 10 years		Dental	Mutans streptococci in saliva	NA	Non-smoking daily snus users	Tobacco non-users	Mean Difference	0.1 log CFU/ml			0.436	No		
	Weak					101 non-smoking daily snus users for >= 10 years 100 tobacco non-users for >= 10 years		Dental	Plaque Index (upper front)	NA	Non-smoking daily snus users	Tobacco non-users	Mean Difference	0.042			0.07	No		
	Weak					101 non-smoking daily snus users for >= 10 years 100 tobacco non-users for >= 10 years		Dental	Gingival Index (upper front)	NA	Non-smoking daily snus users	Tobacco non-users	Mean Difference	0.072			0.003	Yes		
	Weak					101 non-smoking daily snus		Dental	Manifest Caries	NA	Non-smoking daily snus	Tobacco non-users	Mean Difference	-0.09			0.406	No		

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						users for >= 10 years 100 tobacco non-users for >= 10 years					users									
	Weak					101 non-smoking daily snus users for >= 10 years 100 tobacco non-users for >= 10 years		Dental	Number of decayed and filled tooth surfaces (upper front)	NA	Non-smoking daily snus users	Tobacco non-users	Mean Difference	0.1			0.762	No		
	Weak					101 non-smoking daily snus users for >= 10 years 100 tobacco non-users for >= 10 years		Dental	Lactobacilli in saliva	NA	Non-smoking daily snus users	Tobacco non-users	Mean Difference	-0.3 log CFU/ml			0.054	No		
	Weak					101 non-smoking daily snus users for >= 10 years 100 tobacco non-users for >= 10 years		Dental	Salivary secretion rate	NA	Non-smoking daily snus users	Tobacco non-users	Mean Difference	0.3 ml/min			0.005	Yes		
	Weak					101 non-smoking daily snus users for >= 10 years 100 tobacco non-users for >= 10 years		Dental	Buffer capacity	NA	Non-smoking daily snus users	Tobacco non-users	Mean Difference				0.566	No		
	Weak					101 non-smoking daily snus users for >= 10 years 100 tobacco non-users for >= 10 years		Dental	Cariogram value	NA	Non-smoking daily snus users	Tobacco non-users	Mean Difference	0.009			>0.05	No		
	Weak					101 non-smoking daily snus users for >= 10 years 100 tobacco non-users for >= 10 years		Dental	Plaque pH	NA	Non-smoking daily snus users	Tobacco non-users	Mean Difference				>0.05	No		
	Weak					101 non-smoking daily snus users for >= 10 years 100 tobacco non-users for >= 10 years		Dental	Plaque pH fall	NA	Placing snus under the lip	No snus	Mean Difference	Smaller			0.001	Yes		
Hemberg A, Holmberg H,	Moderate	Methodology details are	Swedish "snus"	Cohort	102,857 adults from	71169 snus never users	2001-2013	Other	Groin hernia	age, BMI, education	Former snus	Never snus	HR (95% CI)	1.1	0.96	1.25	0.17	No	Swedish government	"Tobacco use is not a risk factor for requiring a groin

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Norberg M and Nordin P. 2017. Tobacco use is not associated with groin hernia repair, a population-based study. Hernia, 21(4): 517–523.		lacking, including details regarding the relative timings of exposure and outcome assessments. There are no assessments of exclusive snus users nor were the snus results			Vasterbotten, Sweden	10647 former snus users 11679 current snus users who use <4 boxes per week 4170 current snus users who use 4+ boxes of snus per week			repairs		users, males	users, males								hernia repair."
	Moderate	adjusted for smoking and age, both of which are associated with risk of groin hernia repair. However, this is all somewhat mitigated by the fact that the observed associations were inverse, not positive,				71169 snus never users 10647 former snus users 11679 current snus users who use <4 boxes per week 4170 current snus users who use 4+ boxes of snus per week		Other	Groin hernia repairs	age, BMI, education	<4 boxes of snus per week, males	Never snus users, males	HR (95% CI)	0.93	0.82	1.07	0.31	No		
	Moderate	which still supports the statement that there were no increased risk of groin hernia repair associated with tobacco use.				71169 snus never users 10647 former snus users 11679 current snus users who use <4 boxes per week 4170 current snus users who use 4+ boxes of snus per week		Other	Groin hernia repairs	age, BMI, education	4+ boxes of snus per week, males	Never snus users, males	HR (95% CI)	1.04	0.82	1.32	0.72	No		
	Moderate					71169 snus never users 10647 former snus users 11679 current snus users who use <4 boxes per week 4170 current snus users who use 4+ boxes of snus per week		Other	Groin hernia repairs	age, BMI, education	Former snus users, females	Never snus users, females	HR (95% CI)	1.33	0.48	3.72	0.58	No		
	Moderate					71169 snus never users 10647 former snus users 11679 current snus users who use <4		Other	Groin hernia repairs	age, BMI, education	<4 boxes of snus per week, females	Never snus users, females	HR (95% CI)	0.74	0.23	2.36	0.61	No		

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						boxes per week 4170 current snus users who use 4+ boxes of snus per week														
	Moderate					71169 snus never users 10647 former snus users 11679 current snus users who use <4 boxes per week 4170 current snus users who use 4+ boxes of snus per week		Other	Groin hernia repairs	age, BMI, education	4+ boxes of snus per week, females	Never snus users, females	HR (95% CI)	1.22	0.17	8.94	0.84	No		
Hergens M-P, Galanti R, Hansson J, Fredhmd P, Ahlbom A, Son LA, Bellocco R, Eriksson M, Son EIF, Hallqvist J,	Strong	The nature of the reference group does not exclude never smoking former snus users and may have	Swedish "Moist smokeless tobacco (snus)"	Pooled Cohort	127,907 Swedish males from 7 prospective cohort studies	425 current exclusive snus user cases observed 3069 snus nonuser cases observed	Baseline: 1978-2004, follow-up date not provided	Heart/IHD	Atrial Fibrillation	Age, BMI. Education was assessed and made no appreciable difference to the results.	Never smoker, current snus users	Never smoker, non-current snus	HR (95% CI)	1.07	0.97	1.19		No	Swedish Institute of Public Health and the Swedish Council for Working Life and Social Research	"Findings from this large national pooling project indicate that snus use is unlikely to confer any important increase in risk of atrial fibrillation."
Jansson J-H, Knutsson A, Pedersen N, Lagerros YT, Östergren P-O, Magnusson C, Fredlund P, Ahlbom A, Alfredsson L, Bellocco R,	Strong	biased the results toward null. The exposure assessment is likely done at a single timepoint for all cohorts,				425 current exclusive snus user cases observed 3069 snus nonuser cases observed		Heart/IHD	Atrial Fibrillation	Age, BMI. Education was assessed and made no appreciable difference to the results.	Current smoker, current snus users	Never smoker, non-current snus	HR (95% CI)	1.12	1.03	1.23		Yes		
Eriksson M, Fransson EI, Hallqvist J, Jansson J-H, Knutsson A, Pedersen N, Lagerros YT, Östergren P-O and Magnusson C. 2014. Use of Scandinavian moist smokeless tobacco (snus) and the risk of atrial fibrillation. Epidemiology, 25(6): 872–876.	Strong	which likely means non-differential misclassification of exposure and thus likely a bias towards the null.				425 current exclusive snus user cases observed 3069 snus nonuser cases observed		Heart/IHD	Atrial Fibrillation	Age, BMI. Education was assessed and made no appreciable difference to the results.	Former smoker, current snus users	Never smoker, non-current snus	HR (95% CI)	1.09	1	1.19		No		
Hirsch J-M, Wallström M, Carlsson A-P and Sand L. 2012. Oral cancer in Swedish snuff dippers. Anticancer Research,	Weak	The interpretation of the results depend on study participant selection. It is unknown whether the	"Swedish snuff"	Case Series	16 patients with neoplastic oral lesions in the vestibular mucosa	16 exposed	NA	Cancer	Oral Cancer (oral squamous cell carcinoma)	NA	NA	NA	NA	NA	NA	NA			Thuréus Foundation	All 16 examined cases developed oral squamous cell carcinoma at the same location where snus "quid" was placed daily

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32(8): 3327–3330.		16 participants were selected at random or if they were selected because their tumor location and snus quid placement location coincided.																		
Jakobsson U and Larsson C. 2014. Smoking and Chronic Pain Among People Aged 65 Years and Older. Pain Practice, 14(3): 237–244.	Weak	Temporality may be a concern as it is possible that those with snus-associated chronic pain may have quit prior to the study. It is possible that selection and information	Swedish "moist snuff"	Cross-sectional	2000 Swedes 65 or older	90.1% never snus users (n=1028) 5.6% former snus users (n=64) 0.7% occasional snus users (n=8) 3.5% daily snus users (n=40)	2011	Other	Pain Intensity	Age, smoking	Former snus users, males	Never snus users, males	β	0.421	-0.072	0.914	0.094	No	King Gustav V and Queen Victoria's Foundation of Freemasons, the Gyllenstierna Krapperup Foundation, and the Ragnhild and Einar	No relationship was found between chronic pain and using moist snuff (snus).
	Weak	biases, two common features in cross sectional studies, may have been present and biased the results toward the null, but it is difficult to assess the likelihood.				90.1% never snus users (n=1028) 5.6% former snus users (n=64) 0.7% occasional snus users (n=8) 3.5% daily snus users (n=40)		Other	Pain Intensity	Age, smoking	Occasional snus users, males	Never snus users, males	β	0.722	-0.426	1.87	0.284	No	Lundström's Foundation	
	Weak	Similarly, it is possible that non-differential misclassification of exposure or outcome biased the results toward the null, but its effects would have been minor				90.1% never snus users (n=1028) 5.6% former snus users (n=64) 0.7% occasional snus users (n=8) 3.5% daily snus users (n=40)		Other	Pain Intensity	Age, smoking	Daily snus users, males	Never snus users, males	β	0.408	-0.095	0.911	0.112	No		
	Weak					90.1% never snus users (n=1028) 5.6% former snus users (n=64) 0.7% occasional snus users (n=8) 3.5% daily snus users (n=40)		Other	Pain Intensity	Age, smoking	Former snus users, females	Never snus users, females	β	0.447	-0.056	0.839	0.583	No		
	Weak					90.1% never snus users (n=1028) 5.6%		Other	Pain Intensity	Age, smoking	Daily snus users, females	Never snus users, females	β	-0.255	-1.541	1.032	0.697	No		

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						former snus users (n=64) 0.7% occasional snus users (n=8) 3.5% daily snus users (n=40)														
Jiang X, Alfredsson L, Klareskog L and Bengtsson C. 2014. Smokeless tobacco (moist snuff) use and the risk of developing rheumatoid arthritis: results from a case-control study. Arthritis care & research, 66(10): 1582–1586.	Moderate	It is possible that selection and information biases, two common features in case-control studies, may have been present and biased the results toward the null, but it is difficult to gauge the likelihood. Similarly, it is possible that non-differential misclassification of exposure or outcome biased the results toward the null, but its effects would have been minor	"Swedish moist snuff"	Case-control	2451 Swedes	1998 cases 2252 controls	1996-2006	Other	Rheumatoid Arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Ever snus users n=254 exposed cases	Snus non-users	OR (95% CI)	1	0.8	1.2		No	Swedish Research Council for Health, Working Life and Welfare; the Swedish Research Council; Vinnova; the AFA Insurance Company; King Gustaf V's 80-Year Foundation; the Swedish Rheumatism Foundation; and the European Union–funded Innovative Medicines Initiative (BTCure).	The use of moist snuff was not associated with the risk of either anti– citrullinated protein/peptide antibody-positive or anti– citrullinated protein/peptide antibody-negative rheumatoid arthritis. Other inhaled constituents of tobacco smoke than nicotine are more likely to be involved in the pathogenesis of anti–citrullinated protein/peptide antibody-positive RA.
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody positive rheumatoid arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Ever snus users n=172 exposed cases	Snus non-users	OR (95% CI)	1	0.8	1.3		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody negative rheumatoid arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Ever snus users n=82 exposed cases	Snus non-users	OR (95% CI)	0.9	0.7	1.2		No		
	Moderate					1998 cases 2252 controls		Other	Rheumatoid Arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Current snus users n=164 exposed cases	Snus non-users	OR (95% CI)	1.1	0.8	1.4		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody positive rheumatoid arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Current snus users n=109 exposed cases	Snus non-users	OR (95% CI)	1	0.8	1.4		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody negative rheumatoid arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Current snus users n=55 exposed cases	Snus non-users	OR (95% CI)	1	0.7	1.4		No		
	Moderate					1998 cases 2252 controls		Other	Rheumatoid Arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Former snus users n=90 exposed cases	Snus non-users	OR (95% CI)	0.9	0.6	1.2		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody positive rheumatoid arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Former snus users n=63 exposed cases	Snus non-users	OR (95% CI)	1	0.7	1.4		No		

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	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody negative rheumatoid arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Former snus users n=27 exposed cases	Snus non-users	OR (95% CI)	0.8	0.5	1.2		No		
	Moderate					1998 cases 2252 controls		Other	Rheumatoid Arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Never smoking ever snus users n=27 exposed cases	Never smoking snus non-users	OR (95% CI)	1	0.6	1.7		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody positive rheumatoid arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Never smoking ever snus users n=16 exposed cases	Never smoking snus non-users	OR (95% CI)	1	0.5	1.9		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody negative rheumatoid arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Never smoking ever snus users n=11 exposed cases	Never smoking snus non-users	OR (95% CI)	1	0.5	2		No		
	Moderate					1998 cases 2252 controls		Other	Rheumatoid Arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Never smoking current snus users n=22 exposed cases	Never smoking snus non-users	OR (95% CI)	1.2	0.7	2.2		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody positive rheumatoid arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Never smoking current snus users n=11 exposed cases	Never smoking snus non-users	OR (95% CI)	1	0.5	2.2		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody negative rheumatoid arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Never smoking current snus users n=11 exposed cases	Never smoking snus non-users	OR (95% CI)	1.5	0.7	3.3		No		
	Moderate					1998 cases 2252 controls		Other	Rheumatoid Arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Never smoking former snus users n=5 exposed cases	Never smoking snus non-users	OR (95% CI)	0.5	0.2	1.5		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody positive rheumatoi	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Never smoking former snus users n=5 exposed	Never smoking snus non-users	OR (95% CI)	1	0.3	2.8		No		

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									d arthritis		cases									
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody negative rheumatoid arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Never smoking former snus users n=0 exposed cases	Never smoking snus non-users	OR (95% CI)	NA	NA	NA		No		
	Moderate					1998 cases 2252 controls		Other	Rheumatoid Arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Ever smoking ever snus users n=227 exposed cases	Ever smoking snus non-users	OR (95% CI)	1	0.8	1.3		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody positive rheumatoid arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Ever smoking ever snus users n=156 exposed cases	Ever smoking snus non-users	OR (95% CI)	1	0.8	1.4		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody negative rheumatoid arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Ever smoking ever snus users n=71 exposed cases	Ever smoking snus non-users	OR (95% CI)	0.9	0.6	1.2		No		
	Moderate					1998 cases 2252 controls		Other	Rheumatoid Arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Ever smoking current snus users n=142 exposed cases	Ever smoking snus non-users	OR (95% CI)	1	0.8	1.4		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody positive rheumatoid arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Ever smoking current snus users n=98 exposed cases	Ever smoking snus non-users	OR (95% CI)	1.1	0.8	1.5		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody negative rheumatoid arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Ever smoking current snus users n=44 exposed cases	Ever smoking snus non-users	OR (95% CI)	0.9	0.6	1.3		No		
	Moderate					1998 cases 2252 controls		Other	Rheumatoid Arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Ever smoking former snus users n=85 exposed cases	Ever smoking snus non-users	OR (95% CI)	1	0.7	1.4		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody positive	Age, sex, residential area, pack-years of smoking, and alcohol consumptio	Ever smoking former snus users n=58	Ever smoking snus non-users	OR (95% CI)	1	0.7	1.4		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
									rheumatoid arthritis	n.	exposed cases									
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody negative rheumatoid arthritis	Age, sex, residential area, pack-years of smoking, and alcohol consumption.	Ever smoking former snus users n=27 exposed cases	Ever smoking snus non-users	OR (95% CI)	0.9	0.5	1.5		No		
	Moderate					1998 cases 2252 controls		Other	Rheumatoid Arthritis	Age, sex, residential area, and alcohol consumption.	Light, former, or never smoking ever snus users n=71 exposed cases	Light, former, or never smoking snus non-users	OR (95% CI)	0.9	0.7	1.3		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody positive rheumatoid arthritis	Age, sex, residential area, and alcohol consumption.	Light, former, or never smoking ever snus users n=40 exposed cases	Light, former, or never smoking snus non-users	OR (95% CI)	0.9	0.6	1.4		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody negative rheumatoid arthritis	Age, sex, residential area, and alcohol consumption.	Light, former, or never smoking ever snus users n=31 exposed cases	Light, former, or never smoking snus non-users	OR (95% CI)	1	0.7	1.6		No		
	Moderate					1998 cases 2252 controls		Other	Rheumatoid Arthritis	Age, sex, residential area, and alcohol consumption.	Light, former, or never smoking current snus users n=49 exposed cases	Light, former, or never smoking snus non-users	OR (95% CI)	1	0.7	1.5		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody positive rheumatoid arthritis	Age, sex, residential area, and alcohol consumption.	Light, former, or never smoking current snus users n=25 exposed cases	Light, former, or never smoking snus non-users	OR (95% CI)	0.9	0.5	1.4		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody negative rheumatoid arthritis	Age, sex, residential area, and alcohol consumption.	Light, former, or never smoking current snus users n=24 exposed cases	Light, former, or never smoking snus non-users	OR (95% CI)	1.3	0.8	2.1		No		
	Moderate					1998 cases 2252 controls		Other	Rheumatoid Arthritis	Age, sex, residential area, and alcohol consumptio	Light, former, or never smoking former	Light, former, or never smoking snus non-	OR (95% CI)	0.8	0.5	1.4		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
										n.	snus users n=22 exposed cases	users								
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody positive rheumatoid arthritis	Age, sex, residential area, and alcohol consumption.	Light, former, or never smoking former snus users n=15 exposed cases	Light, former, or never smoking snus non-users	OR (95% CI)	1	0.5	1.8		No		
	Moderate					1998 cases 2252 controls		Other	Anti–citrullinated protein/peptide antibody negative rheumatoid arthritis	Age, sex, residential area, and alcohol consumption.	Light, former, or never smoking former snus users n=7 exposed cases	Light, former, or never smoking snus non-users	OR (95% CI)	0.6	0.3	1.4		No		
Juarez SP, Merlo J, Juárez SP and Merlo J. 2013. The Effect of Swedish Snuff (Snus) on Offspring Birthweight: A Sibling Analysis. PLoS ONE, 8(6): e65611.	Strong	Possible survivor bias due to the use of liveborns.	"Swedish snuff (snus)"	Cohort	938,932 Swedish pregnancies/newborns	591,690 non-users during pregnancy 2298 continuous snus users 4934 snus users who quit by 3rd trimester 1107 snus users who relapsed by 3rd trimester	2002-2010	Reproductive	Birthweight	gestational age, birth order, sex, mother's age, and marital status	Use of snus in the first and/or third trimester	No use of snus during pregnancy	β	-19	-27	-11		Yes	Swedish Council for Working Life and Social Research, the Swedish Research Council	"Snus use during pregnancy was associated with a slight reduction in offspring birthweight." However, "the adverse effect of smoking during pregnancy on offspring birthweight may be explained by the combustion or other products of smoking rather than by nicotine."
	Strong					591,690 non-users during pregnancy 2298 continuous snus users 4934 snus users who quit by 3rd trimester 1107 snus users who relapsed by 3rd trimester		Reproductive	Birthweight	gestational age, birth order, sex, mother's age, and marital status	Use of snus throughout pregnancy	No use of snus during pregnancy	β	-47	-63	-47		Yes		
	Strong					591,690 non-users during pregnancy 2298 continuous snus users 4934 snus users who quit by 3rd trimester 1107 snus users who relapsed by 3rd trimester		Reproductive	Birthweight	gestational age, birth order, sex, mother's age, and marital status	Use of snus only in first trimester, quit before third trimester	No use of snus during pregnancy	β	-6	-17	4		No		
	Strong					591,690 non-users during		Reproductive	Birthweight	gestational age, birth order, sex,	Took up snus between	No use of snus during	β	-4	-27	19		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						pregnancy 2298 continuous snus users 4934 snus users who quit by 3rd trimester 1107 snus users who relapsed by 3rd trimester				mother's age, and marital status	first and third trimester	pregnancy								
	Strong					591,690 non-users during pregnancy 2298 continuous snus users 4934 snus users who quit by 3rd trimester 1107 snus users who relapsed by 3rd trimester		Reproductive	Birthweight	gestational age, birth order, sex, mother's age, and marital status	Sibling who experienced snus exposure in first and/or third trimester	Sibling with no snus exposure during pregnancy	β	-12	-25	2		No		
	Strong					591,690 non-users during pregnancy 2298 continuous snus users 4934 snus users who quit by 3rd trimester 1107 snus users who relapsed by 3rd trimester		Reproductive	Birthweight	gestational age, birth order, sex, mother's age, and marital status	Sibling who experienced snus exposure in throughout pregnancy	Sibling with no snus exposure during pregnancy	β	-20	-52	12		No		
	Strong					591,690 non-users during pregnancy 2298 continuous snus users 4934 snus users who quit by 3rd trimester 1107 snus users who relapsed by 3rd trimester		Reproductive	Birthweight	gestational age, birth order, sex, mother's age, and marital status	Sibling who experienced snus exposure only in first trimester	Sibling with no snus exposure during pregnancy	β	-14	-31	3		No		
	Strong					591,690 non-users during pregnancy 2298 continuous snus users 4934 snus users who quit by 3rd trimester 1107 snus users who relapsed by 3rd trimester		Reproductive	Birthweight	gestational age, birth order, sex, mother's age, and marital status	Sibling who experienced snus exposure starting between first and third trimester	Sibling with no snus exposure during pregnancy	β	-14	-46	18		No		
	Strong					591,690 non-users		Reproductive	Birthweight	gestational age, birth	Use of snus at	First pregnanc	β	4	-21	30				

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						during pregnancy 2298 continuous snus users 4934 snus users who quit by 3rd trimester 1107 snus users who relapsed by 3rd trimester				order, sex, mother's age, and marital status	any time point in the first pregnancy	y among those who did not use snus during two pregnancies								
	Strong					591,690 non-users during pregnancy 2298 continuous snus users 4934 snus users who quit by 3rd trimester 1107 snus users who relapsed by 3rd trimester		Reproductive	Birthweight	gestational age, birth order, sex, mother's age, and marital status	Second pregnancy among those who used snus in the first, but not second pregnancy	Second pregnancy among those who did not use snus during two pregnancies	β	12	-14	37		No		
	Strong					591,690 non-users during pregnancy 2298 continuous snus users 4934 snus users who quit by 3rd trimester 1107 snus users who relapsed by 3rd trimester		Reproductive	Birthweight	gestational age, birth order, sex, mother's age, and marital status	First pregnancy among those who used snus in the second, but not first pregnancy	First pregnancy among those who did not use snus during two pregnancies	β	-9	-35	16		No		
	Strong					591,690 non-users during pregnancy 2298 continuous snus users 4934 snus users who quit by 3rd trimester 1107 snus users who relapsed by 3rd trimester		Reproductive	Birthweight	gestational age, birth order, sex, mother's age, and marital status	Second pregnancy among those who used snus in the second, but not first pregnancy	Second pregnancy among those who did not use snus during two pregnancies	β	23	-2	49		No		
	Strong					591,690 non-users during pregnancy 2298 continuous snus users 4934 snus users who quit by 3rd trimester 1107 snus users who relapsed by 3rd trimester		Reproductive	Birthweight	gestational age, birth order, sex, mother's age, and marital status	First pregnancy among those who used snus during two pregnancies	First pregnancy among those who did not use snus during two pregnancies	β	-41	-74	-7		Yes		
	Strong					591,690		Reproductive	Birthweigh	gestational	Second	Second	β	-56	-90	-22		Yes		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						non-users during pregnancy 2298 continuous snus users 4934 snus users who quit by 3rd trimester 1107 snus users who relapsed by 3rd trimester			t	age, birth order, sex, mother's age, and marital status	pregnancy among those who used snus during two pregnancies	pregnancy among those who did not use snus during two pregnancies								
Katsika D, Tuvblad C, Einarsson C, Lichtenstein P, Marschall HU. 2007. Body mass index, alcohol, tobacco and symptomatic gallstone disease: a Swedish twin study. Journal of internal medicine. 262(5):581-7.	Weak	Limited data on tobacco habits. Data missing on over half of cases, and approx. half of controls, thus limiting statistical power, few exposed cases, lack of control for potential confounders	Swedish "Smoke-free tobacco (snuff)"		Swedish Twin Registry with 58,402 twins born 1886-1958 27,692 male 30,710 female	1666 cases (twins with gallstone disease) n=7 exposed cases	1886-1958	Other	Gallstone disease	None	Twins with gallstone disease who reported current smoke-free tobacco use	Twins who reported never using smoke-free tobacco	OR (95% CI)	1.05	0.49	2.23		No	Department of Higher Education, Swedish Scientific Council, AstraZeneca, grants from Swedish Medical Society and Karolinska Institutet	"Smoking or use of smoke-free tobacco did not have a significant impact on symptomatic gallstone disease."
	Weak					1666 cases (twins with gallstone disease) n=20 exposed cases		Other	Gallstone disease	None	Twins with gallstone disease who reported previous smoke-free tobacco use	Twins who reported never using smoke-free tobacco	OR (95% CI)	0.62	0.37	1.04		No		
Lie TM, Bomme M, Hveem K, Hansen JM and Ness-Jensen E. 2017. Snus and risk of gastroesophageal reflux. A population-based case-control study: the HUNT study. Scandinavian Journal of Gastroenterology, 52(2): 193–198.	Weak	The reduced risk among daily current snus users may indicate survivor bias given the increased risk observed in former users. The study focused on severe GERS cases and eliminated those who may have mild cases. It is possible that there was information and selection bias, both of which could have biased the results away from the null. The comparison groups were unclear at times.	Swedish "snus"	Cross sectional	58,634 Norwegians from the Nord-Trøndelag county	24373 snus never-users 1342 former snus users 983 occasional snus users 2104 daily snus users	2006-2008	GI Effects	Severe gastroesophageal reflux disease	Age, sex, smoking status, BMI, and physical exercise	Former snus users	Snus never-users	OR (95% CI)	1.2	1	1.46		No	Not stated	Daily snus users had a reduced risk of GERS. However, previous snus users and subgroups of snus users had an increased risk of GERS indicating that snus use could increase the risk of GERS.
	Weak					24373 snus never-users 1342 former snus users 983 occasional snus users 2104 daily snus users		GI Effects	Severe gastroesophageal reflux disease	Age, sex, smoking status, BMI, and physical exercise	Occasional snus users	Snus never-users	OR (95% CI)	1.21	0.96	1.52		No		
	Weak					24373 snus never-users 1342 former snus users 983 occasional snus users 2104 daily snus users		GI Effects	Severe gastroesophageal reflux disease	Age, sex, smoking status, BMI, and physical exercise	Daily snus users	Snus never-users	OR (95% CI)	0.77	0.64	0.93		Yes		
	Weak					24373 snus never-users 1342 former snus users 983 occasional snus users 2104 daily snus users		GI Effects	Severe gastroesophageal reflux disease	Age, sex, smoking status, BMI, and physical exercise	<2 boxes/month	Snus never-users	OR (95% CI)	1.41	1.02	1.96		Yes		
	Weak					24373 snus never-users		GI Effects	Severe gastroeso	Age, sex, smoking	2-8 boxes/mo	Snus never-	OR (95% CI)	0.93	0.78	1.1		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						1342 former snus users 983 occasional snus users 2104 daily snus users			phageal reflux disease	status, BMI, and physical exercise	nth	users								
	Weak					24373 snus never-users 1342 former snus users 983 occasional snus users 2104 daily snus users		GI Effects	Severe gastroesophageal reflux disease	Age, sex, smoking status, BMI, and physical exercise	>8 boxes/month	Snus never-users	OR (95% CI)	1.16	0.88	1.54		No		
	Weak					24373 snus never-users 1342 former snus users 983 occasional snus users 2104 daily snus users		GI Effects	Severe gastroesophageal reflux disease	Age, sex, smoking status, BMI, and physical exercise	Never smoking ever snus users	Never smoking snus-never users	OR (95% CI)	0.75	0.54	1.03		No		
	Weak					24373 snus never-users 1342 former snus users 983 occasional snus users 2104 daily snus users		GI Effects	Severe gastroesophageal reflux disease	Age, sex, smoking status, BMI, and physical exercise	Former smoking ever snus users	Former smoking snus-never users	OR (95% CI)	0.62	0.48	0.79		Yes		
	Weak					24373 snus never-users 1342 former snus users 983 occasional snus users 2104 daily snus users		GI Effects	Severe gastroesophageal reflux disease	Age, sex, smoking status, BMI, and physical exercise	Occasional smoking ever snus users	Occasional smoking snus-never users	OR (95% CI)	1.39	0.94	2.04		No		
	Weak					24373 snus never-users 1342 former snus users 983 occasional snus users 2104 daily snus users		GI Effects	Severe gastroesophageal reflux disease	Age, sex, smoking status, BMI, and physical exercise	Daily smoking ever snus users	Daily smoking snus-never users	OR (95% CI)	1.12	0.78	1.61		No		
Liu Z, Roosaar A, Axéll T and Ye W. 2017. Tobacco use, oral health, and risk of Parkinson's disease. American Journal of Epidemiology, 185(7): 538–545.	Strong	Minor misclassification of exposure	"Swedish moist snuff (snus)"	Cohort	20,333 Uppsala County residents 15 years or older	3103 never daily user of any tobacco 5298 exclusive ever smoker 1635 exclusive former smoker 3663 exclusive current smoker 865 exclusive snus user 690 dual user	1973-2012	Other	Parkinson's Disease	Age, area of residence, marital status, and alcohol consumption	Exclusive ever smoker	Never daily users of any tobacco	HR (95% CI)	0.68	0.49	0.93		Yes	Swedish Research Council for Health, Working Life and Welfare	Scandinavian moist snuff was associated with a reduced risk of Parkinson's Disease in males.

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	Strong					3103 never daily user of any tobacco 5298 exclusive ever smoker 1635 exclusive former smoker 3663 exclusive current smoker 865 exclusive snus user 690 dual user		Other	Parkinson's Disease	Age, area of residence, marital status, and alcohol consumption	Exclusive former smoker	Never daily users of any tobacco	HR (95% CI)	0.73	0.49	1.09		No		
	Strong					3103 never daily user of any tobacco 5298 exclusive ever smoker 1635 exclusive former smoker 3663 exclusive current smoker 865 exclusive snus user 690 dual user		Other	Parkinson's Disease	Age, area of residence, marital status, and alcohol consumption	Exclusive current smoker	Never daily users of any tobacco	HR (95% CI)	0.64	0.44	0.93		Yes		
	Strong					3103 never daily user of any tobacco 5298 exclusive ever smoker 1635 exclusive former smoker 3663 exclusive current smoker 865 exclusive snus user 690 dual user		Other	Parkinson's Disease	Age, area of residence, marital status, and alcohol consumption	Exclusive snus user n=11 exposed cases	Never daily users of any tobacco	HR (95% CI)	0.51	0.27	0.95		Yes		
	Strong					3103 never daily user of any tobacco 5298 exclusive ever smoker 1635 exclusive former smoker 3663 exclusive current smoker		Other	Parkinson's Disease	Age, area of residence, marital status, and alcohol consumption	Dual user n=3 exposed cases	Never daily users of any tobacco	HR (95% CI)	0.21	0.07	0.67		Yes		

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						865 exclusive snus user 690 dual user														
	Strong					3103 never daily user of any tobacco 5298 exclusive ever smoker 1635 exclusive former smoker 3663 exclusive current smoker 865 exclusive snus user 690 dual user		Other	Parkinson's Disease	Age, area of residence, marital status, and alcohol consumption	Exclusive snus user of <=10 years	Never daily users of any tobacco	HR (95% CI)	0.54	0.2	1.49		No		
	Strong					3103 never daily user of any tobacco 5298 exclusive ever smoker 1635 exclusive former smoker 3663 exclusive current smoker 865 exclusive snus user 690 dual user		Other	Parkinson's Disease	Age, area of residence, marital status, and alcohol consumption	Exclusive snus user of >10 years	Never daily users of any tobacco	HR (95% CI)	0.5	0.23	1.1		No		
	Strong					3103 never daily user of any tobacco 5298 exclusive ever smoker 1635 exclusive former smoker 3663 exclusive current smoker 865 exclusive snus user 690 dual user		Other	Parkinson's Disease	Age, area of residence, marital status, and alcohol consumption	Exclusive snus user of <=10 g/day	Never daily users of any tobacco	HR (95% CI)	0.33	0.12	0.91		No		
	Strong					3103 never daily user of any tobacco 5298 exclusive ever smoker 1635 exclusive former		Other	Parkinson's Disease	Age, area of residence, marital status, and alcohol consumption	Exclusive snus user of >10 g/day	Never daily users of any tobacco	HR (95% CI)	0.76	0.35	1.66		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						smoker 3663 exclusive current smoker 865 exclusive snus user 690 dual user														
Ludvigsson JF, Nordenvall C and Järvholm B. 2014. Smoking, use of moist snuff and risk of celiac disease: A prospective study. BMC Gastroenterology, 14(1).	Strong	Possible misclassification (long follow-up period without reevaluation), no exclusive snus group, although smoking was not associated with Celiac disease	Swedish "moist snuff"		199,185 men and women from the Swedish Construction Worker cohort	82,572 ever / 116,613 never users 597 men and 59 women with biopsy verified celiac disease (310 with data on moist snuff)	Baseline: 1971-1973. Follow-up: 2008	GI Effects	Celiac disease	Person-years stratified for age (10-year age-classes), decennium, sex and tobacco smoking	Ever users	Never tobacco users	RR (95% CI)	1	0.78	1.28		No	Swedish Society of Medicine, the Swedish Research Council, and the Swedish Celiac Society, Swedish Society for Medical Research,	"The most likely explanation for RRs around 1 in both smokers and moist snuff users are that these factors do not play a major role in the aetiology of CD in a Swedish setting." "In conclusion, we found no association between smoking, moist snuff use and CD." Less than 10% of the ever-users reported that they had stopped using moist snuff. Users from 1971-1974 included current users because variable for non-current users included those who did not answer.
	Strong					82,572 ever / 116,613 never users 597 men and 59 women with biopsy verified celiac disease (310 with data on moist snuff)		GI Effects	Celiac disease	Person-years stratified for age (10-year age-classes), decennium, sex and tobacco smoking	Ever users (follow-ed up 10+ years after medical exam)	Never tobacco users	RR (95% CI)	1.05	0.8	1.38		No	Swedish Research council for Health, Working Life and Welfare	
	Strong					82,572 ever / 116,613 never users 597 men and 59 women with biopsy verified celiac disease (310 with data on moist snuff)		GI Effects	Celiac disease	Person-years stratified for age (10-year age-classes), decennium, sex	Ever smokers and snuff users (men only)	Never tobacco users	RR (95% CI)	0.91	0.69	1.19		No		
Morente-Sánchez J, Zandonai T, Mateo-March M, Sanabria D, Sánchez-Muñoz C, Chiamulera C, Zabala Díaz M, Morente-Sanchez J, Zandonai T, Mateo-March M, Sanabria D, Sanchez-Munoz C, Chiamulera C and Zabala Diaz M. 2015. Acute effect of Snus on physical performance and perceived cognitive load on amateur footballers.	Moderate	Small number of participants	1.0-g portion of Snus (Catch White Eucalyptus)	Clinical trial (double-blind randomized crossover with 5-day washout)	18 nonsmoking, non-snus-using male amateur football players in Spain	Half of participants received snus, and half received placebo during two experiments	2014	CV Effects	Acute decrease in heart rate variability (HRV): mean R-R interval (RRi)	NA	1-g portion of snus (8 mg nicotine) at baseline	1-g portion of snus (8 mg nicotine) at 35 minutes following acute intake	Mean difference				<0.001	Yes	Spanish "Ministerio de Educación," Spanish Ministerio de Economía y Competitividad," and Spanish "Junta de Andalucía"	"Regarding HRV, in line with Karakaya et al. (2007) findings, results showed a decrease after Snus administration even before the beginning of the fitness test battery. Results appear to confirm that nicotine leads to a reduced vagal tone." No effect was observed in the placebo session.
	Moderate					Half of participants received snus, and half received placebo during two experiments		CV Effects	Acute decrease in heart rate variability (HRV): root mean square difference of successive normal R-R intervals (rMSSD)	NA	1-g portion of snus (8 mg nicotine)	1-g portion of snus (8 mg nicotine) at 35 minutes following acute intake	Mean difference				<0.05	Yes		
	Moderate					Half of participants received		CV Effects	Acute decrease in heart	NA	1-g portion of snus (8	1-g portion of snus (8	Mean difference				<0.04	Yes		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
Scandinavian Journal of Medicine and Science in Sports, 25(4): e423–e431.						snus, and half received placebo during two experiments			rate variability (HRV): geometric Poincare Plot index (SD1) (instantaneous beat-to-beat variability		mg nicotine)	mg nicotine) at 35 minutes following acute intake								
Munafo MR, Larsson Lonn S, Sundquist J, Sundquist K, Kendler K, Munafò MR, Larsson Lönn S, Sundquist J, Sundquist K and Kendler K. 2016. Snus use and risk of schizophrenia and non-affective psychosis. Drug and Alcohol Dependence, 164: 179–182.	Moderate	Somewhat limited number of exposed cases, reference group not defined, potential for reverse causality, time period between exposure assessment and follow-up not described	"Swedish snuff ("snus")"	Cohort	227,117 Swedish men not diagnosed with non-affective psychosis (including schizophrenia) identified from various national registers, age 18-25 at time of military conscription	60,804 snus users / 166,313 non-users 36 exposed cases	Follow up through 2010 for most registries	Other	Schizophrenia	smoking, neighborhood deprivation, parental education, drug abuse prior to diagnosis	Snus user (adjusted for smoking)	Not stated	HR (95% CI)	1.03	0.7	1.54		No	Not stated	"In conclusion, our data provide some evidence that snus use is associated with the subsequent development of non-affective psychosis. The evidence for an association with schizophrenia is weaker, but broadly consistent."
	Moderate					60,804 snus users / 166,313 non-users 36 exposed cases		Other	Schizophrenia	neighborhood deprivation, parental education, drug abuse prior to diagnosis	Exclusive snus user	Not stated	HR (95% CI)	1.23	0.77	1.98		No		
	Moderate					60,804 snus users / 166,313 non-users 36 exposed cases		Other	Schizophrenia	neighborhood deprivation, parental education, drug abuse prior to diagnosis	Snus user + Light smoker	Not stated	HR (95% CI)	0.42	0.16	1.07		No		
	Moderate					60,804 snus users / 166,313 non-users 36 exposed cases		Other	Schizophrenia	neighborhood deprivation, parental education, drug abuse prior to diagnosis	Snus user + Moderate smoker	Not stated	HR (95% CI)	0.75	0.19	2.92		No		
	Moderate					60,804 snus users / 166,313 non-users 36 exposed cases		Other	Schizophrenia	neighborhood deprivation, parental education, drug abuse prior to diagnosis	Snus user + Heavy smoker	Not stated	HR (95% CI)	1.43	0.29	2.08		No		
	Moderate					60,804 snus users / 166,313 non-users 36 exposed cases		Other	Non-affective psychosis	smoking, neighborhood deprivation, parental education, drug abuse prior to diagnosis	Snus user (adjusted for smoking)	Not stated	HR (95% CI)	1.22	1	1.48		No		
	Moderate					60,804 snus users / 166,313 non-users 36 exposed cases		Other	Non-affective psychosis	neighborhood deprivation, parental education, drug abuse prior to diagnosis	Exclusive snus user	Not stated	HR (95% CI)	1.38	1.09	1.75		Yes		
	Moderate					60,804 snus users / 166,313 non-users 36 exposed cases		Other	Non-affective psychosis	neighborhood deprivation, parental education, drug abuse prior to diagnosis	Snus user + Light smoker	Not stated	HR (95% CI)	0.69	0.45	1.05		No		
	Moderate					60,804 snus users		Other	Non-affective	neighborhood	Snus user +	Not stated	HR (95% CI)	0.97	0.5	1.87		No		

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						/ 166,313 non-users 36 exposed cases			psychosis	deprivation, parental education, drug abuse prior to diagnosis	Moderate smoker									
	Moderate					60,804 snus users / 166,313 non-users 36 exposed cases		Other	Non-affective psychosis	neighborhood deprivation, parental education, drug abuse prior to diagnosis	Snus user + Heavy smoker	Not stated	HR (95% CI)	0.63	0.19	2.06		No		
Neumann A, Norberg M, Schoffer O, Norström F, Johansson I, Klug SJ and Lindholm L. 2013. Risk equations for the development of worsened glucose status and type 2 diabetes mellitus in a Swedish intervention program. BMC public health, 13: 1014.	Moderate	Number of exposed cases not provided, long follow up with exposures assessed only at first exam (possible misclassification), no exclusive snus group	Swedish "Snus"		29,937 adults aged 30, 40, or 50 at first exam living in the Swedish county of Vasterbotten, and followed up 10 years later for a second exam as part of the Vasterbotten Intervention Program (VIP)	No current use: 24,927 ≤4 cans/week: 3,293 >4 cans/week: 973 missing: 744	First exam: 1990-1999 Second exam: 10 years later	Diabetes/MetSy	Progression of normal glucose tolerance to impaired fasting glucose	sex, age, education, triglyceride, blood pressure, BMI, smoking, physical activity, portions of fruits and vegetables, marital status, family history	Current use of snus	No current use of snus	OR (95% CI)	0.92	0.82	1.03		No		"The odds ratios of snus, "five a day" and marital status were all not significant."
	Moderate					No current use: 24,927 ≤4 cans/week: 3,293 >4 cans/week: 973 missing: 744		Diabetes/MetSy	Progression of normal glucose tolerance to impaired fasting glucose and impaired glucose tolerance	sex, age, education, triglyceride, blood pressure, BMI, smoking, physical activity, portions of fruits and vegetables, marital status, family history	Current use of snus	No current use of snus	OR (95% CI)	0.79	0.59	1.05		No		
Nordenstam F, Lundell B, Cohen G, Tessma MK, Raaschou P and Wickstrom R. 2017. Prenatal Exposure to Snus Alters Heart Rate Variability in the Infant. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco, 19(7): 797–803.	Weak	Small number of participants, lack of control for potential confounders	"Swedish snus"	Cohort	56 infants of women who used snus exclusively (n=23) or cigarettes exclusively (n=13) during pregnancy versus tobacco- and nicotine-free controls (n=19). Infants studied 1-2 months after birth.	23 infants of women who used snus, and 19 infants of nicotine-free controls	Not stated	Reproductive	Heart rate variability: max, min, and mean RR, SD RR, VLF, LF, HF, total power, LF/HF ratio	None	Infants of women who used snus exclusively	Nicotine-free controls						Yes	Swedish Medical Research Council, Swedish Council for Working Life and Social research, the Samaritan Foundation, Order of Odd Fellows and Swedish Freemasons Foundation	"We did not observe statistically significant differences between controls, snus or smoke groups in R-R intervals (min, max or mean)." "Infants in the two tobacco exposed groups had a comparable LF/HF ratio, which was significantly higher than that of the control group. The main differences for infants in the snus group (mean difference = 1.16, 95% CI = 0.29–2.02, p = .006)... were statistically significant higher compared to controls." "There were occasional extra beats found in all groups, mostly supraventricular extra systoles and occasionally ventricular extra systoles, but no other arrhythmias were detected." "There was no difference between infants exposed to smokeless versus smoked tobacco, suggesting a common constituent

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
																				(nicotine) altering autonomic cardiac regulation."
Oberg J, Jorde R, Almas B, Emaus N, Grimnes G, Öberg J, Jorde R, Grimnes G, Almås B and Emaus N. 2014. Vitamin D deficiency and lifestyle risk factors in a Norwegian adolescent population. Scandinavian Journal of Public Health, 42(7): 593–602.	Weak	Cross-sectional design, lack of control for potential confounders	Swedish "Snuff"	Cross-sectional	890 Norwegian adolescents (475 boys and 415 girls) from the Tromso Study	Boys: Never snuff users: n=279 Sometimes: n=58 Daily: n=131	2010-2011	Other	25(OH)D (Vitamin D level)	Univariate analysis	Boys snuff use: Sometimes Daily	Boys: Never use of snuff	Trend serum levels				0.01	Yes	The North Norway Regional Health Authority and UiT The Arctic University of Norway	See table 2 for details "Whether snuff affects serum 25(OH)D levels by biological mechanisms or is a marker of an unhealthy lifestyle cannot be settled by this study, as there could be residual confounding factors not included in the model." Serum Vitamin D levels were slightly lower in the "Sometimes" compared to "Daily" group, and both of these groups were lower than the "Never" group (see Table II in study for details).
	Weak					Girls: Never snuff users: n=279 Sometimes: n=58 Daily: n=74		Other	25(OH)D (Vitamin D level)	Univariate analysis	Girls snuff use: Sometimes Daily	Girls: Never use of snuff	Trend serum levels				0.1	No		"Whether snuff affects serum 25(OH)D levels by biological mechanisms or is a marker of an unhealthy lifestyle cannot be settled by this study, as there could be residual confounding factors not included in the model."
Overland S, Skogen JC, Lissner L, Bjerkeset O, Tjora T and Stewart R. 2013. Snus use and cardiovascular risk factors in the general population: The HUNT3 study. Addiction, 108(11): 2019–2028.	Weak	Cross-sectional study design, 53% participation rate-lower among younger (selection bias), adjusted for smoking	Swedish "Snus"	Cross-sectional	50,797 participants in the 3rd wave of the Nord-Trondelag Health Surveys (HUNT3) in the county of Nord-Trondelag, Norway	849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users	2006-2008	Body Weight	Waist circumference	age, smoking, gender, education, physical exercise, frequency of alcohol use	Previous snus use	Never snus use	b	0.78	0.13	1.43		Yes	HUNT Research Centre, Nord-Trøndelag County Council, Central Norway Health Authority and the Norwegian Institute of Public Health	"After adjusting statistically for major confounding variables, Norwegians who use snus extensively have a mixed profile in terms of cardiovascular risk: slightly higher waist circumference and systolic blood pressure but also higher high-density lipoprotein-cholesterol."
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		Body Weight	Waist circumference	age, smoking, gender, education, physical exercise, frequency of alcohol use	Sometimes snus use	Never snus use	b	-0.29	-1.04	0.45		No		"The significant associations between snus use and the cardiovascular risk factors we found were generally quite weak, and not particularly consistent." Stratified results by gender provided in Table 3
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		Body Weight	Waist circumference	age, smoking, gender, education, physical exercise, frequency of alcohol use	Daily snus use	Never snus use	b	-0.32	-0.98	0.35		No		
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		Body Weight	Waist circumference	age, smoking, gender, education, physical exercise, frequency of alcohol use	Extensive snus use	Never snus use	b	1.38	0.59	2.17		Yes		
	Weak	Cross-sectional study design, 53% participation rate-lower among				849 Extensive snus users, 1,214 daily snus users, 941 sometimes		Body Weight	Waist circumference	age, gender, education, physical exercise, frequency of alcohol	No previous current tobacco use	Current snus only	b	-0.41	-0.97	0.15		No		

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		younger (selection bias)				snus users, 1,265 previous snus users				use										
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		Body Weight	Waist circumference	age, gender, education, physical exercise, frequency of alcohol use	Current smoking and snus use	Current snus only	b	0.1	-0.73	0.93		No		
	Weak	Cross-sectional study design, 53% participation rate-lower among younger (selection bias), adjusted for smoking				849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	HDL-cholesterol	age, smoking, gender, education, physical exercise, frequency of alcohol use	Previous snus use	Never snus use	b	0.19	-0.52	0.9		No		
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	HDL-cholesterol	age, smoking, gender, education, physical exercise, frequency of alcohol use	Sometimes snus use	Never snus use	b	0.95	0.14	1.76		Yes		
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	HDL-cholesterol	age, smoking, gender, education, physical exercise, frequency of alcohol use	Daily snus use	Never snus use	b	0.92	0.2	1.64		Yes		
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	HDL-cholesterol	age, smoking, gender, education, physical exercise, frequency of alcohol use	Extensive snus use	Never snus use	b	1.03	0.17	1.89		Yes		
	Weak	Cross-sectional study design, 53% participation rate-lower among younger (selection bias)				849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	HDL-cholesterol	age, gender, education, physical exercise, frequency of alcohol use	No previous current tobacco use	Current snus only	b	-0.81	-1.41	-0.21		Yes		
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265		CV Effects	HDL-cholesterol	age, gender, education, physical exercise, frequency of alcohol use	Current smoking and snus use	Current snus only	b	-1.57	-2.46	-0.69		Yes		

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						previous snus users														
	Weak	Cross-sectional study design, 53% participation rate-lower among younger (selection bias), adjusted for				849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Triglycerides	age, smoking, gender, education, physical exercise, frequency of alcohol use	Previous snus use	Never snus use	b	5.86	0.96	10.76		Yes		
	Weak	smoking				849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Triglycerides	age, smoking, gender, education, physical exercise, frequency of alcohol use	Sometimes snus use	Never snus use	b	6.87	1.26	12.47		Yes		
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Triglycerides	age, smoking, gender, education, physical exercise, frequency of alcohol use	Daily snus use	Never snus use	b	-2.78	-7.77	2.21		No		
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Triglycerides	age, smoking, gender, education, physical exercise, frequency of alcohol use	Extensive snus use	Never snus use	b	3.24	-2.7	9.19		No		
	Weak	Cross-sectional study design, 53% participation rate-lower among younger (selection bias)				849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Triglycerides	age, gender, education, physical exercise, frequency of alcohol use	No previous current tobacco use	Current snus only	b	-2.82	-7.05	1.41		No		
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Triglycerides	age, gender, education, physical exercise, frequency of alcohol use	Current smoking and snus use	Current snus only	b	9.75	3.5	15.99		Yes		
	Weak	Cross-sectional study design, 53% participation rate-lower among younger (selection bias), adjusted for				849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Systolic blood pressure (SBP)	age, smoking, gender, education, physical exercise, frequency of alcohol use	Previous snus use	Never snus use	b	-0.89	-1.8	0.03		No		

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	Weak	smoking				849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Systolic blood pressure (SBP)	age, smoking, gender, education, physical exercise, frequency of alcohol use	Sometimes snus use	Never snus use	b	0.94	-0.1	1.99		No		
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Systolic blood pressure (SBP)	age, smoking, gender, education, physical exercise, frequency of alcohol use	Daily snus use	Never snus use	b	0.44	-0.46	1.37		No		
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Systolic blood pressure (SBP)	age, smoking, gender, education, physical exercise, frequency of alcohol use	Extensive snus use	Never snus use	b	1.98	0.87	3.1		Yes		
	Weak	Cross-sectional study design, 53% participation rate-lower among younger (selection bias)				849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Systolic blood pressure (SBP)	age, gender, education, physical exercise, frequency of alcohol use	No previous current tobacco use	Current snus only	b	-0.77	-1.55	0		No		
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Systolic blood pressure (SBP)	age, gender, education, physical exercise, frequency of alcohol use	Current smoking and snus use	Current snus only	b	-0.66	-1.81	0.48		No		
	Weak	Cross-sectional study design, 53% participation rate-lower among younger (selection bias), adjusted for smoking				849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Diastolic blood pressure (DBP)	age, smoking, gender, education, physical exercise, frequency of alcohol use	Previous snus use	Never snus use	b	0.1	-0.5	0.69		No		
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Diastolic blood pressure (DBP)	age, smoking, gender, education, physical exercise, frequency of alcohol use	Sometimes snus use	Never snus use	b	-1.05	-1.73	0.36		No		
	Weak					849 Extensive		CV Effects	Diastolic blood	age, smoking,	Daily snus use	Never snus use	b	-0.37	-0.98	0.24		No		

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						snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users			pressure (DBP)	gender, education, physical exercise, frequency of alcohol use										
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Diastolic blood pressure (DBP)	age, smoking, gender, education, physical exercise, frequency of alcohol use	Extensive snus use	Never snus use	b	0.32	-0.4	1.05		No		
	Weak	Cross-sectional study design, 53% participation rate-lower among younger (selection bias)				849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Diastolic blood pressure (DBP)	age, gender, education, physical exercise, frequency of alcohol use	No previous current tobacco use	Current snus only	b	-0.5	-1.01	0.01		No		
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		CV Effects	Diastolic blood pressure (DBP)	age, gender, education, physical exercise, frequency of alcohol use	Current smoking and snus use	Current snus only	b	-1.67	-2.42	-0.91		Yes		
	Weak	Cross-sectional study design, 53% participation rate-lower among younger (selection bias), adjusted for smoking				849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		Diabetes/MetSy	Non-fasting glucose	age, smoking, gender, education, physical exercise, frequency of alcohol use	Previous snus use	Never snus use	b	0.7	-0.44	1.85		No		
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		Diabetes/MetSy	Non-fasting glucose	age, smoking, gender, education, physical exercise, frequency of alcohol use	Sometimes snus use	Never snus use	b	1.01	-0.3	2.32		No		
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		Diabetes/MetSy	Non-fasting glucose	age, smoking, gender, education, physical exercise, frequency of alcohol use	Daily snus use	Never snus use	b	-0.51	-1.68	0.66		No		
	Weak					849 Extensive snus users, 1,214 daily		Diabetes/MetSy	Non-fasting glucose	age, smoking, gender, education,	Extensive snus use	Never snus use	b	-1.31	-2.7	0.08		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						snus users, 941 sometimes snus users, 1,265 previous snus users				physical exercise, frequency of alcohol use										
	Weak	Cross-sectional study design, 53% participation rate-lower among younger (selection bias)				849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		Diabetes/MetSy	Non-fasting glucose	age, gender, education, physical exercise, frequency of alcohol use	No previous current tobacco use	Current snus only	b	0.13	-0.83	1.1		No		
	Weak					849 Extensive snus users, 1,214 daily snus users, 941 sometimes snus users, 1,265 previous snus users		Diabetes/MetSy	Non-fasting glucose	age, gender, education, physical exercise, frequency of alcohol use	Current smoking and snus use	Current snus only	b	0.48	-0.95	1.91		No		
Ozga JE, Felicione NJ, Elswick D and Blank MD. 2016. Acute effects of snus in never-tobacco users: a pilot study. American Journal of Drug and Alcohol Abuse. Department of Psychology, West Virginia University, Morgantown, WV, USA: Taylor and Francis Ltd.	Moderate	Participants may have experienced "carryover effects" from previously consumed pouches, small sample size	Swedish snus (General White Large)	Clinical trial	6 men and five women, aged 19-26, who reported fewer than 100 lifetime uses of tobacco, and no tobacco in the past 3 months.	6 men and five women consumed six doses: 0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session	Not stated	CV Effects	Heart rate	None	0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session. 24 mg nicotine over the last 4 hours of the 5-hour session, with ~20–25 minutes separating the end of a pouch and the start of the next pouch.	Differences examined across dose groups	Dose Time Dose x Time				0.012 0.001 0.018	Yes	West Virginia University Department of Psychology	"A significant Dose X Time interaction was observed for HR. As shown in Figure 1A, HR levels generally decreased from pre- to post-dose for the initial snus doses, but then increased toward the end of session. Increases in HR from pre- to post-pouch were significant only for the sixth and final dose (8.0 mg nicotine) (Tukey's HSD; $p < .05$)." "Significant increases in physiological response at some doses suggest that users were exposed to pharmacologically active doses of nicotine. The lack of reliable subjective effects may be the product of the dosing regimen or the relatively small sample size."
	Moderate					6 men and five women consumed six doses: 0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session		CV Effects	Systolic blood pressure (SBP)	None	0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session. 24 mg nicotine over the last 4 hours of the 5-hour session, with ~20–25 minutes separating the end of a pouch and the start of the next pouch.	Differences examined across dose groups	Dose Time Dose x Time				<0.001 0.003 0.014	Yes		"A significant Dose X Time interaction was also observed for SBP. Figure 1B shows that SBP increased from pre- to post-pouch at nearly every active dose. Collapsed across dose, average SBP was 116.9 mmHg (SEM = 1.8) at pre-pouch and 120.1 mmHg (SEM = 1.9) post-pouch. Still, these increases were reliable only for the sixth and final dose (8.0 mg nicotine) (Tukey's HSD; $p < .05$)." "Significant increases in physiological response at some doses suggest that users were exposed to pharmacologically active doses of nicotine. The lack of reliable subjective effects may be the product of the dosing regimen or the relatively small sample size."

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
	Moderate					6 men and five women consumed six doses: 0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session		CV Effects	Diastolic blood pressure (DBP)	None	0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session. 24 mg nicotine over the last 4 hours of the 5-hour session, with ~20–25 minutes separating the end of a pouch and the start of the next pouch.	Differences examined across dose groups	Dose Time Dose x Time				0.021 0.204 0.634	Yes		"For DBP, a significant main effect of Dose was observed (see Figure 1C). Collapsed across time, average DBP was 62.6 mmHg (SEM = 1.6) for 0.0 mg nicotine, 59.2 mmHg (SEM = 1.7) for 1.6 mg nicotine, 62.8 mmHg (SEM = 1.6) for 3.2 mg nicotine, 61.7 mmHg (SEM = 1.4) for 4.8 mg nicotine, 63.1 mmHg (SEM = 1.5) for 6.4 mg nicotine, and 66.9 mmHg (SEM = 1.5) for 8.0 mg nicotine. Average DBP for the 8.0 mg nicotine dose was significantly higher than that for all other doses (Tukey's HSD; $p < .05$)." "Significant increases in physiological response at some doses suggest that users were exposed to pharmacologically active doses of nicotine. The lack of reliable subjective effects may be the product of the dosing regimen or the relatively small sample size."
	Moderate					6 men and five women consumed six doses: 0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session		Other	Nauseous	None	0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session. 24 mg nicotine over the last 4 hours of the 5-hour session, with ~20–25 minutes separating the end of a pouch and the start of the next pouch.	Differences examined across dose groups	Dose Time Dose x Time				0.157 0.082 0.113	No		"Significant increases in physiological response at some doses suggest that users were exposed to pharmacologically active doses of nicotine. The lack of reliable subjective effects may be the product of the dosing regimen or the relatively small sample size."
	Moderate					6 men and five women consumed six doses: 0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session		Other	Dizzy	None	0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session. 24 mg nicotine over the last 4 hours of the 5-hour session, with ~20–25 minutes separating the end of a pouch and the start of the next	Differences examined across dose groups	Dose Time Dose x Time				0.0284 0.112 0.734	No		

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											pouch.									
	Moderate					6 men and five women consumed six doses: 0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session		Other	Lightheaded	None	0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session. 24 mg nicotine over the last 4 hours of the 5-hour session, with ~20–25 minutes separating the end of a pouch and the start of the next pouch.	Differences examined across dose groups	Dose Time Dose x Time				0.308 0.061 0.820	No		
	Moderate					6 men and five women consumed six doses: 0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session		Other	Nervous	None	0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session. 24 mg nicotine over the last 4 hours of the 5-hour session, with ~20–25 minutes separating the end of a pouch and the start of the next pouch.	Differences examined across dose groups	Dose Time Dose x Time				0.349 0.337 0.254	No		
	Moderate					6 men and five women consumed six doses: 0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session		Other	Sweaty	None	0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session. 24 mg nicotine over the last 4 hours of the 5-hour session, with ~20–25 minutes separating the end of a pouch and the start of the next pouch.	Differences examined across dose groups	Dose Time Dose x Time				0.316 0.331 0.331	No		
	Moderate					6 men and five women consumed		Other	Headache	None	0.0, 1.6, 3.2, 4.8, 6.4, and	Differences examined	Dose Time Dose x				0.170 0.116 0.505	No		

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						six doses: 0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session					8.0 mg nicotine in one session. 24 mg nicotine over the last 4 hours of the 5-hour session, with ~20–25 minutes separating the end of a pouch and the start of the next pouch.	across dose groups	Time						
	Moderate					6 men and five women consumed six doses: 0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session		Other	Excessive salivation	None	0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session. 24 mg nicotine over the last 4 hours of the 5-hour session, with ~20–25 minutes separating the end of a pouch and the start of the next pouch.	Differences examined across dose groups	Dose Time Dose x Time				0.751 0.035 0.174	Yes		
	Moderate					6 men and five women consumed six doses: 0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session		Other	Heart Pounding	None	0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session. 24 mg nicotine over the last 4 hours of the 5-hour session, with ~20–25 minutes separating the end of a pouch and the start of the next pouch.	Differences examined across dose groups	Dose Time Dose x Time				0.264 0.397 0.474	No		
	Moderate					6 men and five women consumed six doses: 0.0, 1.6, 3.2, 4.8, 6.4, and		Other	Confused	None	0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session.	Differences examined across dose groups	Dose Time Dose x Time				0.325 0.245 0.323	No		

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						8.0 mg nicotine in one session					24 mg nicotine over the last 4 hours of the 5-hour session, with ~20–25 minutes separating the end of a pouch and the start of the next pouch.									
	Moderate					6 men and five women consumed six doses: 0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session		Other	Weak	None	0.0, 1.6, 3.2, 4.8, 6.4, and 8.0 mg nicotine in one session. 24 mg nicotine over the last 4 hours of the 5-hour session, with ~20–25 minutes separating the end of a pouch and the start of the next pouch.	Differences examined across dose groups	Dose Time Dose x Time				0.331 0.361 0.558	No		
Palmisano S, Schwartzbaum J, Prochazka M, Pettersson D, Bergenheim T, Florentzson R, Harder H, Mathiesen T, Nyberg G, Siesjö P and Feychting M. 2012. Role of tobacco use in the etiology of acoustic neuroma. American Journal of Epidemiology, 175(12): 1243–1251.	Moderate	Potential selection bias (controls less likely to participate: 65% vs. 84%). Nonparticipants were likely to be of lower SES, which is associated with snuff use, and is probably independently associated with acoustic neuroma, no exclusive snuff group	Swedish "Snuff"	Case-control	451 patients diagnosed with acoustic neuroma and 710 population-based controls	Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers	2002-2007	Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education and smoking status	Ever snuff user	Never-user of snuff	OR (95% CI)	0.99	0.65	1.51		No	Swedish Council for Working Life and Social Research	"We observed no evidence of a role for snuff tobacco consumption in acoustic neuroma etiology."
	Moderate					Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers 37 exposed cases		Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education and smoking status	Former snuff user	Never-user of snuff	OR (95% CI)	1.22	0.71	2.1		No		
	Moderate					Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers		Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education	Current snuff user	Never-user of snuff	OR (95% CI)	0.94	0.57	1.55		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						40 exposed cases				and smoking status										
	Moderate					Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers 10 exposed cases		Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education and smoking status	Age started using snuff: <15	Never-user of snuff	OR (95% CI)	1.21	0.36	4.07		No		
	Moderate					Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers 28 exposed cases		Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education and smoking status	Age started using snuff: 15-19	Never-user of snuff	OR (95% CI)	0.95	0.53	1.68		No		
	Moderate					Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers 40 exposed cases		Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education and smoking status	Age started using snuff: ≥20	Never-user of snuff	OR (95% CI)	1.01	0.6	1.68	0.98 (trend)	No		
	Moderate					Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers 7 exposed cases		Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education and smoking status	Years since starting: <10	Never-user of snuff	OR (95% CI)	0.8	0.31	2.06		No		
	Moderate					Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers 15 exposed cases		Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education and smoking status	Years since starting: 10-19	Never-user of snuff	OR (95% CI)	1	0.45	2.19		No		
	Moderate					Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers 26 exposed		Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education and	Years since starting: 20-29	Never-user of snuff	OR (95% CI)	1.6	0.77	3.28		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						cases				smoking status										
	Moderate					Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers 30 exposed cases		Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education and smoking status	Years since starting: ≥30	Never-user of snuff	OR (95% CI)	0.86	0.51	1.65	.63 (trend)	No		
	Moderate					Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers 19 exposed cases		Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education and smoking status	Total years: <10	Never-user of snuff	OR (95% CI)	0.913	0.41	1.77		No		
	Moderate					Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers 21 exposed cases		Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education and smoking status	Total years: 10-19	Never-user of snuff	OR (95% CI)	1.2	0.6	2.42		No		
	Moderate					Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers 16 exposed cases		Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education and smoking status	Total years: 20-29	Never-user of snuff	OR (95% CI)	0.96	0.45	2.06		No		
	Moderate					Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers 16 exposed cases		Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education and smoking status	Total years: ≥30	Never-user of snuff	OR (95% CI)	0.91	0.46	1.82	.97 (trend)	No		
	Moderate					Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers 12 exposed cases		Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education and smoking	Years since stopped: ≥20	Never-user of snuff	OR (95% CI)	1.29	0.53	3.13		No		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
										status										
	Moderate					Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers 7 exposed cases		Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education and smoking status	Years since stopped: 10-19	Never-user of snuff	OR (95% CI)	0.64	0.24	1.68		No		
	Moderate					Cases: 78 snuff users, 152 nonusers Controls: 119 users, 239 nonusers 16 exposed cases		Other	Acoustic neuroma	Controls matched on gender, region, and age within 5 years. Adjusted for highest level of education and smoking status	Years since stopped: >1-9	Never-user of snuff	OR (95% CI)	1.56	0.68	3.59	.57 (trend)	No		
Parn T, Grau Ruiz R, Kunovac Kallak T, Ruiz JR, Davey E, Hreinsson J, Wanggren K, Salumets A, Sjostrom M, Stavreus-Evers A, Ortega FB, Altmae S, Pärn T, Grau Ruiz R, Kunovac Kallak T, Ruiz JR, Davey E, Hreinsson J, Wånggren K, Salumets A, Sjöström M, Stavreus-Evers A, Ortega FB and Altmäe S. 2015. Physical activity, fatness, educational level and snuff consumption as determinants of semen quality: findings of the ActiART study. Reproductive BioMedicine Online, 31(1): 108–119.	Weak	Cross-sectional design includes smokers, lack of control for potential confounders, small number of participants, generalizability a concern with IVF population, recall bias possible, unknown response rate		Cross-sectional	62 male non azoospermic partner from couples visiting IVF clinic for the first time in Uppsala University Hospital, Sweden	43 non-snuff users 17 snuff users	2011-2014	Reproductive	Semen volume	None	Snuff consumption	No snuff consumption	Pearson Correlation	-0.048		1.47		No	Karolinska Institutet Foundation grants, Estonian National Kristjan Jaak scholarship program, Spanish Ministry of Economy and Competitiveness, European Research Council, Marie Curie Actions, Intra-European Fellowships, Uppsala University, the Family Planning Foundation, Uppsala, Estonian Ministry of Education and Research	"In our study, snuff users had significantly lower sperm concentration, motile sperm number, motile sperm concentration and motile sperm percentage."
	Weak					43 non-snuff users 17 snuff users		Reproductive	Sperm concentration	None	Snuff consumption	No snuff consumption	Pearson Correlation	-0.314			0.006	Yes		
	Weak					43 non-snuff users 17 snuff users		Reproductive	Total sperm	None	Snuff consumption	No snuff consumption	Pearson Correlation	-0.299			0.002	Yes		
	Weak					43 non-snuff users 17 snuff users		Reproductive	Motile concentration	None	Snuff consumption	No snuff consumption	Pearson Correlation	-0.375			0.003	Yes		
	Weak					43 non-snuff users 17 snuff users		Reproductive	Total motile sperm	None	Snuff consumption	No snuff consumption	Pearson Correlation	-0.349			0.006	Yes		
	Weak					43 non-snuff users 17 snuff users		Reproductive	Total motility	None	Snuff consumption	No snuff consumption	Pearson Correlation	-0.299			0.02	Yes		
	Weak					43 non-snuff users 17 snuff users		Reproductive	Semen volume	None	Snuff consumption	No snuff consumption	ANOVA		~3.1 (2.64-3.55)	~3.0 (2.3-3.6)		No		
	Weak					43 non-snuff users 17 snuff users		Reproductive	Sperm concentration	None	Snuff consumption	No snuff consumption	ANOVA		~7 (6-8)	~4.5 (3-6.5)	0.02	Yes		
	Weak					43 non-snuff users 17 snuff users		Reproductive	Total sperm	None	Snuff consumption	No snuff consumption	ANOVA		~175 (125-225)	~100 (25-210)		No		
	Weak					43 non-snuff users 17 snuff users		Reproductive	Motile concentration	None	Snuff consumption	No snuff consumption	ANOVA		~5.2 (4.5-6.1)	~3 (1.75-4.75)	0.07	Yes		
	Weak					43 non-snuff users 17 snuff users		Reproductive	Total motile sperm	None	Snuff consumption	No snuff consumption	ANOVA		~4 (3.5-4.5)	~2.5 (1.6-3.6)	0.008	Yes		
	Weak					43 non-snuff users 17 snuff		Reproductive	Total motility	None	Snuff consumption	No snuff consumption	ANOVA		~58 (53-65)	~45 (35-55)	0.009	Yes		

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						users														
Pedersen W and von Soest T. 2014. Tobacco use among Norwegian adolescents: From cigarettes to snus. Addiction, 109(7): 1154–1162.	Weak	Cross-sectional design	Swedish "Snus"		6,217 Norwegian adolescents (aged 16-17) (population-based)	304 daily snus users / 2,303 no daily tobacco use	2010	Other	Depressive symptoms	gender, age, country of birth, alcohol intoxication, use of cannabis, conduct problems	Daily snus use	No daily tobacco use	OR (95% CI)	1.19	0.98	1.44		No	Not stated	Not addressed by authors
	Weak					304 daily snus users / 2,303 no daily tobacco use		Other	Depressive symptoms	gender, age, country of birth, alcohol intoxication, use of cannabis, conduct problems, parental characteristics, school adjustment, perceived social acceptance, sport and leisure-time activities	Daily snus use	No daily tobacco use	OR (95% CI)	1.27	1.06	1.51		Yes		See Table 3 in study for covariates in additional categories.
Pettersson K, Saers J, Lindberg E and Janson C. 2016. Sleep disturbances among Swedish soldiers after military service abroad. Upsala Journal of Medical Sciences, 121(1): 65–69.	Weak	Cross-sectional design, potential confounding (lack of information on combat experience, depression, anxiety, PTSD), number of exposed cases not provided	Swedish "Moist snuff"		1,080 Swedish soldiers and officers who had completed at least one period of military service abroad were compared with 26,723 Swedes from a general population sample	297 participants from the military population reported use of moist snuff (783 nonusers), while 2,886 from the general population reported use (23,837 nonusers) # of exposed cases was not provided	Not stated	Other	Snoring	Military assignment, age, sex, BMI, asthma history, smoking history, educational level, physical exercise	Daily moist snuff use	No current use of moist snuff	OR (95% CI)	1.28	1.15	1.41		Yes	EU FP6 project GA2LEN, the Centre for Allergy Research at Karolinska Institutet, the Swedish Heart Lung Foundation, the Swedish Heart and Lung Association, and the Swedish Asthma and Allergy Association	Veterans were combined with control group in these analyses. "The main finding in the present study was that the Swedish veterans had fewer problems with insomnia and daytime sleepiness than a matched control group from the general Swedish population." "Smoking and oral tobacco were related to a higher risk of snoring and DIS, which confirms the effects of smoke and nicotine on sleep (20,21)." "The Swedish veterans were almost three times more likely to use oral tobacco than the reference group."
	Weak					297 participants from the military population reported use of moist snuff (783 nonusers), while 2,886 from the general population reported use (23,837 nonusers) # of exposed cases was not provided		Other	Difficulty inducing sleep	Military assignment, age, sex, BMI, asthma history, smoking history, educational level, physical exercise	Daily moist snuff use	No current use of moist snuff	OR (95% CI)	1.65	1.48	1.83		Yes		
	Weak					297 participants		Other	Difficulty maintainin	Military assignment	Daily moist	No current	OR (95% CI)	0.74	0.67	0.82		Yes		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						from the military population reported use of moist snuff (783 nonusers), while 2,886 from the general population reported use (23,837 nonusers) # of exposed cases was not provided			g sleep	, age, sex, BMI, asthma history, smoking history, educational level, physical exercise	snuff use	use of moist snuff								
	Weak					297 participants from the military population reported use of moist snuff (783 nonusers), while 2,886 from the general population reported use (23,837 nonusers) # of exposed cases was not provided		Other	Early morning awakenings	Military assignment, age, sex, BMI, asthma history, smoking history, educational level, physical exercise	Daily moist snuff use	No current use of moist snuff	OR (95% CI)	0.81	0.72	0.92		Yes		
	Weak					297 participants from the military population reported use of moist snuff (783 nonusers), while 2,886 from the general population reported use (23,837 nonusers) # of exposed cases was not provided		Other	Insomnia	Military assignment, age, sex, BMI, asthma history, smoking history, educational level, physical exercise	Daily moist snuff use	No current use of moist snuff	OR (95% CI)	1.02	0.94	1.11		No		
	Weak					297 participants from the military population reported use of moist snuff (783 nonusers), while 2,886 from the		Other	Excessive daytime sleepiness	Military assignment, age, sex, BMI, asthma history, smoking history, educational level, physical exercise	Daily moist snuff use	No current use of moist snuff	OR (95% CI)	1.11	1.02	1.22		Yes		

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
						general population reported use (23,837 nonusers) # of exposed cases was not provided														
Rasouli B, Andersson T, Carlsson P-O, Grill V, Groop L, Martinell M, Midthjell K, Storm P, Tuomi T and Carlsson S. 2017. Use of Swedish smokeless tobacco (snus) and the risk of Type 2 diabetes and latent autoimmune diabetes of adulthood (LADA). Diabetic Medicine, 34(4): 514–521.	Moderate	Possible recall bias; small number of cases among never smokers	"Swedish smokeless tobacco (snus)"	Case-control (ESTRID) and cross-sectional (HUNT)	ESTRID/ANDIS: all people with incident latent autoimmune diabetes of adulthood (LADA) recorded into the All New Diabetes in Scania (ANDIS) study since 2010 (Scania is a region in Southern Sweden);a random sample of people with Type 2 diabetes; and diabetes-free controls randomly selected from the Scania population	200 LADA cases, 724 Type 2 diabetes cases, 699 controls	2010-2015	Diabetes/MetSy	Type 2 diabetes incidence, verified by blood sample	age, BMI, family history of diabetes	Current snus use, never smokers (27 cases/36 controls)	Never snus use, never smokers	OR (95% CI)	1.17 0.53	0.58 0.20	2.37 1.39		No	Swedish Medical Research Council; Swedish Research Council for Health, Working Life, and Welfare; AFA Insurance Company; Swedish Diabetes Association; ALF-Swedish Research Council; Research Grant from Swedish Government; HUNT Research Centre; Nord-Trondelag County Council; Norwegian Institute of Public Health; GlaxoSmith Kline Norway	The authors reported a lack of association between snus use and Type 2 diabetes and LADA. Analyses of smokers only or formerly smoking snus users showed associations with diabetes, but the association was not seen when analyses were restricted to never smokers. Smoking-adjusted results were not materially different from exclusive snus user results, and were higher powered.
											Former snus use, never smokers (11 cases/104 controls)									
	Moderate					200 LADA cases, 724 Type 2 diabetes cases, 699 controls		Diabetes/MetSy	Type 2 diabetes incidence, verified by blood sample	age, BMI, family history of diabetes	<5 boxes/week (ever snus users, 22 cases/46 controls)	Never snus use, never smokers	OR (95% CI)	0.83 1.01	0.41 0.42	1.71 2.41		No		
											5+ boxes/week (ever snus users, 16 cases, 26 controls)									
	Moderate					200 LADA cases, 724 Type 2 diabetes cases, 699 controls		Diabetes/MetSy	Type 2 diabetes incidence, verified by blood sample	age, BMI, family history of diabetes	<10 box-years (ever snus users, 13 cases/39 controls)	Never snus use, never smokers	OR (95% CI)	0.74 1.00	0.31 0.47	1.77 2.11		No		
											10+ box-years (ever snus users, 22 cases/32 controls)									
	Moderate					200 LADA cases, 724 Type 2 diabetes cases, 699 controls		Diabetes/MetSy	Latent autoimmune diabetes of adulthood (LADA) incidence	age, BMI, family history of diabetes	Current snus use, never smokers (13 cases/41 controls)	Never snus use, never smokers	OR (95% CI)	0.98 0.46	0.45 0.15	2.11 1.43		No		
											Former snus use, never smokers (4 cases/31 controls)									
	Moderate					200 LADA cases, 724 Type 2 diabetes cases, 699 controls		Diabetes/MetSy	Latent autoimmune diabetes of adulthood (LADA) incidence	age, BMI, family history of diabetes	<5 boxes/week (ever snus users, 10 cases/46 controls)	Never snus use, never smokers	OR (95% CI)	0.75 0.67	0.34 0.24	1.67 1.86		No		
											5+ boxes/we									

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
											ek (ever snus users, 6 cases, 26 controls)									
	Moderate					200 LADA cases, 724 Type 2 diabetes cases, 699 controls		Diabetes/MetSy	Latent autoimmune diabetes of adulthood (LADA) incidence	age, BMI, family history of diabetes	<10 box-years (ever snus users, 5 cases/39 controls) 10+ box-years (ever snus users, 11 cases/32 controls)	Never snus use, never smokers	OR (95% CI)	0.46 1.01	0.16 0.45	1.31 2.29		No		
	Weak	Cross-sectional measurements of exposure and outcome; recall bias more likely among prevalent cases				200 LADA cases, 724 Type 2 diabetes cases, 699 controls		Diabetes/MetSy	Type 2 diabetes (cross-sectional measurement)	age, BMI, family history of diabetes	Ever snus users among never-smokers (27 cases)	Never snus use, never smokers	OR (95% CI)	1.12	0.72	1.72		No		
	Weak					200 LADA cases, 724 Type 2 diabetes cases, 699 controls		Diabetes/MetSy	Type 2 diabetes (cross-sectional measurement)	age, BMI, family history of diabetes	Ever snus users among never-smokers, <3 boxes/week (23 cases) ever snus users among never-smokers, 3+ boxes/week (2 cases)	Never snus use, never smokers	OR (95% CI)	1.15 0.89	0.72 0.21	1.82 3.78		No		
Rygh E, Gallefoss F and Reiso H. 2016. Use of snus and smoking tobacco among pregnant women in the Agder counties. Tidsskrift for den Norske Laegeforening, 136(16): 1351–1355.	Weak	Non-English translation. Unclear if snuff group included occasional and/or daily users. No adjustment for potential confounders such as SES, and no quantitative details of results.	Swedish "Snus"	Cohort	10,583 births, with data obtained from electronic food records at Sorlandet Hospital, Norway.	351 daily snuff users before pregnancy, 141 during 1st trimester, and 90 during 3rd trimester	2012-2014	Reproductive	Birthweight and Apgar score (health summary of newborn)	NA	Snuff use	Non-users of snuff						No	The first author has received a scholarship from the Medical Association's general medical research committee	Translation: "The average birth weight for children of mothers who had smoked daily or occasionally in the last trimester was 3 331 g, against 3 533 non-smokers. The average reduction in birth weight of 202 g was statistically significant (p <0.001). No significant difference in birth weight was found between children of mothers who had used snuff and the children of those who had not used snuff. There was also no difference in Apgar score where mothers had used snuff or smoking tobacco in the last trimester, compared with non-users."
Skaug E-AE-A, Nes B, Aspenes ST and Ellingsen O. 2016. Non-Smoking tobacco affects endothelial function in healthy men in one of the largest health studies ever	Weak	Cross-sectional design, potential selection bias (self-selection of participants from the healthiest part of the population + exclusion of participants	Swedish "Snuff"	Cross-sectional	5,633 men and women from the HUNT Fitness study, a subset of participants from the third wave of the Nord-Trondelag Health Study (HUNT3)	238 exclusive snuff users, 21 dual users, 447 exclusive smokers, 886 non-users of tobacco	2006-2008	CV Effects	Endothelial Function: Flow mediated dilation (FMD) (percent difference in vessel diameter)	age, education, income, and physical activity index	Exclusive snuff	Non-user of tobacco	Difference (*b*)	-0.53	-1.09	0.02		No	HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology NTNU), Nord-Trøndelag County Council and	"In our study snuff-users had a clear tendency towards lower endothelial function compared to non-users, and were no better than in smokers, despite younger age and a more favourable cardiovascular risk profile. Inactive snuff-using men had lower endothelial function than their physically active counterparts, indicating that physical activity and cardiorespiratory fitness
	Weak					238 exclusive snuff users, 21 dual		CV Effects	Endothelial Function: Flow mediated	age, education, income, and	Dual users	Non-user of tobacco	Difference (*b*)	-0.93	-2.6	0.73		No		

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performed; the nord-trøndelag health study in Norway; HUNT3. PLoS ONE, 11(8): e0160205.		with established CVD)				users, 447 exclusive smokers, 886 non-users of tobacco			dilation (FMD) (percent difference in vessel diameter)	physical activity index									The Norwegian Institute of Public Health	modified the effect of snuff on endothelial function."
	Weak					238 exclusive snuff users, 21 dual users, 447 exclusive smokers, 886 non-users of tobacco		CV Effects	Endothelial Function: Flow mediated dilation (FMD) (percent difference in vessel diameter)	age, education, income	Exclusive snuff, recommended physical activity level	Non-user of tobacco	Difference (*b*)	-0.29	-1.25	0.68		No		
	Weak					238 exclusive snuff users, 21 dual users, 447 exclusive smokers, 886 non-users of tobacco		CV Effects	Endothelial Function: Flow mediated dilation (FMD) (percent difference in vessel diameter)	age, education, income	Exclusive snuff, not recommended physical activity level	Non-user of tobacco	Difference (*b*)	-0.83	-1.59	-0.06		Yes		
	Weak					238 exclusive snuff users, 21 dual users, 447 exclusive smokers, 886 non-users of tobacco		CV Effects	Endothelial Function: Flow mediated dilation (FMD) (percent difference in vessel diameter)	age, education, income	Exclusive snuff, high aerobic capacity	Non-user of tobacco	Difference (*b*)	-0.19	-0.96	0.57		No		
	Weak					238 exclusive snuff users, 21 dual users, 447 exclusive smokers, 886 non-users of tobacco		CV Effects	Endothelial Function: Flow mediated dilation (FMD) (percent difference in vessel diameter)	age, education, income	Exclusive snuff, low aerobic capacity	Non-user of tobacco	Difference (*b*)	-0.74	-1.55	0.07		No		
Varga T V, Hallmans G, Hu FB, Renström F and Franks PW. 2013. Smoking status, snus use, and variation at the CHRNA5-CHRNA3-CHRNB4 locus in relation to obesity: The GLACIER study. American Journal of Epidemiology, 178(1): 31–37.	Weak	Cross-sectional design (exposure and outcome assessed at baseline), lack of adjustment for potential confounders (alcohol consumption was positively associated, and diet was negatively associated with snus use - as was BMI)	Swedish "Snus (Oral moist tobacco)"	Cross-sectional	16,426 participants from the Gene-Lifestyle Interactions and Complex Traits Involved in Elevated Disease Risk (GLACIER) study, a population-based cohort nested within the Vasterbotten Health Survey in Northern Sweden	2,680 ever and 1,582 current snus users / 12,479 never users	1985-2004	Body Weight	BMI	None	Current snus users	Never snus users	b	0.35	0.12	0.58	0.003	Yes	Novo Nordisk, the Swedish Heart-Lung Foundation, the Swedish Diabetes Association, Påhlssons Foundation, the Swedish Research Council, Umeå Medical Research Foundation, and The Heart Foundation of Northern Sweden.	"In the present study, we identified an inverse association between smoking and BMI and a positive association between snus use and BMI. These findings are compatible with those reported elsewhere." "As shown in Table 3, the correlation coefficients differ in magnitude and sometimes direction between smoking status or snus use and the putative confounders, which supports our hypothesis that although cigarettes and snus share the factor that is believed to be causally related with obesity (i.e., nicotine), they do not share the same confounding factors in this population. Although it is possible that cigarettes contain active substances absent from snus that drive the interactions described above, it seems more plausible that it is the obesogenic correlates of snus (i.e., confounders) that underlie the association of snus with obesity, rather than

Reference	Evidence Quality Strong, Moderate, Weak, Excluded, Commentary	Limitations + Potential Biases, or reason for exclusion	Product Description (Brand and type of snus, as applicable, author description)	Study design	Population (description, and total number before exclusions)	Number of cases/controls or exposed / unexposed # exposed cases	Study period	Endpoint Category (Non-cancer Oral, Dental, Cancer, CVD, Heart/IHD, Stroke, CV Effects, Diabetes/MetSy, Body Weight, GI Effects, Reproductive, Other)	Endpoint Analyzed	Covariates	Exposed Group	Referent Group	Risk Estimate Description	Risk Estimate	LCL	UCL	p Value (if available)	Statistically Significant? (Yes/No)	Funding Source	Author Conclusion + Comments
Wilson KM, Markt SC, Fang F, Nordenvall C, Rider JR, Ye W, Adami H-O, Stattin P, Nyren O and Mucci LA. 2016. Snus use, smoking and survival among prostate cancer patients. International journal of cancer, 139(12): 2753–2759.	Moderate	Tobacco use after diagnosis was not assessed, only on average 20 years prior to diagnosis (potential misclassification), lack of covariate data with BMI assessed only at study entry	"Snus (Scandinavian smokeless tobacco)"	Cohort	Swedish construction workers admitted to cohort between 1971 and 1992. Total cohort included 336,831 construction workers. Nested study included 9,582 prostate cancer cases. Mean age of nested exclusive snus user cases: 71.3 years. Mean age of never tobacco user cases: 70.4 years.	460 exclusive snus users / 2,762 never-users.	1971-2007	Other	Overall mortality	Age group at diagnosis, time period of diagnosis, BMI, time between examination and diagnosis.	Exclusive snus users (full cohort; includes all 9,582 men diagnosed with prostate cancer during follow-up) n=261 exclusive snus user deaths	Never tobacco users n=1,207 never tobacco user deaths	HR (95% CI)	1.19	1.04	1.37		Yes	Prostate Cancer Foundation Young Investigator Awards, National Cancer Institute	a direct causal effect of snus." "We found that a history of both smoking and snus use was associated with increased risk of prostate cancer-specific mortality and total mortality among men with prostate cancer in a large cohort in Sweden. Our results suggest that nicotine or other carcinogens in smokeless tobacco products may promote cancer progression independent of the combustion products of tobacco smoke"
	Moderate					460 exclusive snus users / 2,762 never-users.		Other	Overall mortality	Age group at diagnosis, time period of diagnosis, BMI, time between examination and diagnosis, clinical risk category	Exclusive snus users (in subcohort with "clinical data," which includes 5,346 men diagnosed after 1995 with available tumor characteristics from the National Prostate Cancer Register) n=261 exclusive snus user deaths	Never tobacco users n=1,207 never tobacco user deaths	HR (95% CI)	1.15	0.88	1.51		No		
	Moderate					460 exclusive snus users / 2,762 never-users.		Other	Prostate cancer mortality	Age group at diagnosis, time period of diagnosis, BMI, time between examination and diagnosis.	Exclusive snus users (full cohort; includes all 9,582 men diagnosed with prostate cancer during follow-up) n=141 exclusive snus user deaths	Never tobacco users n=640 never tobacco user deaths	HR (95% CI)	1.24	1.03	1.49		Yes		
	Moderate					460 exclusive snus users / 2,762 never-users.		Other	Prostate cancer mortality	Age group at diagnosis, time period of diagnosis, BMI, time between examination and diagnosis, clinical risk category	Exclusive snus users (in subcohort with "clinical data," which includes 5,346 men diagnosed after 1995 with	Never tobacco users n=640 never tobacco user deaths	HR (95% CI)	1.28	0.88	1.88		No		

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											available tumor characteristics from the National Prostate Cancer Register) n=141 exclusive snus user deaths								
	Moderate					460 exclusive snus users / 2,762 never-users.		Other	Overall mortality among nonmetastatic risk groups (includes men in "low"/"intermediate"/"high" categories, excludes "regionally metastatic" and "distant metastases" classification)	Age group at diagnosis, time period of diagnosis, BMI, time between examination and diagnosis, clinical risk category	Exclusive snus users (in subcohort with "clinical data," which includes 5,346 men diagnosed after 1995 with available tumor characteristics from the National Prostate Cancer Register) n=25 exclusive snus user deaths	Never tobacco users n=107 never tobacco user deaths	HR (95% CI)	1.36	0.88	2.11		No		
	Moderate					460 exclusive snus users / 2,762 never-users.		Other	Prostate cancer mortality among nonmetastatic risk groups (includes men in "low"/"intermediate"/"high" categories, excludes "regionally metastatic" and "distant metastases" classification)	Age group at diagnosis, time period of diagnosis, BMI, time between examination and diagnosis, clinical risk category	Exclusive snus users (in subcohort with "clinical data," which includes 5,346 men diagnosed after 1995 with available tumor characteristics from the National Prostate Cancer Register) n=14 exclusive snus user deaths	Never tobacco users n=28 never tobacco user deaths	HR (95% CI)	3.17	1.66	6.06		Yes		
Wrangsjö K, Alderling M, Lindahl G, Meding B, Wrangsjo K, Alderling M, Lindahl G and Meding B. 2015. Hand	Moderate	Cross-sectional measurements of exposure and outcome; not possible to estimate	"snus (Swedish Moist Snuff)"	Cross-sectional	47,931 people aged 18-64 years randomly chosen from the Stockholm, Sweden population register. 27,466	2,925 daily exclusive snus users 431 daily dual users (snus/smoking) # exposed cases	2006	Other	Hand eczema (prevalence in past year)	Unclear; likely stress, obesity, and physical exercise	Daily exclusive snus use, total Daily exclusive snus use, men	No tobacco use	Prevalence proportion ratio (PPR), 95% CI	0.813 0.820 1.081	0.686 0.692 0.855	0.964 0.971 1.366	0.017 0.022 0.515	Yes Yes No	FORTE: The Swedish Research Council for Health, Working Life, and Welfare	The authors found no positive association between snus use and hand eczema.

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eczema and use of snus (Moist snuff) – A population-based study.		causality			respondents included in study.	reported as percentage: 7.5% of exclusive snus users were cases					Daily exclusive snus use, women									
Acta Dermato-Venereologica, 95(3): 298–302.	Moderate					2,925 daily exclusive snus users 431 daily dual users (snus/smoking) # exposed cases reported as percentage: 7.5% of exclusive snus users were cases		Other	Hand eczema (prevalence in past year)	Unclear; likely stress, obesity, and physical exercise	Daily dual use (snus+ smoking), total Daily dual use (snus+ smoking), men Daily dual use (snus+ smoking), women	No tobacco use	Prevalence proportion ratio (PPR), 95% CI	1.187 1.235 0.883	0.851 0.886 0.474	1.655 1.722 1.647	0.313 0.214 0.697	No No No		The authors found no positive association between snus use and hand eczema or psoriasis.
	Moderate					2,925 daily exclusive snus users 431 daily dual users (snus/smoking) # exposed cases reported as percentage: 7.5% of exclusive snus users were cases		Other	Psoriasis (prevalence in past year)	Unclear; likely stress, obesity, and physical exercise	Exclusive snus use	No tobacco use	Prevalence proportion ratio (PPR), 95% CI	1.064	0.861	1.316	0.566	No		
Yang F, Pedersen NL, Ye W, Liu Z, Norberg M, Forsgren L, Trolle Lagerros Y, Bellocco R, Alfredsson L, Knutsson A, Jansson J-H, Wennberg P, Galanti MR, Lager ACJ, Araghi M, Lundberg M, Magnusson C and Wirdefeldt K. 2016. Moist smokeless tobacco (Snus) use and risk of Parkinson's disease. International journal of epidemiology.	Strong	Possible misclassification of exposure, as snus exposure was measured at baseline and may have changed over time. Different adjustments in different subcohorts. Relatively small number of exposed cases.	Swedish "Moist smokeless tobacco (Snus)"	Cohort	351,640 participants in the Swedish Collaboration on Health Effects of Snus Use (7 pooled cohort studies)	Among never smokers, fully adjusted model: 531 unexposed cases, 27 cases among ever snus users, 10 cases among former snus users, 17 cases among current snus users	Recruitment into 7 cohorts from 1978-2013	Other	Parkinson's disease incidence ICD-7: 350 ICD-8: 342 ICD-9: 332.0 ICD-10: G20	adjusted differently in different subcohorts; covariates include age, education, alcohol, physical activity, coffee intake	Ever snus users Former snus users Current snus users	Never tobacco users	HR (95% CI)	0.41 0.68 0.38	0.28 0.36 0.23	0.61 1.28 0.63	Not reported (p for heterogeneity among cohorts was reported; see Table 2)	Yes for ever and current; No for former	Swedish Research Council; regional agreement on medical training and clinical research between Stockholm County and Karolinska Institutet	"In conclusion, data from this large pooling project showed that non-smoking men who used snus had a substantially reduced risk of Parkinson's disease. Results also indicated an inverse dose-response relationship between use of snus and subsequent risk of Parkinson's disease. Our findings hence suggest that nicotine or other components of tobacco leaves may influence the development of Parkinson's disease and explain the inverse association between cigarette smoking and Parkinson's disease risk."
	Strong					Among never smokers, fully adjusted model: 531 unexposed cases, 27 cases among ever snus users, 10 cases among former snus users, 17 cases among current snus users		Other	Parkinson's disease incidence ICD-7: 350 ICD-8: 342 ICD-9: 332.0 ICD-10: G20	adjusted differently in different subcohorts; covariates include age, education, alcohol, physical activity, coffee intake	Light snus use (<2 cans/week; 7 cases) Moderate-heavy snus use (2+ cans/week, 9 cases)	Never tobacco users	HR (95% CI)	0.71 0.41	0.35 0.19	1.43 0.90	Not reported (p for heterogeneity among cohorts was reported; see Table 2)	No for light, Yes for moderate-heavy		
	Strong					Among never smokers,		Other	Parkinson's disease incidence	adjusted differently in different	1-20 years of snus use	Never tobacco users	HR (95% CI)	0.56 0.44	0.19 0.24	1.68 0.83	Not reported (p	No for 1-20 years, Yes for		

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						fully adjusted model: 531 unexposed cases, 27 cases among ever snus users, 10 cases among former snus users, 17 cases among current snus users			ICD-7: 350 ICD-8: 342 ICD-9: 332.0 ICD-10: G20	subcohorts; covariates include age, education, alcohol, physical activity, coffee intake	(6 cases) 21+ years of snus use (10 cases) Per year of using snus (16 cases)			0.96	0.94	0.98	for heterogeneity among cohorts was reported; see Table 2)	20+ years and per year		
Zandonai T, Tam E, Bruseghini P, Pizzolato F, Franceschi L, Baraldo M, Capelli C, Cesari P and Chiamulera C. 2016. The effects of oral smokeless tobacco administration on endurance performance. Journal of Sport and Health Science. Neuropsychopharmacology Laboratory, Department of Diagnostic and Public Health, University of Verona, Verona 37134, Italy: Elsevier B.V.	Moderate	small sample size	"Swedish snus, Catch White Eucalyptus" 8 mg nicotine	Clinical trial (double-blind, randomized crossover)	14 healthy male (18-45 years old) non-smokers and non-snus users that used snus or a snus placebo during exercise	12 participants (received either Swedish snus or Snus placebo, crossover)	Not stated	CV Effects	Heart rate (HR)	None	Swedish snus (SS)	Snus Placebo (SP)						No	University of Verona: Neurosciences, Biomedicine and Movement Sciences, and	"Q and HR in SS and SP conditions were not significantly different during the time trial."
	Moderate					12 participants (received either Swedish snus or Snus placebo, crossover)		CV Effects	Cardiac output (Q)	None	Swedish snus (SS)	Snus Placebo (SP)						No	Diagnostic and Public Health	
	Moderate					12 participants (received either Swedish snus or Snus placebo, crossover)		CV Effects	Systolic blood pressure (SBP)	None	Swedish snus (SS)	Snus Placebo (SP)						No		Not addressed by authors
	Moderate					12 participants (received either Swedish snus or Snus placebo, crossover)		CV Effects	Diastolic blood pressure (DBP)	None	Swedish snus (SS)	Snus Placebo (SP)					0.0068	Yes		"DBP at TTE [time to exhaustion] was significantly smaller in SS (73.10 ± 8.53 mmHg) than in SP (80.70 ± 8.56 mmHg) (p = 0.0068)." "In our non-smokers and non-snus users, nicotine induced diastolic hypotension at exhaustion."
	Moderate					12 participants (received either Swedish snus or Snus placebo, crossover)		Other	Respiratory responses (V_E, VO_2, VCO_2)	None	Swedish snus (SS)	Snus Placebo (SP)						No		"No significant differences between SP and SS were observed throughout the trials as for V_E, VO_2, and VCO_2. The average RER during exercise was the same (1.03 ± 0.04) in both SS and SP."