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Comparative disease risks associated with cigarette smoking and use of moist smokeless tobacco and snus: an umbrella review of epidemiological evidence from the United States and Western Europe

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Abstract

Background Cigarette smoking causes many serious diseases, including lung cancer, Chronic Obstructive Pulmonary Disease (COPD), mouth cancer, and tobacco-related heart disease. For adults who smoke and are unable or unwilling to quit all tobacco, switching completely from cigarettes to lower-risk smoke-free tobacco products, may reduce the health risks associated with tobacco use. In this review, we summarize epidemiological findings and provide evidence about the potential risk differential between cigarette smoking and the use of oral smoke-free tobacco products used in the US, Sweden, and Norway. Due to the wide range of compositions and health risks associated with ST products around the world and to provide evidence most relevant to the US and Western European populations, we focused on epidemiological studies conducted in these regions only.

Methods We used a two-stage approach to obtain recent risk estimates from relevant publications. First, we identified relevant meta-analyses and systematic reviews published from Jan. 2000- Feb. 2022. Second, we identified relevant individual studies published subsequent to the most recent meta-analysis or systematic review. Studies were selected using pre-defined inclusion/exclusion criteria. All eligible studies were assessed using National Heart, Lung, and Blood Institute Study Quality Assessment Tools. The relative risk estimates (RR) are reported compared to nonusers.

Results Our search identified 25 systematic reviews. Meta-analyses consistently showed large and statistically robust RRs for cigarette smoking and lung cancer (i.e., RR ranging from 10.1 to 14.6), whereas no statistically significant associations (null associations) were observed for ST products used in the US, Sweden, and Norway, congruent with the lack of pulmonary exposure with the use of oral tobacco products. For COPD, mouth cancer, and heart diseases, we consistently observed higher RRs for cigarette smoking compared to using these ST products. Findings from individual studies are generally in line with these results. Importantly, a few studies documented those individuals

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who stopped cigarette smoking and used ST products from these regions (i.e., individuals who switched) had lower risks of lung cancer, mouth cancer, and heart diseases compared to those who continued to smoke. We identified no such studies for COPD, yet the risk estimates were generally comparable between those who switched and those who quit all tobacco products.

Conclusion Findings from our literature review suggest that, relative to continued smoking, switching from cigarette smoking to the ST products commonly used in the US, Sweden, and Norway is associated with reduced risks of lung cancer, mouth cancer, COPD, and tobacco-related heart diseases. Future longitudinal studies that directly measure switching behavior will provide further evidence about the potential benefits of switching and the magnitude of the harm reduction potential.

Keywords Lung cancer, COPD, Heart diseases, Mouth cancer, Cigarette smoking, Smokeless tobacco, Review

Introduction

Cigarette smoking causes lung cancer, heart disease, chronic obstructive pulmonary disease (COPD) and other serious diseases. People who smoke are far more likely to develop such serious diseases than non-smokers [1–3]. Health risks from cigarette smoking are mainly attributed to the inhalation of cigarette smoke, which contains various harmful and potentially harmful constituents, many of which are produced by the combustion of tobacco [1]. Tobacco contains nicotine, which is addictive; but not directly responsible for tobacco-caused cancer, lung disease, or heart disease [4]. Indeed, public health experts acknowledge that tobacco products and other nicotine-containing products exist along a continuum of risk, ranging from combusted products (e.g., cigarettes) posing the highest risk and smoke-free (non-combusted) products at the lower end [4–8]. This presents an opportunity for tobacco harm reduction. While quitting all tobacco is the best option to reduce the risk of smoking related diseases, for adults who smoke and are unable or unwilling to quit all tobacco, switching from cigarettes to lower-risk smoke-free tobacco products may reduce the health risks associated with tobacco use [9].

Oral tobacco products are a type of smoke-free tobacco products that are not risk free; however, they are lower on the continuum of risk compared to cigarettes [4–8]. These smoke-free products are typically used orally by placing the product between the gum and the cheek or lip [10]. The saliva in the mouth extracts and carries nicotine and flavors, following an oral route, and they are discarded after use. The most common traditional oral tobacco products used in the United States (US) are called moist smokeless tobacco (MST) products which are sold loose with fine cut (sometimes referred to as snuff) or long cut formats and also available in a pouched format. However, other forms of smokeless tobacco (ST) products such as chewing tobacco and dry snuff have been used for decades in the US. Because not all epidemiological studies we reviewed in the US differentiate between specific ST products used or do not include only MST, for the purposes of this review, we will refer to all ST products used in the US as "ST Products (US)." Predominantly the only form ofST products historically used in Sweden and Norway are called snus, which is sold loose and pouched, and will be referred to as "snus (Sweden/Norway)" throughout this review. Snus has more recently become available in the US, although it has not been available long enough to be included in epidemiological studies in the US population.

While both MST products and snus contain cut tobacco that can be loose or pouched, they differ in their manufacturing and compositions. The main difference between MST products and snus is that MST products typically contain both air-cured and fire-cured tobaccos that are fermented, whereas snus typically contains air-cured tobaccos that are heat treated (pasteurized). While both MST products and snus expose users to harmful and potentially harmful constituents, snus generally contains much lower levels (e.g., Tobacco Specific Nitrosamines) compared to MST products [11–13].

Although there is overwhelming evidence [14] that quitting cigarette smoking results in significant reductions in tobacco-related morbidity and mortality, around 28 million adults in the US still to smoke [15]. These individuals, particularly those unable or unwilling to quit cigarettes, may benefit by completely switching from cigarettes to smoke-free tobacco products such as the ST products used in the US or snus used in Sweden and Norway [16]. According to published literature, a little more than 2% of adults in the US (approximately 5.2 million), predominately men, use some form of ST products [15]. In Sweden and Norway, snus is also more commonly used by men with recent estimates closer to 20% of adults using snus [17, 18].

ST products sold in the US and snus in Sweden and Norway are not safe. The U.S. Surgeon General and other public health authorities have determined that these products are addictive and can cause serious diseases, some of which are addressed by the federally mandated warnings. While there is debate on their role in tobacco harm reduction, the overwhelming scientific evidence suggests that ST products sold in the US and snus in

Sweden and Norway, are substantially less hazardous than cigarettes [6, 16, 19, 20]. Despite evidence demonstrating that these smoke-free tobacco products likely bear significantly less risk than cigarettes, misperceptions about their relative risks are widespread. Many adult tobacco consumers in the US who smoke perceive ST products equally or more harmful than cigarette smoking [21–23]. For example, using data from the Population Assessment of Tobacco and Heath (PATH) study, a nationally representative study among US adults, Fong and colleagues found that almost 90% of US adults held the misperception that ST product use was about the same (60.9%) or more harmful (23.9%) than cigarette smoking; only 8.6% believed ST product use was less harmful than cigarette smoking [23]. This is consistent with findings from a review that evaluated tobacco relative risk perception from 30 studies (83 samples) and found that respondents in a majority of just 18% of samples held the correct relative risk perception [24].

Studies have shown that ST products can be viable options for adults who smoke cigarettes and use of these oral tobacco products can lead to smoking cessation and reduced morbidity and mortality [17, 20, 25, 26]. While quitting tobacco use is the most effective means of reducing the risk of tobacco-related disease, misperception about the lower risks of ST products can deter adults who smoke from considering ST products as a harm-reduction alternative if they wish to continue to use tobacco products [27, 28].

Results from well-conducted population-based observational studies can provide evidence about the potential health effects of switching from cigarette smoking to traditional oral tobacco products. While there is substantial evidence of the elevated risks of lung cancer, COPD, mouth cancer, and heart diseases among individuals who smoke cigarettes and the health benefits of quitting all tobacco [1], few studies have systematically assessed the totality of evidence comparing the disease risks between cigarette smoking and ST product use as well as the potential harm reduction that may occur when adults who smoke switch from cigarettes to these smoke-free alternatives. In this umbrella review, our aim was to summarize findings from epidemiologic studies conducted in the US, Sweden, and Norway on risks of these diseases associated with cigarette smoking, traditional oral tobacco products, and switching from cigarette smoking to these products to provide additional evidence about risk differential and highlight the potential benefits of switching from combustible cigarettes to ST products for adults who smoke and are unable or unwilling to quit all tobacco. Considering morbidity and mortality risks associated with tobacco use may go beyond lung cancer, COPD, mouth cancer, and heart diseases, we also summarize the literature on all-cause mortality, which refers to combined deaths from all documented causes and may include tobacco-related disease (e.g., respiratory) as well as conditions not related to tobacco use (e.g., accidents). All-cause mortality comparisons between tobacco users and nonusers help us understand the overall risks to health associated with these groups.

It is important to note that numerous studies have documented substantial differences in types, compositions, use behaviors, and health risks of ST products used around the world [29–33]. For example, substantially higher health risks have been associated with ST product use in South Asia and the eastern Mediterranean regions [29, 34, 35], where many common ST products (e.g., gutkha, zarda, paan, khaini, Toombak) contain high quantities of carcinogens, notably tobacco-specific nitrosamines and heavy metals, compared to products commonly used in western Europe and the US [33, 36–38]. Therefore, to provide evidence most relevant to the US and Western European populations, we focused on epidemiological studies conducted in these regions only. This enabled us to assess the comparative disease risks associated with cigarette smoking and the use of traditional oral tobacco products typically used in the US, Sweden, and Norway.

Materials and methods

General approach

In this umbrella review, we used a two-stage approach to identify and summarize relevant epidemiological evidence of risks of lung cancer, mouth cancer, COPD, and smoking-related heart diseases among individuals who use traditional oral tobacco products in the US, Sweden, and Norway as well as individuals who smoke cigarettes. Because oral tobacco products vary widely across countries, we limited studies on oral tobacco products to the US, Sweden, and Norway in order to produce findings most relevant to these populations [33, 36–38]. We searched for articles published since 2000 and indexed in Medline, Embase, and Scopus databases for broad coverage of scientific literature. Literature not indexed in those databases (e.g., grey literature) is not included in the review because we wanted to ensure that all sources of evidence had gone through the rigorous peer-review process. We begin with a focus on meta-analyses published since 2000 to align with the approach's increased use and popularity at that time and given that meta-analyses commonly include studies published far earlier. All publications from the literature search were assessed based on pre-defined inclusion/exclusion criteria (see Sect. 2.3).

In the first stage, we identified meta-analyses and systematic reviews published from January 2000 to February 2022 on the risk of lung cancer, COPD, mouth cancer, and heart diseases associated with cigarette smoking, ST product use, and snus use. We emphasize systematic

reviews and meta-analyses because they represent a higher level of evidence compared to individual studies [39] and provide efficient risk summaries. In the second stage, we identified individual studies published subsequent to the most recent meta-analysis or systematic review for each condition and for switching related estimates. While we focused on epidemiological evidence specific to smoking-related diseases, we also assessed the overall risk of ST products and snus compared to cigarettes by reviewing all-cause mortality associated with the use of these tobacco products.

Search strategy

The search strategy underwent development and refinement with librarian support. Strategy details, search strings, and details of articles collected are available in Supplemental materials. The stage 1 meta-analysis search strategy relied on controlled vocabulary indexing in the Medline and Embase databases, complemented by free-text searching among Medline records that have not yet been indexed. Additionally, analogous free-text searching was run in the Scopus database among records not indexed by either Medline or Embase.

For stage 2, we broke down the composite strategy used to search for meta-analyses or systematic reviews to query one disease at a time among individual studies. In place of the restriction to meta-analyses or systematic reviews, we employed a publication date range based on the coverage of the most recent review and included studies on a given outcome published after the coverage range of the most recent review. In addition, we also scanned references from relevant studies identified from these searches to seek additional publications that may meet our eligibility criteria.

By using this approach, we aim to identify relevant publications in an efficient manner. However, this approach can suffer from publication bias (studies with more positive findings are more likely to be published), language bias (studies published in non-English language are not included), database bias (articles not indexed in Medline, Embase, and Scopus are not included), and time-lag bias (articles in press or published after the completion of the search were not included), which are general limitations to most literature reviews. Of note, we searched MEDLINE, which is the primary component of PubMed, to focus on peer-reviewed and indexed literature. Although the Cochrane Library is a valuable source of high-quality systematic reviews, its scope is primarily focused on interventions and randomized controlled trials. Since our review aimed to assess the association between ST use and health outcomes—an area where randomized trials are not feasible—we chose to focus on systematic reviews based on observational evidence, which are more comprehensively indexed in MEDLINE, Embase, and Scopus. Moreover, systematic reviews published in the Cochrane Database are also indexed in MEDLINE and Embase, which we included in our search strategy. Therefore, while we did not search the Cochrane Library separately, we likely captured Cochrane reviews through our MEDLINE and Embase searches.

Eligibility criteria

Meta-analyses, systematic reviews, and individual studies that met the following inclusion criteria were considered:

a. studies conducted in humans;
b. published in English;
c. included primary research;
d. included relevant outcomes and tobacco exposure;
e. conducted among North American, Swedish, or Norwegian populations; and.
f. rated as adequate quality.

Meta-analyses, systematic reviews, and individual studies were excluded if they met the following conditions:

a. tobacco exposures did not include snus, chewing tobacco, oral snuff, unspecified ST, or cigarettes;
b. did not assess lung cancer, mouth cancer, COPD, smoking-related heart diseases (excluding cerebrovascular diseases, hypertension, or cardiac death), or all-cause mortality as outcomes;
c. did not provide risk estimate (e.g., relative risk, hazard ratio, odds ratio, etc.) for outcome specified in b for tobacco use specified in a;
d. not an epidemiological study conducted in the general population;
e. not original peer-reviewed studies, meta-analyses, or systematic reviews.

We first screened titles and abstracts to identify potential articles and then evaluated these articles for inclusion using above criteria by reading the full text.

Evaluation of quality and risk of biases

Quality of all eligible studies was assessed using National Heart, Lung, and Blood Institute Study Quality Assessment Tools [40]. These tools included 8 questions to evaluate meta-analyses (e.g., focused research question, publication bias, heterogeneity) and 14 questions for individual studies (e.g., well defined study population, temporality, appropriate exposure assessment). A 'yes' or 'no' assessment was issued for each quality and bias question for each study. Studies were considered as 'adequate' or 'inadequate' based on judgement of validity and potential for bias with comments recorded. The Supplemental material includes a list of all questions used to guide quality evaluation, documentation of the 'yes' or

'no' assessment for each question per study, and ultimate 'adequate' or 'inadequate' evaluation for each study.

Data extraction

For all included studies, we extracted comparative risk measures (and 95% confidence intervals, CI), such as relative risk, odds ratio, and hazard ratio along with information about the study, including authors, year of publication, country, study design, study population, sample size, tobacco product use, disease outcome, and covariates adjusted. Any disagreement in study selection, quality assessment, and data extraction were resolved by discussion between assessors.

Data synthesis and analysis

We used Forest Plots to visualize comparative risk measures from identified studies by each outcome (i.e., lung cancer, COPD, mouth cancer, and tobacco-related heart diseases). Because most published reviews and studies compared risks between users and nonusers of a product (e.g., cigarettes), we presented meta-analytic summary by tobacco products (i.e., cigarettes, ST, and snus).

In three studies [41–43], the original meta-analytic summary estimate included studies conducted outside of the US, Sweden, or Norway. For these studies, we generated meta-analytic summary estimates using comparative risk measures and their 95% confidence intervals from original publications of studies conducted in the US, Sweden, and Norway. We used random effect models to produce meta-analytic summary estimates [44] because heterogeneity test indicated large variations in estimates across studies (i.e., p values of heterogeneity tests < 0.05 and I^2 >75%) [45].

Results

We summarize epidemiological findings and provide evidence about the potential risk differential between cigarette smoking and the use of ST products sold in the US, Sweden, and Norway. We focus our review on lung cancer, COPD, mouth cancer, tobacco-related heart disease, and all-cause mortality.

Results of the literature search

Following the procedure described in the Methods section, we identified 25 systematic reviews and meta-analyses on the risk of lung cancer, COPD, mouth cancer, and tobacco-related heart diseases associated with cigarette smoking and the use of traditional oral tobacco products in the US, Sweden, and Norway; 4 of these 25 systematic reviews including one additional study identified through other methods assessed all-cause mortality. Figure 1depicts article identification, screening, and selection processes for stage 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) diagrams [46] and evidence tables summarizing the studies and findings from our stage 1 and stage 2 literature review are available in Supplemental material.

Results of the risk of bias assessment are included in evidence tables in Supplemental material. Included publications were at low risk for bias and only a single meta-analysis [47] was found to be inadequate and was excluded due to lack of systematic approach and other biases. Of the studies included, some risk of bias was observed. Using the National Heart, Lung, and Blood Institute Study Quality Assessment Tools [40] (see Supplemental material), we observed that several meta-analysis lacked dual review for study inclusion [43, 48–55] or dual reviewer quality appraisal for internal validity [43, 48–57]. Five meta-analyses lacked documentation of publication bias assessment [54, 56–59] and a single meta-analysis lacked an assessment of heterogeneity [54]. A few studies lacked a clearly defined [60], uniform [61] study population, or lacked satisfactory participation [62], or follow-up rate [63–66]; more studies did not include sample size justification [60–63, 65, 67–101] or blinded outcome assessment [62, 63, 67, 70, 71, 74–76, 79, 82–86, 88–90, 92, 96, 100–108]. Some studies lacked sufficient information on definition of exposures [99], lacked granularity in exposure levels [61, 64, 66, 73, 86, 88, 98, 109], or lacked a repeated exposure assessment [61, 64–66, 68–70, 72–74, 77, 78, 83–87, 91, 95, 97–99, 101–103, 109, 110]. In some studies, it was unknown if the exposure occurred before the measured outcome [73, 84, 86, 97, 110, 111] or if confounders were appropriately assessed [63, 64, 69, 85, 86].

Risk of lung cancer

Figure 2 summarizes the relative risk of morbidity and/or mortality of lung cancer from published meta-analyses collected during our review. Cigarette smoking estimates show a consistently and highly elevated risk of lung cancer (i.e., RR ranging from 10.1 to 14.6). In contrast, ST product (US) and snus (Sweden/Norway) estimates showed no statistically significant elevated risk.

NOTE: In our forest plot figures, a value of one represents a null relationship and is shown as a solid line. A value greater than one represents a positive association, and a value less than one represents an inverse association. The 95% confidence intervals represent the precision of the estimates. A 95% confidence interval including the null value (i.e., one) is not considered statistically significant. For studies that calculated risk estimates for more than one type of tobacco product (e.g., cigarettes, ST products, and snus), they are listed more than once in the figures. [1]ALCS Pooled estimates for studies conducted in the US using a random-effect meta-analysis model.

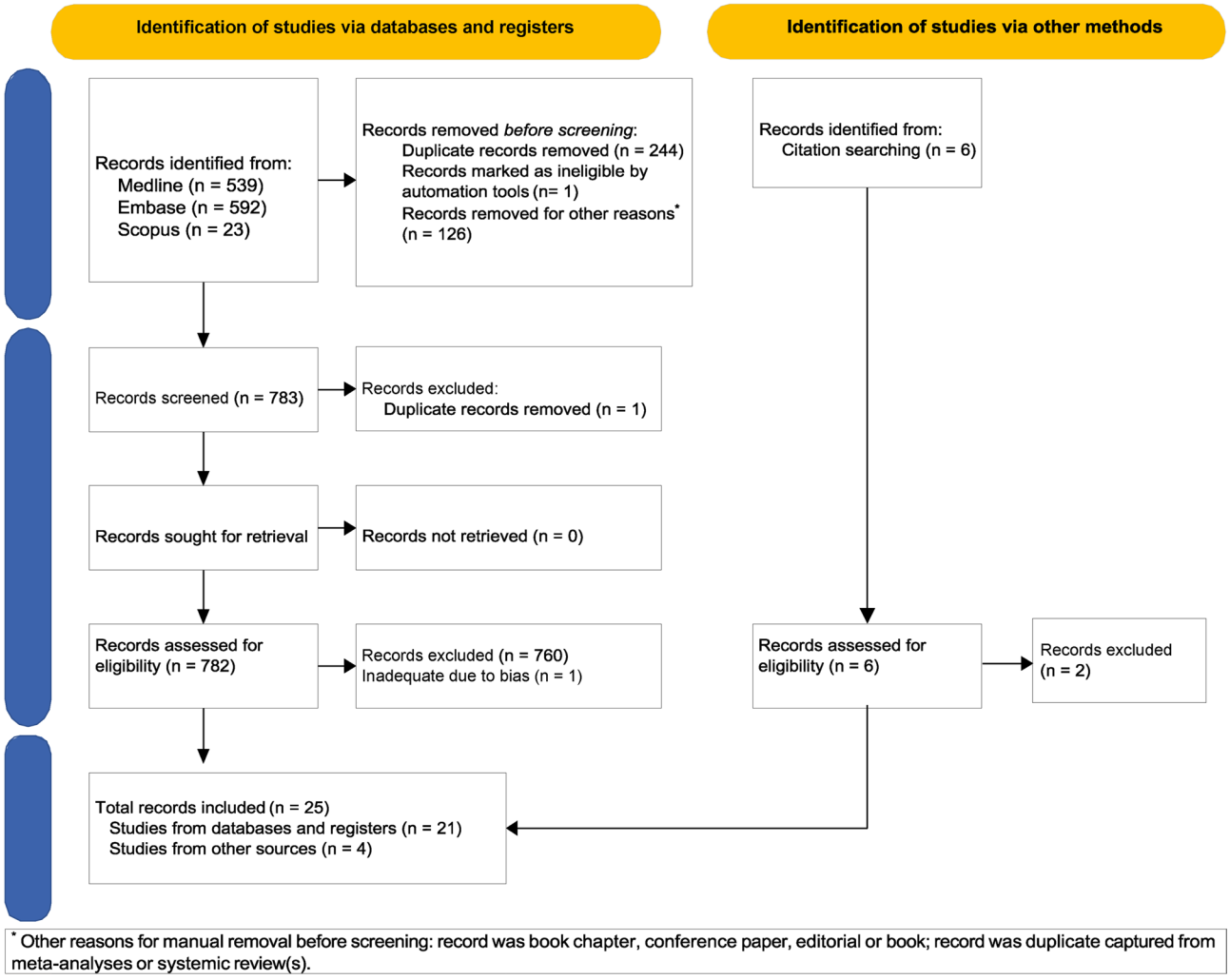

Fig. 1 Meta-analysis and systematic review PRISMA diagram

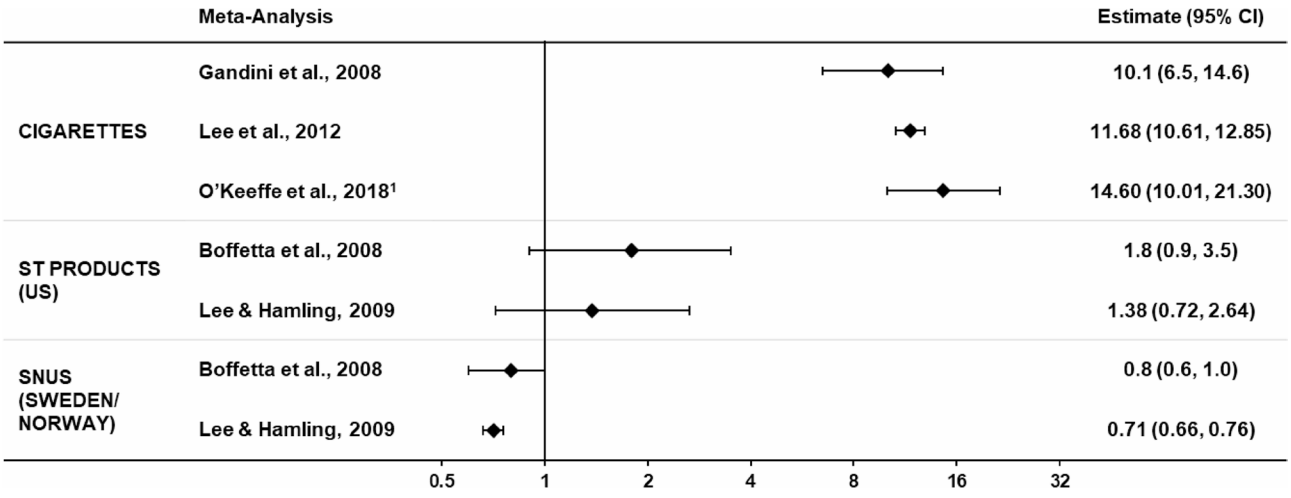

Fig. 2 Estimated relative risk of morbidity and/or mortality of *Lung Cancer* from published epidemiological meta-analyses on cigarette smoking and traditional oral tobacco products used in the US and Western Europe

Cigarette smoking

Our review of studies in the US, Sweden, and Norway identified three meta-analyses related to cigarette smoking, all of which found significantly elevated risk of lung cancer among smokers compared to non-smokers [41, 52, 112]. Despite variations in coverage of time periods and methodology across the three meta-analyses, all three studies consistently showed that individuals who smoked cigarettes were more than 10 times likely to have or die of lung cancer compared to individuals who did not smoke cigarettes. In addition, Lee and colleagues documented a gradient of decreasing risk of lung cancer with increasing duration of quitting smoking (quit ~ 3 years hazard ratio (HR) = 8.60, quit ~ 7 years HR = 5.08, quit ~ 12 years HR = 2.97) [52], providing further evidence of the role of cigarette smoking and the risk of lung cancer (see Fig. 2).

Our search identified six studies published after the most recent meta-analysis was conducted, including those from the National Institutes of Health-American Association of Retired Persons Diet and Health Study (NIH-AARP) Diet and Health cohort and the Framingham Heart Study Original and Offspring Cohorts [62, 63]. Findings from these studies aligned with findings from meta-analyses showing highly elevated risks of lung cancer among individuals who smoked. For example, Inoue-Choi et al. states "Associations were observed for lifelong smoking of ≤ 10 CPD [cigarettes per day] with lung cancer (HR = 9.65, 95% CI = 6.93–13.43)" [62]. These studies also showed a gradient of increasing risk of lung cancer with increasing exposure to cigarette smoking (measured as the frequency of smoking, duration of smoking, or pack-years) and decreasing duration of quitting smoking.

ST products (US)

During our review, we identified two meta-analyses on ST product use, both of which showed no statistically significant increase in lung cancer risk among individuals who used ST products compared to those who did not use ST products with point estimates of relative risk < 2 [53, 59] (see Fig. 2).

Our search identified one additional study published on ST product use and lung cancer after the most recent meta-analysis. This study found that males who switched from cigarette smoking to ST use (defined as currently used ST products, formerly smoked cigarettes, and had begun using ST at the time of or after they quit cigarette smoking) had an elevated lung cancer mortality (HR = 5.61) compared to those who had never used any tobacco products using data from the CPS-II cohort [113]. Also using data from the CPS-II study, Rostron and colleagues found that males who currently smoked had much higher risk of lung cancer compared males who had never smoked (HR = 23.26) [64]. These results are in line with findings from systematic reviews and suggest lower risk of lung cancer for males who switched from cigarette smoking to ST product use compared to those who continued to smoke. However, ST products are not risk free. For example, Henley observed that after 20 years of follow-up, switchers had a higher rate of death from lung cancer (HR 1.46, 95% CI 1.24 to 1.73) than those who quit all tobacco [113].

Snus (Sweden/Norway)

During our review, we identified two meta-analyses on snus use, both of which showed that individuals who used snus do not have an increase in risk of lung cancer compared to those who did not use snus after adjusting for smoking (e.g., RR = 0.71, 95% CI = 0.66 to 0.76) [53, 59](see Fig. 2). Our search did not identify any additional studies published on snus use and lung cancer after the most recent meta-analysis.

Based on these findings, it is reasonable to infer that ST product use in the US, Sweden, and Norway is associated with lower risks of lung cancer compared to cigarette smoking.

Risk of COPD

Figure 3 summarizes the relative risk of morbidity and/or mortality of COPD from published studies collected during our review. The cigarette smoking estimate shows an elevated risk of COPD (RR = 3.48) while in contrast, ST and snus estimates showed no or low risk.

NOTE: In our forest plot figures, a value of one represents a null relationship and is shown as a solid line. A value greater than one represents a positive association, and a value less than one represents an inverse association. The 95% confidence intervals represent the precision of the estimates. A 95% confidence interval including the null value (i.e., one) is not considered statistically significant. For studies that calculated risk estimates for more than one type of tobacco product (e.g., cigarettes, ST products, and snus), they are listed more than once in the figures. [1]Meta-analysis. Study was on morbidity and RRs were expressed relative to never smokers. [2]Study was on mortality with HRs relative to never use of ST. Estimates for ST and snus are from individual studies because no meta-analyses were identified from the literature search. [3] Study investigated the risk of COPD among switchers from cigarettes to ST compared to no tobacco use. Switchers were defined as smokers who were former exclusive cigarette smokers and were currently using ST and having begun doing so at the time of or after they quit exclusive cigarette smoking. Estimates from the fully adjusted model provided. [4] The outcome of the Roosaar et al. study is respiratory death, which includes COPD.

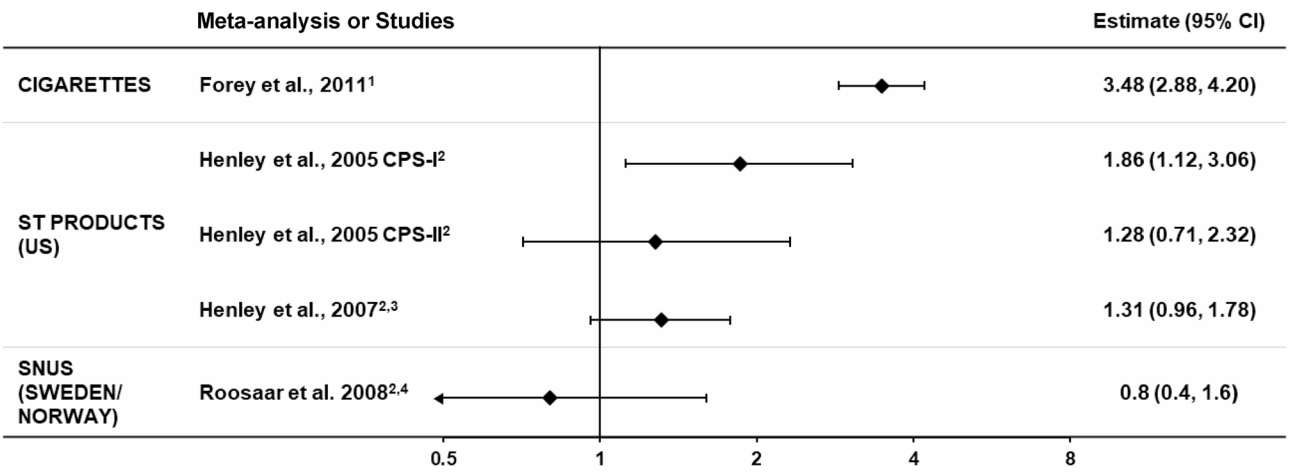

Fig. 3 Estimated relative risk of morbidity and/or mortality of *COPD* from published epidemiological analysis on cigarette smoking and traditional oral tobacco products used in the US and Western Europe

Cigarette smoking

Based on the meta-analysis identified from our literature search, individuals who had ever smoked were 3.5 times likely to have COPD (RR = 3.48, 95% CI = 2.88 to 4.20) compared to those who had never smoked when pooling results from 35 studies conducted in North America published by 2006 [114]. Further analysis with all studies combined showed a clear gradient in the relationship between cigarette consumption and the risk of COPD where pooled relative risk estimates (vs. individuals who had never smoked) increased from 2.89 (95% CI = 2.41 to 3.45), to 6.21 (95% CI = 4.72 to 8.17), and to 9.50 (95% CI = 7.38 to 12.22) for those who smoked approximately 5, 20, and 45 cigarettes per day, respectively (see Fig. 3) [114].

Findings from several individual studies published after 2006 were consistent with the conclusion drawn from the meta-analysis, with each showing elevated risks of COPD among individuals who smoked (estimated relative risks varied from 2.4 to 45, with approximately half of the studies documenting a 5-fold or greater risk). For example, in a nationally representative longitudinal study of 357,420 participants, Christensen and colleagues found a substantially elevated risk of developing COPD among individuals who smoked daily (HR = 11.62; 95% CI = 10.24 to 13.18) and non-daily (HR = 7.66; 95% CI = 6.09 to 9.64) compared to individuals who had never used tobacco [115]. Focusing on mortality, Thun and colleagues used data from large nationally representative cohorts and documented that individuals who currently smoked had greater than 20-fold risk of dying from COPD compared to those who had never smoked (HR = 22.4 for females and HR = 25.6 for males) [116]. Moreover, there was a gradient in the risk of dying from COPD by the age of quitting smoking. This is congruent with findings from another study showing that the duration of smoking was a robust predictor for the risk of COPD [117].

ST products (US)

ST product use in the US is largely not associated with an elevated risk of COPD based on the two publications identified from our literature review (Fig. 3). One study on the risk of COPD mortality and ST product use conducted separate analyses using data from Cancer Prevention Study (CPS) -I and CPS-II cohorts, respectively. Another study focused on COPD mortality among former cigarette smokers who substitute ST products for cigarette smoking. No meta-analysis was identified on the risk of COPD associated with ST products. A lack of plausible mechanism linking ST products and COPD may have contributed to the paucity of evidence (see Fig. 3) [118].

With a focus on COPD mortality and ST product use, Henley and colleagues found that exclusive ST product use (including snuff and chewing tobacco) was not statistically significantly associated with a higher risk of dying from COPD (HR = 1.28, 95% CI = 0.71 to 2.32) among men who never used other tobacco products after adjusting for relevant demographic characteristics (e.g., age, race, educational level, employment status and type) and lifestyle variables related to health (e.g., BMI, fat consumption, fruit/vegetable intake, and aspirin use) when using data from the CPS-II. These results contrast with findings from Cancer Prevention Study I (CPS-I, 1959–1972) from which an elevated risk of 1.86 (95% CI = 1.12 to 3.06) was observed for ST product use after adjusting for covariates. We consider the result from CPS-II to be more informative because (a) the ST product use question in CPS-II study was more sensitive in identifying (and therefore excluding) former ST product users, and (b) CPS-II estimate was adjusted for employment, which

can be important for studies on COPD due to occupation-related exposures, whereas CPS-I estimate was not. Furthermore, based on data from CPS-II, there was no evidence of an increasing risk of COPD with increasing frequency or duration of ST product use: none of the estimates were statistically significant, and the largest point estimate (2.45, 95% CI = 0.77–7.74) was seen for the least frequent user group, which does not support any "dose-response" relationship (estimates for the intermedium and the most frequent group were 1.02 and 1.41, respectively.) [65][1]. Therefore, findings from CPS studies do not appear to support a causal relationship between ST product use and COPD in the US.

In addition, another study investigated the risk of COPD among individuals who switched from smoking to ST product use (defined as individuals who were former exclusive cigarette smokers and were currently using ST products and having begun doing so at the time of or after they quit exclusive cigarette smoking) and those who quit tobacco entirely using data from CPS-II [113]. This study found that after adjusting for history of smoking, demographics, and lifestyle variables, there were no differences in risks of COPD mortality between those who switched and those who quit tobacco entirely. Moreover, the death rate due to COPD among switchers reported in this study was lower compared to death rates due to COPD among current smokers reported in the Thun et al. study [116].

Snus (Sweden/Norway)

We did not identify any systematic review of the risk of COPD and snus use. We found one study on respiratory death, which includes death due to COPD, and snus use. In this population-based cohort study of Swedish males with almost 30 years of follow-up, ever (vs. never) snus use was not associated with respiratory death among individuals younger than 80 years of age (HR = 0.8, 95% CI = 0.4–1.6) (see Fig. 3). Among those who were 80 years of age or older, there was an elevated risk of respiratory death (HR = 1.8, 95% CI = 1.2–2.7), which, as the authors noted, may be attributed to potential confounding and higher tobacco specific nitrosamines in older products [66].

Based on these findings, it is reasonable to infer that the risk of COPD is higher among those who smoke cigarettes compared to those who use ST products (US) or snus (Sweden/Norway) but do not smoke.

Risk of mouth cancer

Mouth cancer, also referred to as oral cancer, includes various cancers diagnosed in the oral cavity (e.g., lips, gums, tongue, inner lining of cheeks, roof or floor of the mouth, and pharynx). Published literature reporting cancer in the oral cavity sometimes considers specific sites separately, while others have combined these sites. While we intended to focus on cancer of only the oral cavity, we included a discussion of head and neck cancer in a few individual studies because they were large studies that provided valuable insights.

Figure 4 summarizes the relative risk of morbidity and/or mortality of mouth cancer from published

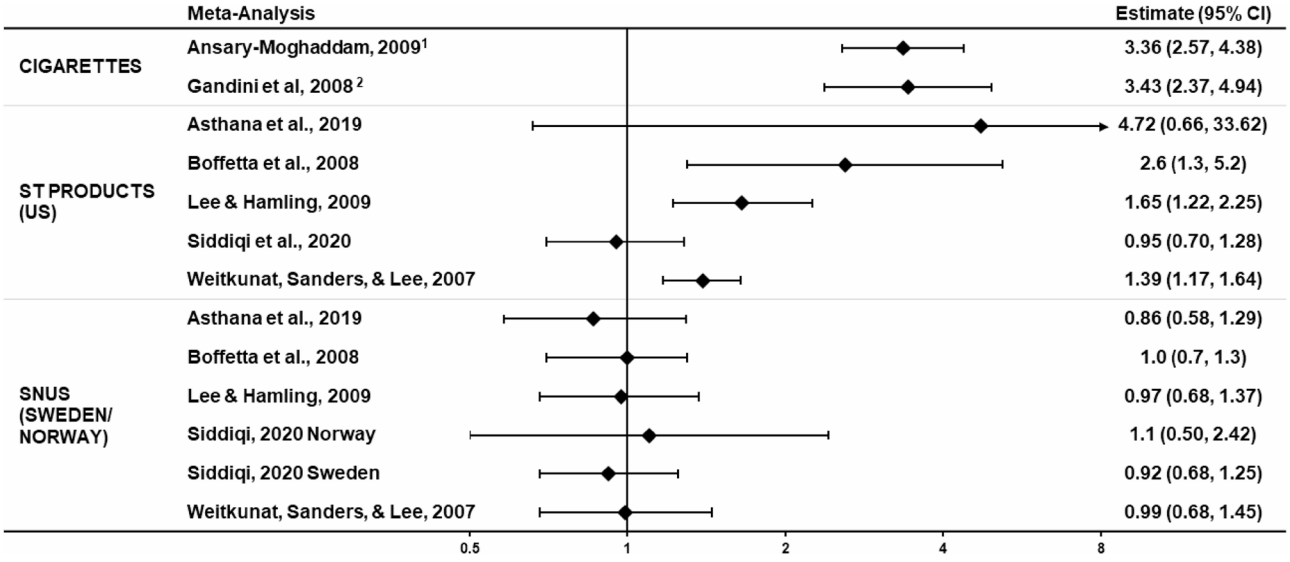

Fig. 4 Estimated relative risk of morbidity and/or mortality of *Mouth Cancer* from published epidemiological meta-analyses on cigarette smoking and traditional oral tobacco products used in the US and Western Europe

[1] The relationship between frequency of use and COPD using CPS-I was not reported.

meta-analyses collected during our review. Cigarette smoking estimates show a consistently elevated risk of mouth cancer while ST product (US) estimates were a mix of elevated and null results and snus (Sweden/Norway) estimates showed no elevated risk.

NOTE: In our forest plot figures, a value of one represents a null relationship and is shown as a solid line. A value greater than one represents a positive association, and a value less than one represents an inverse association. The 95% confidence intervals represent the precision of the estimates. A 95% confidence interval including the null value (i.e., one) is not considered statistically significant. For studies that calculated risk estimates for more than one type of tobacco product (e.g., cigarettes, ST products, and snus), they are listed more than once in the figures. [1]ALCS pooled estimates for studies conducted in the US using a random-effect meta-analysis model. [2]Estimate shown in the plot from the Gandini et al. study was for oral cavity cancers; the pooled estimate for pharynx cancers was 6.76 (95% CI = 2.86 to 15.98). All other estimates shown in the plot were for oral cavity and pharynx cancers combined.

Cigarette smoking

The two meta-analyses on cigarette smoking and mouth cancer showed highly consistent estimates of a 3.4-fold risk of mouth cancer among individuals who were currently smoking compared to those who had never smoked [43, 112][2]. Following the publication of these meta-analyses, several individual large-scale epidemiological studies have been published, including data from the NIH-AARP cohort, National Health Interview Study (NHIS) linked mortality, and CPS-II [64, 71, 72]. All of these studies consistently showed an elevated risk of mouth cancer (RR ranging from 3.6 to 4.8-fold) for cigarette smokers (See Supplementary Material, Table S3). The NIH-AARP study also showed incremental risks of mouth cancer with increasing pack-years and cigarettes smoked per day [72]. An additional two studies focusing on head and neck cancers, including mouth cancers, found elevated risk among individuals who were currently smoking (HR = 3.63, 95% CI = 2.16–6.12) and individuals who had ever smoked (OR = 2.47; 95% CI = 2.23 to 2.74 and HR = 2.47; 95% CI = 1.55 to 3.95) compared to those who had never smoked (see Fig. 4) [70, 73].

Overall, epidemiological evidence demonstrates an elevated estimated relative risk of mouth cancer among individuals who currently smoke compared to those who have never smoked.

[2] In order to create a US-specific estimate, we identified all estimates from US studies found by the author and calculated a pooled estimate random-effects meta-analysis.

ST products (US)

Of the five meta-analyses identified that included ST product use in the US, three showed elevated risks of mouth cancer among individuals who used ST products [53, 55, 59]. In the Lee and Hamling study, there was a significant association between ST product use and oropharyngeal cancer in the US (smoking adjusted RR = 1.65, 95% CI = 1.22–2.25); however, this became non-significant (RR = 1.04, 95% CI = 0.80–1.35) once additionally adjusted for alcohol consumption [53]. It should be noted that both the Lee and Hamling [53] and Boffetta et al. [59] meta-analyses included two studies conducted in the 1970 s and 1980 s among female users of snuff, including dry snuff with high tobacco specific nitrosamine concentrations, both of which found associations between snuff use and oral cancer contributing to the elevated risk represented in these meta-analyses [119, 120]. The more recent studies included in the meta-analysis by Lee and Hamling and Boffetta et al. showed no significant associations. Weitkunat performed a meta-analysis of studies published over a wide time frame (1920 to 2005) and determined a US-specific smoking-adjusted oral cancer estimate was RR = 1.39 (95% CI = 1.17–1.64) times higher in ST product users than non-users during the overall study time frame. Weitkunat also revealed a decreasing risk estimate over time among US and Scandinavian studies, especially in studies published after 1980 (see Fig. 4) [55].

Two meta-analyses showed a non-significant elevated risk of mouth cancer and ST product use in the US. The Asthana et al. meta-analysis showed an elevated but non-significant point estimate due to a very wide 95% CI. This was due in part to the inclusion of only three US studies with low numbers of cases and high heterogeneity, two of which included only female snuff users [120] or unclear exposure and smoking adjustment [121]. The Siddiqi et al. [29] meta-analysis showed a null association between mouth cancer and ST product use in the US. Siddiqi's meta-analysis updates US and worldwide ST product oral cancer estimates using studies from 1990 onward and found no elevated risk of oral cancer for ST products used in the US but elevated rates in the South Asia and eastern Mediterranean regions.

Two relevant studies were identified after the most recent meta-analysis. They provide additional information on ST product use and mouth cancer even though both focused on head and neck cancers [70, 73]. Wyss and colleagues did not find differences in the incidence of head and neck cancer between individuals who used snuff (OR = 1.58; 95% CI = 0.86–2.89) or chewing tobacco (OR = 0.80; 95% CI = 0.40–1.60) compared to individuals who had never used tobacco. In contrast, they found a greater incidence of head and neck cancers among individuals who used combustible tobacco products (OR = 2.47, 95%

CI = 2.23–2.74) [73]. Using data from the Agricultural Health Study, Andreotti, and colleagues also documented null differences in the hazard of developing head and neck cancers among individuals who had ever used ST products (HR = 1.54, 95% CI = 0.72 to 3.3) compared to those who had never used tobacco, whereas greater hazards were found among individuals who had ever smoked cigarettes (HR = 2.47; 95% CI = 1.55 to 3.95) [70].

In a 2019 study and subsequent corrigendum, Inoue-Choi used 1991–2010 NHIS behavioral data linked to mortality files with follow-up through 2015 to assess oral cancer mortality among individuals who smoked at the time of the survey and those who used ST products compared to individuals who had never used tobacco. Exclusive smoking and ST product use were each associated with increased mortality (Smoking HR = 5.12, 95% CI = 2.87 to 9.16; ST product use HR = 8.78, 95% CI = 1.43 to 53.96). It should be noted that the confidence intervals in the Inoue-Choi assessment were extremely wide, and the ST product use estimate was based on fewer than 5 individuals [104].

While not all studies show consistent results or necessary precision, in most cases, they provide evidence that mouth cancer risks are lower among ST product (US) users compared to cigarette smokers. Overall, these studies support the conclusions of the meta-analyses discussed above, that the preponderance of evidence demonstrates lower risk of mouth cancer among individuals who used ST products in the US compared to those who smoked cigarettes.

Snus (Sweden/Norway)

All six estimates from the five meta-analyses identified for snus use showed null associations for mouth cancer and snus use with estimated relative risk varying from 0.86 to 1.1 (see Fig. 4) [29, 53, 55, 59, 122]. Additionally, a recent pooled analysis of nine prospective studies, including participants of varying ages from across Sweden, found a null association between oral cancer and ever use (HR = 0.90, 95% CI = 0.74–1.09) or current use (HR = 0.79, 95% CI = 0.63-1.00) of snus [123]. These studies collectively support the idea that snus use is not associated with mouth cancer.

Our literature search identified one study that focused on switching from smoking to snus and mouth cancer [124]. In this study, Lee and colleagues found marginally lower odds of oral cancer among individuals who formerly smoked and currently used snus as a proxy for switching compared to the odds among individuals who continued to smoke cigarettes (OR = 0.43; 95% CI = 0.18 to 1.02). Moreover, the odds of oral cancer among individuals who switched were similar to those who quit tobacco use (OR = 0.83, 95% CI = 0.34 to 1.99) [50]. These findings aligned with our observation from meta-analyses and studies showing consistently elevated risks of mouth cancer associated with cigarette smoking and null association with snus use.

In summary, even though not all epidemiological studies have shown null associations between mouth cancer and ST product use in the US, they tended to show lower estimated risk of mouth cancer than those of cigarette smoking [29, 53, 55, 59, 122] with meta-analyses that include the more recent epidemiological studies showing no elevated risk of mouth cancer associated with ST product use in the US [29]. Epidemiological studies show snus use is not associated with mouth cancer.

Risk of smoking-related heart diseases

In our literature search, we identified studies on overall cardiovascular disease (CVD) as well as more specific disorders such as coronary heart disease (CHD) or ischemic heart disease (IHD). When reported, we also extracted estimates for myocardial infarction (MI, a pathology due to CHD). Figure 5 summarizes the relative risk of morbidity and/or mortality of smoking-related heart diseases from published meta-analyses collected during our review. Cigarette smoking estimates show a consistently elevated risk of heart disease, ST product (US) estimates were a mix of null association and elevated results, and snus (Sweden/Norway) estimates showed null association.

NOTE: In our forest plot figures, a value of one represents a null relationship and is shown as a solid line. A value greater than one represents a positive association, and a value less than one represents an inverse association. The 95% confidence intervals represent the precision of the estimates. A 95% confidence interval including the null value (i.e., one) is not considered statistically significant. For studies that calculated risk estimates for more than one type of tobacco product (e.g., cigarettes, ST products, and snus), they are listed more than once in the figures. [1]ALCS pooled estimates for studies conducted in the US using a random-effect meta-analysis model. [2]Study investigated the risk of heart disease among switchers from cigarettes to snus. The estimate compares individuals who were current snus users who formerly smoked to individuals who continued to smoke.

Cigarette smoking

Cigarette smoking is consistently associated with an elevated risk of heart disease based on the two meta-analyses and 21 studies (published after the meta-analysis) identified from our literature review. Both meta-analyses on smoking and the risk of heart disease outcomes, one on coronary heart disease and the other on sudden cardiac death; showed a 2.4-fold risk associated with cigarette smoking (see Fig. 5) [42, 48]. In addition, Hackshaw and colleagues also found that risks of coronary heart

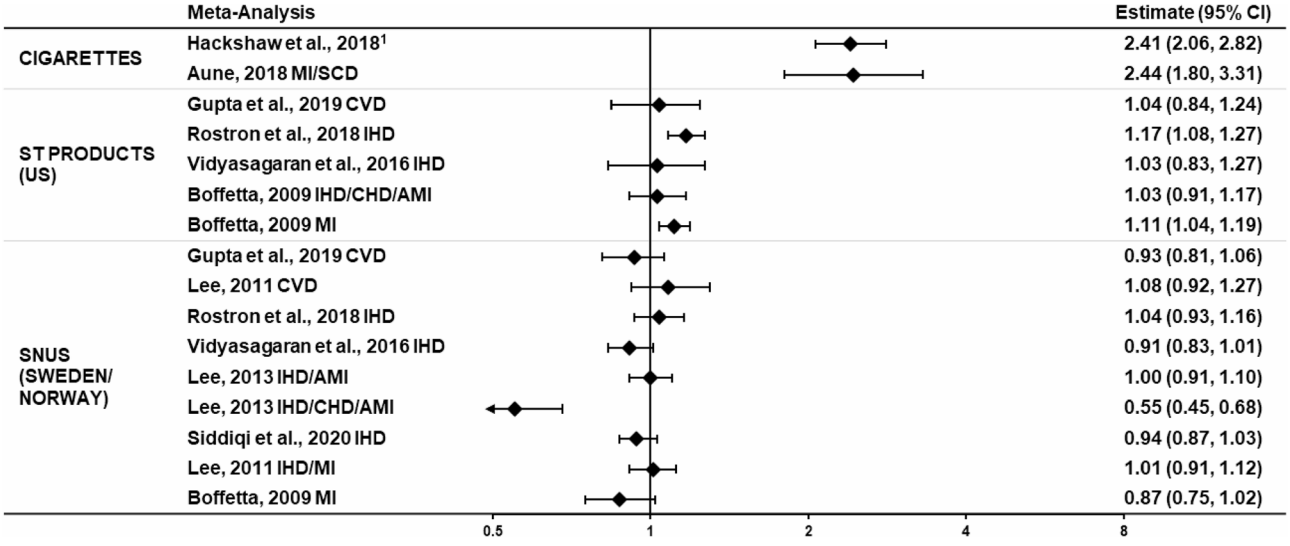

Fig. 5 Estimated relative risk of morbidity and/or mortality of *Heart Diseases* from published epidemiological meta-analyses on cigarette smoking and traditional oral tobacco products used in the US and Western Europe

disease increased in a dose-response fashion as cigarette consumption increased pooled Hazard Risk (HR, versus never smoker) was 1.4 (95% CI = 1.2–1.7), 1.5 (95% CI = 1.3–1.8), and 2.4 (95% CI = 2.1–2.8) for those who smoked approximately one, five, and 20 cigarettes per day, respectively, based on 16 prospective studies from the US[3]; this pattern was observed across sex- and age-groups [42].

Findings from the 21 studies published after 2017 are consistent with the conclusion drawn from the meta-analyses discussed above, showing elevated risks of heart diseases among individuals who smoked cigarettes (RR/OR/HR varied from 1.5 to 2.8) compared to those who did not smoke [60, 92–94, 96, 101, 107, 111, 125]; there is also evidence of a dose-response relationship – the risk of heart disease increased as cigarette consumption increased [92, 94, 101]. Similar to the graded relationship between cigarette consumption and risk of heart disease, the risk of heart disease decreased as the duration of quitting increased [89]. Moreover, the risk among individuals who quit smoking for more than 30 years was not different from the risk among those who had never smoked.

ST products (US)

In contrast to the consistently documented elevated risk of heart diseases associated with cigarette smoking, epidemiological evidence showed a much weaker, and in most cases null, association between ST product use and heart diseases, with point estimates varying from 1.03 to 1.2. Our literature search identified four meta-analyses on the risk of heart disease and ST product use in the US. Two of the five estimates from four meta-analyses found a slightly elevated risk of heart diseases among individuals who used ST products, whereas three estimates show a null association (see Fig. 5) [126–129].

Findings from individual studies identified in our literature search after the latest meta-analysis unanimously showed null associations between ST product use in the US and heart disease outcomes [111]. Moreover, seeking evidence for a potential dose-response relationship between ST product use and cardiovascular diseases in addition to the overall association, Nahhas et al. analyzed four waves of data from the Population Assessment of Tobacco and Health (PATH), a US nationally representative cohort study, and failed to find such a dose-response relationship: ST product use was not associated with a history of cardiovascular diseases overall (OR = 1.2, 95% CI = 0.7–2.1 comparing ever established ST use with never established ST use), and estimates did not show an incremental increase with the duration of ST product use (p-value for trend = 0.237 when stratified by years of ST product use). In contrast, such a dose-response relationship was found for cigarette smoking in the same study [111]. While the risk of heart disease is substantially lower among ST product users compared to those who smoke cigarettes, Henley et al. observed that after 20 years or follow-up, among those who switched from cigarette smoking to ST product use had a higher rate of death from coronary heart disease (HR 1.13, 95% CI 1.00 to 1.29) than those who quit all tobacco [113].

[3] The original study did not report estimates based on studies conducted in the US only. Estimates were summarized for studies conducted in the US using a random-effect meta-analysis model. Estimates were similar as reported in the publication when all studies were included (See Supplemental Material).

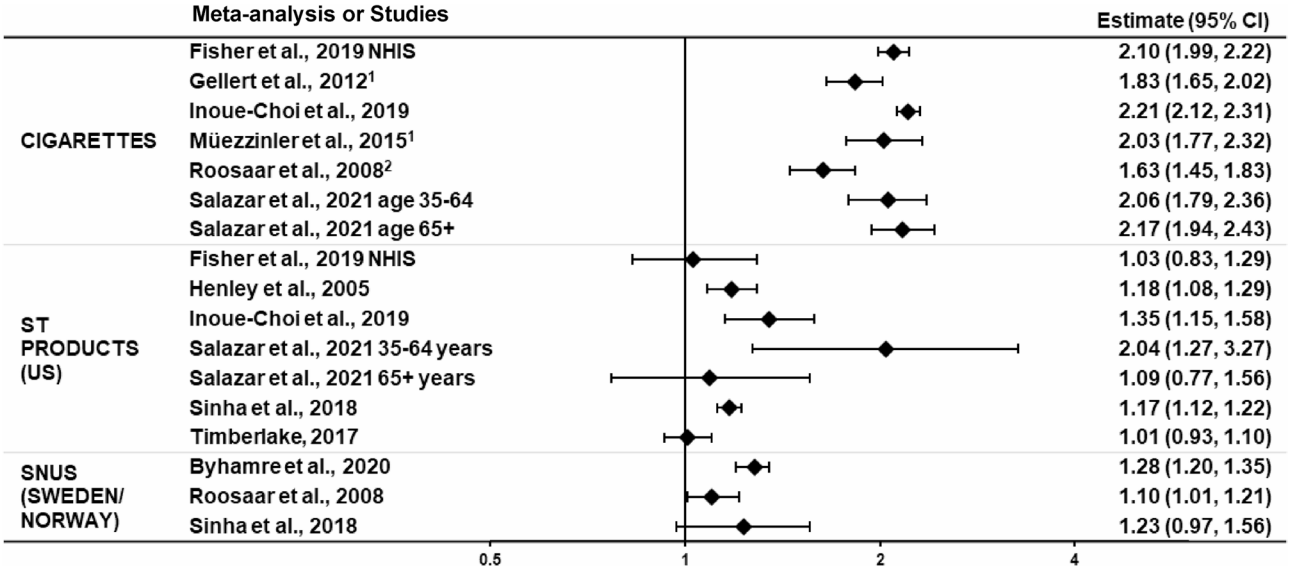

Fig. 6 Estimated hazard ratio or relative risk of all-cause mortality published epidemiological analysis on cigarette smoking and traditional oral tobacco products used in the US and Western Europe

Snus (Sweden/Norway)

Epidemiological evidence from Western Europe showed null, except for one inverse, associations between snus use and heart diseases, with point estimates varying from 0.55 to 1.08 (see Fig. 5) [29, 49, 56, 126–129]. Findings from the only individual study identified in our literature search after the latest meta-analysis also showed null associations between snus use and heart disease outcomes [100].

Particularly relevant to this section, a review by Lee found reduced risk (meta-analytic RR = 0.55, 95% CI = 0.45–0.68) of common heart diseases (i.e., IHD/CHD/MI) among individuals who switched from cigarette smoking to snus (i.e., current snus users who formerly smoked; "switchers") compared to that of individuals who continued to smoke [50]. In addition, there was no difference in risks of heart diseases between individuals who switched and individuals who quit tobacco (i.e., smokers who had quit smoking and never used snus; meta-analytic RR = 1.02; 95% CI = 0.83 to 1.26)) with high consistency across the four studies (i.e., estimates ranged from 0.80 to 1.23 and none were statistically significant).

The nearly two-fold risk (1/0.55 = 1.8) of heart diseases among individuals who continued to smoke compared to those who switched, as found in the Lee meta-analysis, is consistent with evidence summarized from meta-analyses identified by our literature search showing a 2.4-fold risk of heart diseases associated with smoking and null risk associated with snus use [50].

In summary, existing epidemiological studies consistently provide evidence of a strong association between cigarette smoking and smoking-related heart diseases. In contrast, epidemiological evidence supports a much weaker, and in most cases null, association between ST product (US) and snus (Sweden/Norway) use and smoking-related heart diseases.

Risk of all-cause mortality

Figure 6 summarizes the all-cause mortality risk from published studies collected during our review. The cigarette smoking estimates shows a consistent elevated risk of all-cause mortality while ST product (US) and snus (Sweden/Norway) estimates show lower or no risk.

NOTE: In our forest plot figures, a value of one represents a null relationship and is shown as a solid line. A value greater than one represents a positive association, and a value less than one represents an inverse association. The 95% confidence intervals represent the precision of the estimates. A 95% confidence interval including the null value (i.e., one) is not considered statistically significant. For studies that calculated risk estimates for more than one type of tobacco product (e.g., cigarettes, ST products, and snus), they are listed more than once in the figures. For cigarette smoking, estimates from Gellert et al. and Müezzinler et al. were from systematic review; Shavelle et al. was excluded from the figure because an overall estimate was not computed. For ST products in the US and snus products in Sweden and Norway, estimates from the Sinha et al. study were from systematic review; all others were from individual studies. [1]60 years and older. [2]Age < 75 years.

Cigarette smoking

Two meta-analyses identified from our literature search consistently demonstrate that individuals who smoked cigarettes had twice the risk of dying from any cause

compared to those who had never smoked. In addition, they also documented dose-response relationships between mortality and smoking in two ways: (a) increased risk of premature death with increasing cigarette consumption and (b) decreased risk of premature death with increased duration of quitting [58, 130].[4]

Congruent with findings from these meta-analyses, several publications using data from large longitudinal studies have shown individuals who smoked were at approximately two times the mortality risk compared to individuals who had never smoked, including three analyses that linked NHIS data to mortality record [90, 104, 131]. These estimates were seen for both males and females and younger (35–64 years of age) and older (65 years of age and older) adults (see Fig. 6) [131].

ST products (US)

We identified one meta-analysis that included three US cohort studies [65, 132][5] and calculated a 1.17-fold (95% CI = 1.12 to 1.22) increased risk of all-cause mortality among individuals who used ST products compared to those who had never used tobacco [133]. Two of these studies investigated dose-response relationships but did not find such evidence [65]. The small number of studies included in the meta-analysis makes an evaluation of recent studies worthwhile, and these individual studies are included in Fig. 6.

In an NHIS-linked-mortality analysis, Fisher and colleagues found ST product use was not associated with all-cause mortality, whereas smoking was associated with a two-fold all-cause mortality risk as mentioned above (HR = 2.10, 95% CI = 1.99 to 2.22) [90]. The null association between ST product use and all-cause mortality was also documented by Timberlake and colleagues using data from the Tobacco Use Supplement to the Current Population Survey, linked to mortality records [134]. An analysis by Inoue-Choi and colleagues found a slightly increased risk of all-cause mortality among individuals who used ST products compared to those who had never used tobacco (HR = 1.35, 95%CI = 1.15 to 1.58). Consistent with what other studies have shown, the magnitude of the excess hazard is lower than that of cigarette smoking (HR = 2.21, 95% CI = 2.12 to 2.31) [104]. Most recently, Salazar and colleagues found increased all-cause mortality risks associated with ST product use among the male 35–64 age group (HR = 2.04; 95% CI = 1.27 to 3.27) but not the 65 + age group (HR = 1.09; 0.77 to 1.56) (see Fig. 6). Further inspection revealed that the elevated all-cause mortality risk in the male 35–64 age group was attributed to non-ST-related causes (HR = 2.80, 95% CI: 1.50 to 5.25), which included accidents, Alzheimer's disease, nephritis, nephrotic syndrome, and nephrosis, and all other causes. ST was not associated with ST-related mortality, which included diseases of the heart, malignant neoplasms, cerebrovascular diseases, and diabetes mellitus. Based on these observations, authors concluded that "the elevated ACM [all-cause mortality] HR among young male adults could be associated with other lifestyle factors (e.g., drug overdose, alcohol abuse) besides ST use behaviors, disease-specific mortality associated with SLT [smokeless tobacco] use, or other unknown underlying factors that were not controlled for in this study."

To seek evidence about switching, three studies investigated mortality outcomes (e.g., all-cause mortality and smoking-related mortality) for individuals who stopped cigarettes and were using ST products in the US, a proxy for switching [90, 113, 131]. These studies showed lower HR of all-cause mortality for switching compared to continued smoking. For example, Fisher and colleagues reported an HR of 1.31 (95% CI = 1.02 to 1.68) for switching and an HR of 2.10 (95% CI = 1.99 to 2.22) for continued smoking [90]. These findings are consistent with the results of our literature review described above, characterizing higher all-cause mortality for smoking cigarettes compared to ST product use. While the available scientific evidence supports that cigarette smoking carries a much higher risk of all-cause mortality compared to ST product use, these oral products are not risk free. For example, Henley observed that "after 20 years of follow-up, switchers had a higher rate of death from any cause (HR 1.08, 95% CI 1.01 to 1.15)" than those who quit all tobacco [113]. This highlights the point that the best option for harm reduction is to quit all tobacco.

Snus (Sweden/Norway)

Most research on snus and health has taken place in Sweden. These studies showed that snus use was associated with slightly higher all-cause mortality; nonetheless, the magnitude was lower than that for cigarette smoking [66, 135]. Sinha summarized estimates from two Swedish cohorts recruited in the 1970s through meta-analysis and found a non-significant association between all-cause mortality and snus use (HR = 1.23, 95% CI = 0.97 to 1.56). Most recently, a pooled analysis of eight Swedish cohort studies examined the association of snus, all-cause mortality, and mortality from other causes. Males who had never smoked were recruited from 1978 to 2010 and followed until the mid-2010's. The study found that "compared with never-users of tobacco, exclusive current snus users had an increased risk of all-cause mortality (HR = 1.28, 95% CI = 1.20 to 1.35)." Upon further inspection of causes of death, snus use was associated with death from

[4] The Gellert analysis provided a US-specific risk of all-cause mortality. The two dose-response relationships, amount of cigarettes smoked and time since quit, were calculated among a worldwide collection of studies.

[5] Accortt - First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study; Henley - Cancer Prevention Study I and Cancer Prevention Study II.

CVD (HR = 1.27, 95% CI 1.15 to 1.41) as well as deaths from other causes (HR = 1.37, 95% CI = 1.24–1.52) signaling the possibility of residual confounding from uncontrolled differences between individuals who used snus and individuals who did not use tobacco [136]. In short, snus use is associated with slightly elevated all-cause mortality risk, but this risk may be explained by other factors distinct from snus consumption and this risk is far less than the risk among cigarette smokers (see Fig. 6).

In summary, the scientific evidence indicates that cigarette smoking poses a greater risk of all-cause mortality when compared to the use of ST product (US) or snus (Sweden/Norway) use.

Discussion

In this umbrella review, we found evidence supporting lower risks of lung cancer, COPD, mouth cancer, and tobacco-related heart diseases associated with ST product use in the US and snus use in western Europe compared to cigarette smoking. Specifically, we found highly consistent evidence of substantially elevated risks of lung cancer, COPD, mouth cancer, heart diseases, and all-cause mortality associated with cigarette smoking. In contrast, we found that ST product (US) and snus (Sweden/Norway) use was not consistently associated with these conditions. In addition, excess risks associated with ST product and snus use, if present, were much lower compared to those associated with cigarette smoking. The risk differential is further supported by a few studies that found lower disease risks for switching to ST products compared to continued smoking. These findings suggest that ST product (US) and snus (Sweden/Norway) use, even though they may not be risk free, is associated with lower risks of lung cancer, COPD, mouth cancer, and tobacco-related heart diseases compared to cigarette smoking.

As it may not be feasible to conduct an experimental study to randomly assign adults who smoke cigarettes to use and not use ST products, the best evidence may be drawn from high-quality observational studies. Hill's criteria for causality have been a widely used tool to help infer causality in epidemiology [137]. Based on findings from our literature review, we saw evidence of strength of association (i.e., the risk differential), consistency (consistently larger RR estimates for smoking compared to ST product or snus use), temporality (many included studies were prospective), biologic gradient (increasing risks with duration of smoking and decreasing risks with duration of quitting and no such gradient for ST product or snus use), and coherence (observed risk differential aligned with the natural history and biology of the disease).

Epidemiological evidence demonstrates that switching from cigarette smoking to ST products commonly used in the US or snus products typically used in Sweden and Norway may reduce the risk of lung cancer, COPD, mouth cancer, and heart diseases. This is biologically plausible because, unlike cigarette smoking, use of these oral tobacco products does not involve inhalation of smoke produced by combustion of tobacco, the process that produces numerous harmful and potentially chemicals, including carcinogens such as 1.3 butadiene, benzo[a]pyrene, formaldehyde, hydrogen cyanide, and benzene [138]. In addition, carbon monoxide, which is released when tobacco is burned, reduces the amount of oxygen the blood can carry and is associated with increased risks of coronary heart disease [139, 140]. The use of ST products does not involve burning tobacco and does not directly expose the respiratory system to harmful chemicals because of the oral route of administration, which lays the foundation for reduced risk of lung cancer and COPD compared to cigarette smoking. Indeed, the public health community and many government agencies across the globe, including the US Food and Drug Administration, have acknowledged the scientific basis for differential health risks across tobacco products in which cigarettes pose the highest health risks and oral products at the lower end [141–145].

Our findings are consistent with extensive epidemiological evidence from Sweden showing that switching to snus from cigarette smoking has led to over 30% of reduction in the prevalence of smoking and significantly reduced mortality in Sweden during 2003–2011 [20]. As a result, Sweden has one of the lowest male smoking prevalence and smoking-related mortality among European Union countries [17, 25, 146]. Our findings highlight the potential of ST products, like snus, in tobacco harm reduction.

Findings from this study should be interpreted with the following limitations in mind. First, we found a limited number of publications that directly measured switching behaviors. Future longitudinal studies that directly measure switching behaviors will provide more definitive evidence about the potential benefit of switching, especially those with detailed assessment of smoking/switching history that can help demonstrate "dose-response relationships" between switching and disease outcomes. Second, all publications included in this study were observational in nature, where differential self-selection cannot be completely ruled out. For example, individuals who chose to use ST products may have an inherent higher or lower risk for certain health conditions compared to individuals who chose to smoke cigarettes. Future studies using an experimental design (e.g., smoking cessation trial) will provide more definitive evidence for causal inference. Moreover, the timing of tobacco use and the onset of

the four diseases was not always clear in cross-sectional studies; however, the four diseases – lung cancer, COPD, heart diseases, and mouth cancer – typically occur later in life, well after the average age of onset of tobacco use. Therefore, we do not consider reversed temporal relationship a significant bias. Nonetheless, future longitudinal studies with long-term follow-up will be able to shed an important light on the timing of switching and potential health benefits. Third, we excluded studies from geographical regions other than the US and Western Europe due to substantial differences in ST products in other regions of the world. Therefore, our findings may not be applicable to populations outside of the US and Western Europe. Future studies focused on those regions will help elucidate the risk profile of ST products, especially in countries where ST product use was more prevalent. Fourth, we found limited evidence about COPD and ST product use, likely due to the lack of biological mechanisms. Nonetheless, COPD is a common tobacco-related disease. Future studies may consider including COPD as an endpoint of interest to benchmark risk differentials to help quantify the harm reduction potential of ST products. Finally, this review does not address dual use of cigarettes and ST products. When dual using, users are exposed to both the cigarette smoke and ST product harmful and potentially harmful constituents which would impact the harm reduction potential of switching to ST products. Dual use has been identified by several researchers as a potential transitory period when switching from combustible cigarettes to smoke-free tobacco products [147–150]. Correcting the misperceptions about relative risk between cigarettes and ST products could encourage those that dual use to completely switch to the less harmful alternative if they wish to continue to use tobacco products [27, 28].

Conclusion

The U.S. Surgeon General and other public health authorities have determined that ST products cause serious diseases such as cancer, cardiovascular disease and other diseases of the mouth, gums and teeth; cause adverse reproductive effects and should not be used during pregnancy; and are not a safe alternative to smoking. No tobacco product is safe, and they should not be used by underage individuals (e.g., those under the age of 21). Nevertheless, findings from this literature review support lower risks of lung cancer, COPD, mouth cancer, and heart diseases associated with ST products commonly used in the US and snus used in Sweden and Norway compared to cigarette smoking. This should inform tobacco harm reduction strategies.

Our findings highlight the importance of addressing public misperception of the relative risks associated with cigarette smoking and oral tobacco product use. These misperceptions can deter adults who smoke from considering oral tobacco products as a harm-reduction alternative if they wish to continue to use tobacco products [27, 28]. While the best option for harm reduction is to quit all tobacco, for adults who smoke cigarettes and are unwilling or unable to quit all tobacco, switching completely to less harmful oral tobacco products like those commonly used in the US (i.e., MST products) and in Sweden and Norway (i.e., snus) may reduce risks of lung cancer, COPD, mouth cancer, and heart diseases and, therefore, may prevent premature deaths. Future longitudinal studies that directly measure switching behavior will provide further evidence about the potential benefits of switching and the magnitude of the harm reduction potential.

Abbreviations

CHD	Coronary Heart Disease
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPS	Cancer Prevention Study
CVD	Cardiovascular Disease
HR	Hazard Ratio
IHD	Ischemic Heart Disease
MI	Myocardial Infarction
MST	Moist Smokeless Tobacco
NHIS	National Health Interview Study
NIH-AARP	National Institutes of Health-American Association of Retired Persons
OR	Odds Ratio
PATH	Population Assessment of Tobacco and Health
RR	Relative Risk
ST	Smokeless Tobacco
US	United States

Supplementary Information

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Supplementary Material 1.

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Jason Flora and Hui Cheng conceptualized the review. Hui Cheng and Brendan Noggle designed the search strategy and evaluated studies. All authors made major contribution to writing the manuscript. All authors read and approved the final manuscript.

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No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
All authors were employed by Altria Client Services LLC at the time of preparing this review. Altria Group, Inc.'s wholly owned subsidiaries include Philip Morris USA Inc., which is engaged in the manufacture and sale of cigarettes in the United States, and UST LLC, which, through its wholly owned subsidiary U.S. Smokeless Tobacco Company LLC, is engaged in the manufacture and sale of moist smokeless tobacco products.

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