The Health Impact of Smokeless Tobacco Products: A Systematic Review
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Abstract

Introduction
The objective was to systematically review studies reporting on health outcomes from smokeless tobacco (SLT) products.

Methods
We included published literature on the health impact of SLT from 01/01/2015 until 01/02/2020 following the PRISMA protocol using PubMed, Embase, Scopus and Google Scholar.

Results
Of 321 studies identified, 53 met eligibility criteria; 23(43%) were rated as poor, 21(39%) fair and 9(17%) as good.

Health outcomes differed starkly between SLT products and global regions. SLT products in Asia, Middle East and Africa were associated with higher mortality (overall, cancer, CHD, respiratory but not CVD), and morbidity (CVD, oral and head and neck cancers), with odds ratios as high as 39 (shammah use).

European studies showed no excess mortality (overall, CVD, from cancers) or morbidity (IHD, stroke, oral, head and neck, pancreatic or colon cancers) from several meta-analyses but single studies reporting elevated risk of rectal cancer and respiratory disorders. Pooled studies showed a protective effect against developing Parkinson’s disease.

US studies showed mixed results for mortality (raised overall, CHD, cancer and smoking-related cancer mortality; no excess risk of respiratory or CVD mortality). Morbidity outcomes were also mixed, with some evidence of increased IHD, stroke and cancer risk (oral, head and neck).

No studies reported on the health impact of switching from cigarettes to SLT products.

Conclusion
Our review has demonstrated stark differences between different SLT products in different regions on health impact, ranging from no harm from European snus to greatly increased health risks from SLT products used in Asia, Middle East and Africa. The literature on the impact of SLT products for harm reduction is incomplete and potentially misinforming policy and regulation.

Implications
Our systematic review including 53 studies investigating health outcomes from the use of SLT products has demonstrated stark differences on health impact between different SLT products in different regions, ranging from no harm from European snus to greatly increased health risks from SLT products used in AMEA regions and lesser harms from US SLT products. Studies on the impact of
SLT products for harm reduction are lacking and are urgently warranted to inform policy and their regulation.
Introduction

The use of smokeless tobacco (SLT) products exceeds that of all other forms of tobacco use in some parts of the world. The prevalence of SLT product use in men is 30% in India, 6% in Iceland and 20% in Sweden. SLT is rising in parts of Europe and some have attributed its use to the concomitant reduction in smoking prevalence.

There are numerous types of SLT products available globally which differ markedly in terms of their preparation, method of use and toxicity. For example, in India SLT products are made by individual farmers and small companies with little control over fermentation and curing, which affects the production of potential carcinogens called tobacco-specific nitrosamines (TSNAs). In India, SLT products are often combined with additives such as betel leaf (Piper betle), sliced areca nut (Areca catechu) and/or powdered agricultural lime, additives that enhance the toxicity as well as the psychotropic effect of tobacco.

SLT products are not a homogeneous category, even in western countries. In the US, three traditional types of SLT products are used: powdered dry snuff, loose leaf chewing tobacco and moist snuff. Dry snuff is made from fermented, fire-cured tobacco that is pulverized into powder. Loose-leaf chewing tobacco consists of air-cured leaf tobacco typically used in large volumes, resulting in large quantities of saliva that users usually expectorate. However, use of dry snuff and chewing tobacco has rapidly declined in the US. Moist snuff consists of fire- and air-cured dark tobaccos that are used by a "pinch" between the thumb and forefinger and placing inside the lip and is the most popular form of SLT product in the US.

There is a long tradition of moist snuff use in Scandinavia, especially in Sweden, where "snus" (the generic term for moist snuff in Swedish, pronounced "snoose") is essentially the only type of SLT product in use.

There are differences in how American and Swedish moist snuff products are manufactured. Traditional American products undergo fermentation, which results in higher concentrations of unwanted bacterially mediated by-products, especially TSNAs and nitrite. In Swedish manufacturing of snus air cured tobacco leaves are subjected to pasteurization, yielding virtually sterile products containing very low levels of TSNAs. Manufacturing refinements have resulted in further lowering of levels of TSNAs making American and Swedish moist snuff similar for risks related to TSNA content.

Other SLT products also exist, for example, traditional tobacco pouches may contain moist or dry snuff, or small pieces of leaf tobacco and pellets of compressed tobacco. Nicotine pouches contain either tobacco-derived nicotine or synthetic nicotine, but no tobacco leaf, dust, or stem, and are described as either similar to or being a tobacco-free version of snus.
The commonest SLT products globally are shown in table 1.

| SLT PRODUCT | GLOBAL REGION | PREPARATION | USE |
|-------------|---------------|-------------|-----|
| SWEDISH SNUS | Europe (WHO Region A) | Heat Treatment process | Placed between gum and upper lip |
| SNUFF (US), SNUUS (US), PLUG | Americas (WHO regions A and B) | Plug: air cured, Dry or moist snuff, finely ground and fire cured | Snuff: kept between lip and gum, Dry snuff can be insufflated (inhaled), Snus: Placed between gum and upper lip |
| THCHIMO | Americans (WHO region B) | Tobacco paste made from tobacco leaves | Kept between lip or cheek and gum |
| NASS (NASWAR) | Europe & Eastern Mediterranean (WHO regions B and D) | Sun dried and powdered | Kept between lip or cheek and gum |
| SNUFF (N AND W AFRICAN) | Africa (WHO region D) | Dry snuff, finely ground | Inhaled as a pinch |
| SNUFF (African) | Africa (WHO region E) | Dry snuff, finely ground | Inhaled as a pinch |
| KHAINI | SE Asia Western Pacific (WHO Regions B and D) | Shredded | Kept between lip and gum |
| ZARDA | Eastern Mediterranean Europe (WHO regions A and D) | Shred tobacco leave are boiled and dried | Chewed and spat |
| GUTKHA | SE Asia Europe (WHO regions A and B) | Commercially manufactured | Sucked, chewed and spat |

Table 1. Types of SLT product by World Health Organisation global region, preparation and use
Adapted from World Health Organisation.13

There have been limited studies on the health impact from SLT products. There has been no clear consensus on the safety profiles of the different SLT products although it is generally accepted that they pose a lower health risk than cigarette smoking. Nevertheless, safety concerns have resulted in varying regulations and bans on their sale and use globally. Despite the many differences described above, SLT products are often regarded together as a single product with regards to their regulation.

The objective of this systematic review was to identify, narratively synthesize, assess the strength and quality of evidence and critically appraise studies that have reported health outcomes associated with use of different SLT products in different regions of the world.

Methods
We conducted a systematic review of published literature on the health impact of smokeless tobacco (SLT) products between 1st January 2015 and 1st February 2020. SLT products included all types including snus, chewing tobacco, snuff and other products included in table 1. For the purpose of this review we reported findings according to three geographical regions which best align with the different types of SLT products consumed, namely Europe, the Americas, and SE Asia, Eastern
Mediterranean and Africa (AMEA) regions. The study followed PRISMA guidelines for reporting of systematic reviews.14

Search strategy and eligibility criteria
A literature search was conducted between 1st October 2019 and 26th February 2020 using the databases PubMed, Embase, Scopus and Google Scholar using medical subject headings. There were two domains: one for SLT products and one for health outcomes, specifically cardiovascular disease (CVD), cancer, respiratory disease, and mortality and ‘other’ health outcomes. Search results were restricted to English language, human studies and studies published from 01/01/2015 until 01/02/2020. The references of relevant reviews were manually searched for additional eligible citations. The detailed search strategy is provided in Appendix 1.

The titles, abstracts and full texts of the search results were sequentially screened by two reviewers independently for inclusion using the eligibility criteria below, with disagreements resolved via blind review by a third reviewer.

Figure 1 shows the inclusion and exclusion criteria used. Reasons for excluding studies are shown in figure 2.

Data extraction and quality assessment
For included studies, data were extracted including author, year, country, aim, study design, sample size, participants and relevant findings such as effect sizes and nature of impact on health outcomes. Studies were categorized by region to best match types of products used into Asia, Middle East and Africa (AMEA), Americas (US) and Europe (EU). A level of evidence category was assigned using the Oxford Centre for Evidence Based Medicine framework 15 and a similar approach used to categorise methodological quality as “good”, “fair” or “poor” utilizing the National Institutes for Health (NIH) Quality Assessment Tools.16 Data extraction and synthesis was performed by two reviewers independently with blind assessment by a third reviewer for cases with rater disagreement. Findings of all studies were independently reviewed, coded and compared between studies to identify relationships and themes.

Results
Of the 53 studies included, six included global data, 32 were exclusively from AMEA, nine exclusively from US and six exclusively from Europe. The number of studies by study design and health outcomes are shown in table 2.
Table 2. Number of Studies by Health Outcome and Study Design. Totals for each health outcome and region may include duplication studies that examined more than one health outcome.

Table 2 shows the health outcomes and study designs of included studies by region. All six global studies were meta-analyses (100%), with all but one pooling data from case-control studies. In AMEA, the most common study design was case control (16; 50%), with predominantly hospital-based recruitment, followed by cross-sectional (8; 25%). The most common study design was meta-analyses in Europe (4; 57%) and cohort (4; 28%). In the US, cross-sectional (3; 38%) and cohort (2; 28%) were the most common study designs. Cancer was the most common outcome reported. More than two-thirds (23; 72%) of studies in AMEA examined cancer and 15 (65%) of these were case-control studies. Mortality was also reported commonly across all regions.

Nine studies reported on other health outcomes, including chronic health conditions, alcohol dependence, reproductive health, respiratory health, oral health, obesity and mental health.
Table 3 summarises the quality ratings assigned to studies by health outcome. Raters 1 and 2 agreed on 49 out of 53 (92%) for quality and level of evidence categories. A ‘poor’ rating was most common (23; 43%), followed by fair (21; 39%), nine (17%) studies were rated as ‘good’. Global (4; 66%) and AMEA studies (16; 50%) were more likely to be rated as ‘poor’. A ‘fair’ rating was given to 71% (5) of EU studies, 38% (12) of AMEA studies and 38% (3) US studies. ‘Good’ ratings were given to 33% (2) of global studies, 28% (2) of Europe studies, 6% (2) of AMEA studies and 38% (3) of US studies.

| HEALTH OUTCOME | GOOD QUALITY | FAIR QUALITY | POOR QUALITY |
|----------------|--------------|--------------|--------------|
| GLOBAL         |              |              |              |
| MORTALITY      | 1            | 0            | 3            |
| MORBIDITY      | 2            | 0            | 3            |
| SUB-TOTAL      | 3            | 0            | 6            |
| AMEA           |              |              |              |
| Mortality      | 0            | 1            | 1            |
| Morbidity      | 2            | 12           | 16           |
| Sub-total      | 2            | 13           | 17           |
| EUROPE         |              |              |              |
| Mortality      | 0            | 2            | 0            |
| Morbidity      | 2            | 3            | 0            |
| Sub-total      | 2            | 5            | 0            |
| US             |              |              |              |
| Mortality      | 3            | 1            | 0            |
| Morbidity      | 0            | 2            | 2            |
| Sub-total      | 3            | 3            | 2            |
| Total          | 10           | 22           | 26           |

Table 3. Quality Ratings Assigned to studies by Outcome  
 Totals may reflect duplicated studies that examined more than one health outcome. Quality assigned as “good”, “fair” or “poor” utilizing NIH Quality Assessment Tools.16  

There were only two studies that reported on benefits from SLT product use; a cross-sectional study on hypertension and a meta-analysis on Parkinson’s disease in Europe.

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Table 4 in the appendix provides a description, study design, key outcomes, level of evidence and quality rating for the included studies by region.

Health Outcomes by Region

**Global**
Six studies reported on combined global SLT product data.17 18 19 20 21 61

**Mortality**
A meta-analysis rated as good17 that pooled results from 20 studies on snuff (but not Swedish snus), chewing tobacco and naswar together from Europe, the US, Southeast Asia, and the Mediterranean region found a borderline association of SLT (combined products) with fatal CHD (OR=1.10; 95% CI: 1.00-1.20), increased risk in naswar users (OR=1.30; 95% CI: 1.06-1.54) but not in chewing tobacco users, among smoking adjusted studies. A meta-analysis rated as poor included 14 studies in Europe, US, Southeast Asia, and the Mediterranean, and found SLT product users (combined products) to have higher risk of fatal stroke (OR=1.27; 95% CI: 1.15-1.39) compared with non-users, after excluding or adjusting for smoking.18 Another good-rated meta-analysis of 19 studies across North
America, Asia and Europe found overall an increased risk of IHD deaths (OR=1.15; 95% CI: 1.01-1.30) and stroke deaths (OR=1.39; 95% CI: 1.29-1.49) among ever-users of SLT compared to those who have never used any type of tobacco.\textsuperscript{19}

A meta-analysis rated as poor due to pooling together of different SLT products from 16 global studies reported an increased risk of overall mortality (OR=1.22; 95% CL: 1.11-134).\textsuperscript{20} The study found significant heterogeneity but no publication bias.

Another poor-rated meta-analysis of 32 global studies used a comparative risk assessment method to report on absolute deaths and disability-adjusted life years (DALYs) from cancers of the mouth, pharynx and oesophagus due to SLT product use.\textsuperscript{21} They estimated SLT product use led to 1.7 million DALYs lost and 62,283 deaths in 2010 globally. Although data were available by country, only global mortality and DALY results from SLT product use were reported. Most of the 32 studies adjusted for, but did not exclude, smoking.

**Cardiovascular Outcomes**

There were three global studies identified reporting on cardiovascular outcomes. One of the better-quality meta-analyses included 19 studies of SLT products (chewing tobacco, dip, snuff and snus) from Sweden, North America and Asia.\textsuperscript{19} In studies that had excluded former smokers, there was no increase in ischaemic heart disease (IHD) for combined regions (OR=1.4; 95% CI: 0.92-1.42).\textsuperscript{19}

Another meta-analysis rated as good of 20 studies from four WHO regions, including snuff, chewing tobacco and naswar, found overall no increased risk of CHD, including only studies that excluded or adjusted for smoking status overall (OR=1.05; 95% CI 0.95-1.16) or for chewing tobacco (OR=1.13; 95% CI: 0.92-1.06), but did so for naswar (OR=1.30; 95% CI: 1.06-1.54).\textsuperscript{17} There was statistical evidence of publication bias.

A meta-analysis on SLT products and stroke which did not account for heterogeneity and variation in handling of smoking status between studies reported an association between SLT products and stroke globally (OR=1.18; 95% CI: 1.04-1.32).\textsuperscript{18} An association was reported with stroke for chewing tobacco (OR=1.35; 95% CI: 1.20-1.50), but not for snuff (OR=1.03; 95% CI: 0.93-1.13) or Naswar (OR=0.98; 95% CI: 0.57-1.39). No significant publication bias was found in the included studies.

**Cancer**

**Oral Cancer**

A poor-rated global meta-analysis of 32 studies found an association with oral cancer overall (OR=3.43; 95% CI: 2.26-5.19).\textsuperscript{21}

**Head and Neck Cancer**

Of studies investigating SLT product use and head and neck cancer (HNC), a poor-rated meta-analysis reported an association with pharyngeal cancer for all countries combined (OR=2.23; 95% CI: 1.55-3.20) and for India (OR=2.60; 95% CI: 1.76 - 3.85) and oesophageal cancer for all countries combined (OR=2.17; 95% CI 1.70-2.78), India (OR=2.57; 95% CI: 2.20-3.00) and Pakistan (OR=8.20; 95% CI: 1.45-27.47).\textsuperscript{21}

**Other Cancers**

A meta-analysis of 16 global studies found SLT (combined product) use to be associated with mortality due to all cancers (HR=1.31; 95% CI: 1.16-1.47); upper aero digestive tract (UADT) cancer (HR=2.17; 95% CI: 1.47-3.22); Stomach cancer (HR=1.33; 95% CI: 1.12-1.59 and Cervical cancer (HR=2.07; 95% CI: 1.64-2.61).\textsuperscript{20}
SE Asia, Middle East, Africa (AMEA)

42 studies reported on SLT product data from AMEA, of which 32 were exclusively from AMEA region.

Mortality

There were three studies reporting on mortality and SLT products from AMEA region.20-22 A meta-analysis rated as poor of 16 global studies found an increased risk of overall mortality for the South East Asian Region (SEAR) (OR=1.25; 95% CI: 1.08-1.44).20 The study found significant heterogeneity but no publication bias. A longitudinal study of 50,045 participants from Iran found that nass (naswar) use in never smokers was associated with increased overall mortality (HR=1.17; 95% CI: 1.00-1.36) and cancer mortality (HR=1.40; 95% CI: 1.01-1.95), which was further elevated in dual (cigarette and nass) users (overall mortality: HR=1.28; 95% CI: 1.00-1.64; cancer mortality: HR=1.67; 95% CI: 1.02-2.75).22 There was no elevated risk of IHD, CVD or respiratory mortality. A poor-rated Indian case-control study found increased overall mortality (RR=1.3; 95% CI: 1.2-1.4) and respiratory deaths (RR=1.5; 95% CI: 1.4-1.7) for chewing tobacco users amongst never smokers.23

Cardiovascular Outcomes

There were eight studies identified reporting on cardiovascular outcomes, including five examining exclusively AMEA. One of the better-quality global meta-analyses on 19 studies of SLT products (chewing tobacco, dip, snuff and snus) found, in studies that had excluded former smokers, an increase in IHD in Asia (OR=1.40; 95% CI 1.01-1.95).19

A poor-rated meta-analysis on SLT products and stroke reported an association between SLT products and stroke in SE Asia (OR=1.35; 95% CI: 1.18-1.51), but not in the Mediterranean region.18

A poor-rated cohort study in India found an association between SLT products and stroke (OR=3.71; 95% CI: 1.57-9.05) and myocardial infarction (MI) (OR=2.34; 95% CI: 1.10-5.40) but had not excluded former smokers.24

A cross-sectional study in India showed no association between SLT product use and diabetes or hypertension in exclusive SLT product users,25 although former smoking was not accounted for. One small cross-sectional study of 36 individuals with mental and behavioral disorders in India showed no association with CHD compared with exclusive smokers,26 and another with 30 exclusive SLT product users showed strong associations with dyslipidaemia (OR=6.37; 95% CI: 1.4-27.3) and hypertension (OR=6.97; 95% CI: 1.7-28.0) compared to non-tobacco users.27

Cancer

Of 25 studies on cancer in AMEA region, only one28 was rated as being of good quality; 18 of the studies were on oral cancer, three on head and neck cancers and two each on breast and gastrointestinal cancers.

Oral Cancer

A meta-analysis of six studies in Pakistan, rated as good, found an association between Naswar use and oral cancer (OR=11.8; 95% CI: 11.4-25.3), although only four of the six studies adjusted for smoking.28 A poor-rated meta-analysis of 32 global studies reported an association between SLT products (combined products) with oral cancer in India (OR=5.12; 95% CI: 3.27-8.02) and Pakistan (OR=8.81; 95% CI: 3.14 - 24.69).29

A poor-rated meta-analysis of 25 studies from India studying exclusive use of all SLT product types, reported increased oral cancer risk (OR=5.65; 95% CI: 3.83-8.40).29 Another poor-rated meta-analysis of three case-control studies of Shammah in Middle East and North Africa,30 only one of which adjusted for smoking, reported a greatly elevated risk of oral cancer (OR=38.7; 95% CI: 19.50-76.96).
There were several small, predominantly hospital-based case-control studies on oral cancer. Two such studies in Saudi Arabia found elevated risks with exclusive Shammah use (OR=29.30; 95% CI: 10.33-83.13),31 (OR=33.01; 95% CI: 3.22-39.88)32 and lower risk with dual use of shammah and cigarettes (OR = 10.10; 95% CI = 0.50-20.40).32 A study of gutka use in Pakistan found elevated risk (OR=5.54; 95% CI: 2.83-10.83), also for chewing tobacco (OR=5.32; 95% CI: 1.14-24.77).33 Another study in India reported elevated risks with chewing tobacco (OR=8.51; 95% CI: 4.90-14.77),34 and another reported elevated risks from Tokomak dipping in Sudan (OR=3.8; 95% CI: 1.7-8.6), after adjusting for smoking.35 Another study of Naswar use in Pakistan found elevated risk for current users (OR=23.4; 95% CI: 6.6-82.1), ever users (OR=21.0; 95% CI: 6.1-72.1) and former users (OR=16.4; 95% CI: 4.1-65.4), after adjusting for smoking.36

Another study in India found an elevated risk of oral cancer for SLT products combined (OR=6.0; 95% CI: 2.6-15.5), for Gutkha (OR=5.1; 95% CI: 2.0-10.3), for Supari (OR=11.4; 95% CI: 3.4-38.2) and for betel quid (OR=6.4 (95% CI: 2.6-15.5), but not for snuff (OR=1.0; 95% CI: 0.3-3.0), after adjusting for smoking.37 Another study in India reported elevated risk in sole users of chewing tobacco (OR=2.8; 95% CI: 1.2-7.0) but not in dual users (OR=0.7; 95% CI: 0.2-2.6).38 Another hospital-based case-control study in Pakistan found elevated risk for all SLT products combined (OR=4.71; 95% CI: 2.53-8.74), for snuff (OR=4.82; 95% CI: 2.37-9.80), betel leaf (OR=4.42; 95% CI: 1.66-11.91) and supari/chalia (OR=4.67; 95% CI: 1.14-19.12) after adjusting for smoking.39 There were in addition two case series40,41 and one ecological study.42

**Head and Neck Cancer**

Of studies investigating SLT product use and head and neck cancer (HNC), a poor-rated meta-analysis reported an association in India with pharyngeal cancer (OR=2.60; 95% CI=1.76-3.85) and with oesophageal cancer in India (OR=2.57; 95% CI: 2.20-3.00) and Pakistan (OR=8.20; 95% CI: 1.45-27.47).21 A poor-rated meta-analysis from India found an association between SLT products (combined products including gutka and snus) and both pharyngeal cancer (OR=2.69; 95% CI: 2.28-3.17) and oesophageal cancer (OR=3.17; 95% CI: 2.76-3.63).29

A case-control study from Nepal found an association between chewing tobacco and head and neck cancer (OR=2.39; 95% CI: 1.77-3.23) increasing in the heaviest users (≥6 times per day) (OR=2.91; 95% CI: 2.06-4.12) and in those using for over 20 years duration (OR=2.92; 95% CI: 2.08-4.11).43 One study described the commonest sites for chewing tobacco as the gingivobuccal complex and those with smoking as the larynx.40 An ecological analysis of population based cancer registries in India found that the prevalence of Khaini use correlated with hypopharynx cancer incidence in different regions (r = 0.48 for males, r = 0.29 for females), gutika use correlated with mouth cancer incidence in males (r = 0.54, r=-0.19 for females) and oral tobacco correlated with mouth cancer incidence in both males and females (r = 0.46, r=0.17 in females).42 ‘Other’ types of SLT product use (combined) correlated with hypopharynx cancer incidence (r = 0.47). The study did not account for smoking.

**Other Cancers**

Two hospital-based case-control studies showed associations between chewing tobacco and breast cancer (OR=2.35; 95% CI: 1.3-4.15),44 with one study (OR=2.35; 95% CI: 1.01-5.51) showing a dose response effect for >5 times per day (OR=10.13; 95% CI: 5.41-18.23) and for duration of use ≥10 years (OR=31.13; 95% CI: 11.67-39.82).45 A poorly rated meta-analysis from India found an association between all types of SLT products (including gutka and snus), with stomach cancer (borderline significance, OR=1.26; 95% CI: 1.00-1.60) and laryngeal cancer (OR=2.84; 95% CI: 2.18-3.70), but both became non-significant in random effects models (OR=1.31; 95% CI: 0.92, 1.87, OR=1.79; 95% CI: 0.70-4.54). There was no relationship found with lung cancer (OR=0.91; 95% CI: 0.76-1.09).29 A hospital-based case-control study in Yemen found gastric cancer to be associated
with SLT product use (OR=4.37; 95% CI: 1.92 to 9.95), but not with smoking cigarettes. Another Indian hospital case-control study found SLT product use to be associated with colorectal cancer (OR=1.53; 95% CI: 0.58-4.00) after adjusting for cigarette smoking.

Other Health Outcomes
A hospital case-control study reported worse oral health including gingival bleeding (OR=1.710; 95% CI: 1.2-2.43), loss of attachment (OR=2.393; 95% CI: 1.55-3.69) and attrition (OR=2.496; 95% CI: 1.73-3.61) in users of chewing tobacco in India. Other studies reported poorer self-reported health issues in India including chronic health conditions, obstetric and neonatal health but not of gastrointestinal, urinary disease or asthma, and reduced risk of chronic lung disease (OR=0.64; 95% CI: 0.45-0.91).

United States
15 studies reported on SLT product data from US, of which eight were exclusively from US region.

Mortality
One of the studies with the highest level of evidence that pooled two longitudinal studies with 365,000 US participants on the use of SLT products in the US, found no increase in overall mortality in never smoking SLT product users compared with never-smoking never SLT product users. Nor did they find any excess mortality from smoking-related cancers or CVD. Those who were dual users of SLT and cigarettes had similar excess mortality (HR=2.21; 95% CI: 1.50-3.26-HR=2.14; 95% CI: 1.27-3.59) to exclusive smokers (non-SLT product users) (HR=2.10; 95% CI: 1.99-2.22-HR=1.88; 95% CI: 1.75-2.02), compared with never tobacco users.

A large US longitudinal study rated as good found exclusive SLT product users had increased all-cause mortality (HR=1.44; 95% CI: 1.12-1.84) but not mortality from any specific causes of death. A large longitudinal study of 350,000 participants in the US that excluded all former and current smokers but included both snuff and chewing tobacco together found no association between SLT product use and overall mortality or mortality from cancer and CVD. It did report higher CHD mortality (OR=1.25; 95% CI: 1.05-1.46) in SLT product users. A poor-quality rated population based cohort study of 65,000 individuals from the US found SLT product use in never smokers to be associated with higher overall mortality (HR=1.36; 95% CI: 1.17-1.59), CHD mortality (HR=1.63; 95% CI: 1.27-2.09), cancer mortality (HR=1.48; 95% CI: 1.04-2.12) and smoking-related cancer (HR=1.76; 95% CI: 1.07-2.90), but not respiratory-related or CVD mortality. There was a dose-response effect with higher risk of overall mortality in daily SLT product users (HR=1.41; 95% CI: 1.20-1.66), but not non-daily users.

Of global studies including US data, a poor-rated meta-analysis of 16 studies globally reported an increased risk of overall mortality in America (OR=1.17; 95% CI: 1.12-1.22), as well as all cancer mortality (OR=1.14; 95% CI: 1.01-1.29). There was also a significantly elevated risk of stroke mortality (OR=1.44; 95% CI: 1.30-1.59), and elevated risk of IHD mortality (OR=1.16; 95% CI: 1.05-1.28). The study found significant heterogeneity but no publication bias.

Cardiovascular Outcomes
Of studies reporting US-exclusive data, a good-rated meta-analysis of SLT products (including snuff and chewing tobacco) of 24 US studies found elevated risk of IHD (RR=1.17; 95% CI: 1.08-1.27) and stroke (RR=1.28; 95% CI: 1.01-1.62) compared with non-users, although there was variation in handling of smoking status between the studies. A meta-analysis rated as poor on SLT products and stroke reported no association between SLT products and stroke in US data.
sectional study reported lower self-reported hypertension (OR=0.88; 95% CI: 0.79-0.98) in SLT product users after adjusting for smoking status and duration.56

Cancer
Oral Cancer
A review that pooled results from 11 US-exclusive studies found SLT product use (snuff and chewing tobacco) to be associated with cancers of the oral cavity (OR=1.81; 95% CI: 1.04, 3.17).57 A large but poor-rated global meta-analysis found no association with oral cancer in North America.21

Head and Neck Cancer
Of studies investigating SLT product use and head and neck cancer (HNC), the largest was a poor-rated global MA.21 For pharyngeal and oesophageal cancers there were associations for all countries combined (OR=2.23; 95% CI: 1.55-3.20; OR=2.17; 95% CI: 1.70-2.78, respectively) but not for North America, albeit from a single study (OR=1.59; 95% CI: 0.84-3.01; OR=1.20; 95% CI 0.10-14.40, respectively). Another study that pooled results from 11 US studies found increased odds for HNC were (OR=1.71; 95% CI: 1.08-2.70) in snuff users but not for ever-tobacco chewers compared with never users.57 HNC risk increased with increasing duration of snuff use (Ptrend = 0.007).

Other Cancer
There was no exclusive US data on other cancers.

Other Health Outcomes
One study reported on mental health and although cross-sectional, reported no significant association with a mental health diagnosis or depression in users of SLT product in the US.58

Europe
Europe had less exclusive data than AMEA or US; 16 studies reported on SLT product data from Europe, of which seven were exclusively from EU.

Mortality
A fair-rated study that pooled 9 Swedish cohort studies including almost 420,000 subjects found no association between exclusive current snus use and all-cause mortality (HR=1.16; 95% CI: 0.89-1.50), compared with non-snus use in never-smokers.59 A fair-rated cohort study on around 10,000 prostate cancer patients in Sweden found increased overall mortality (HR=1.19; 95% CI: 1.04-1.37) in snus users compared with non-snus users, in never smokers.60 This was similar to the risk of mortality in those using both snus and cigarettes (ever users of both snus and smoking, either concurrently or sequentially) (OR=1.17; 95% CI: 1.06-1.28). A poor-rated meta-analysis of 16 studies globally reported in Europe no significant associated with all-cause mortality or all-cancer mortality.20 There was an elevated risk of IHD mortality (OR=1.16; 95% CI: 1.05-1.28), but not stroke mortality.

Cardiovascular Outcomes
Two meta-analyses of 17 and 19 mixed-design studies, found no association between snus use in Sweden and IHD (RR=1.04; 95% CI: 0.93-1.16),55 (OR=0.91; 95% CI: 0.83-1.01).19 Stroke outcomes were reported by two studies and found not to be associated with snus use (OR=1.04, 95% CI: 0.94-1.15),18 (RR=1.04; 95% CI: 0.92-1.17).55 One of the better quality meta-analyses on 19 studies of SLT products (chewing tobacco, dip, snuff and snus) from Sweden, North America and Asia found in studies that had excluded former smokers found no increase in IHD or stroke in Sweden.19 A poor-rated meta-analysis found no association between SLT products and CHD in Europe.17
Cancer

Oral Cancer
There were no region-specific studies of oral cancer in Europe. A poor-rated global meta-analysis showed no association between SLT products (combined products) and oral cancer in Sweden or Norway. A global meta-analysis on 37 case-control and cohort studies found no association between use of snus and moist snuff with oral cancer compared with never users in European data.61

Head and Neck Cancer
A poor-rated meta-analysis showed no association between SLT products (combined products) and pharyngeal cancer in Sweden but did show excess risk of oesophageal cancer in Sweden (OR=1.26; 95% CI: 1.02-1.56) and in a single study from Norway (OR=1.40; 95% CI: 1.61-3.21).21

Other Cancer
A fair-rated study that pooled 9 cohort Swedish studies including around 420,000 subjects found, compared with never-smoking non-snus users, no association with colorectal cancer for current (HR=1.22; 95% CI: 0.91, 1.64), or former exclusive snus users (HR=1.12; 95% CI: 0.75, 1.67); no association with colon cancer (HR=1.02; 95% CI: 0.81, 1.29) in current exclusive snus users but increased risk of rectal cancer in current snus users (HR=1.38; 95% CI: 1.07, 1.77).62 There was no evidence of dose-response association between snus use and colorectal cancer for quantity (cans/week) or duration. No association was found with pancreatic cancer pooling the same Swedish cohort studies.63

Other Health Outcomes
A good-rated meta-analysis of Swedish cohort studies on 350,000 subjects found snus users had dramatically lower Parkinson’s disease risk (pooled HR=0.41; 95% CI: 0.28-0.61) compared with never-snus users in never-smokers, with a strong dose-response effect.64 Moderate-heavy snus quantity (pooled HR=0.41; 95% CI: 0.19-0.90) and long-term current-snus use (pooled HR=0.44; 95% CI 0.24-0.83) had lower risk. One Swedish cross-sectional study reported increased asthma (OR=1.49; 95% CI: 1.20-1.85), chronic bronchitis (OR=1.47; 95% CI: 1.21-1.78) and chronic rhinosinusitis (OR=1.37; 95% CI: 1.11-1.70) in snus-using never smokers.65

Discussion
This is one of the first articles to systematically review health outcomes from SLT product use, and in particular, to differentiate between the different types of products used in Asia, Middle East and Africa, Sweden, other parts of Europe and the US.

Two-thirds of global studies and a half of US studies evaluated mortality (66%; 50%), whereas AMEA studies mostly evaluated cancer (23%; 72%). Meta-analyses made up 100% of global studies and 57% of Europe studies. Case-control represented 50% of AMEA studies.

The most obvious flaw in study design was the combining of data of different SLT products such as in global meta-analyses.17-18,19,20,21 The findings of this review confirm the invalidity of studying different SLT products together due to their vastly different safety profiles. Despite presenting global combined data, one study went on to discuss that SLT product consumption in South East Asia leads to a much greater burden of disease than in Sweden, despite its use being equally prevalent, due to much lower levels of tobacco-specific nitrosamines and the pH in SLT products in Sweden compared to those found in South-East Asia.21

Another common flaw was the widespread failure to account for dual and former cigarette smoking, which is discussed in detail later.
Health Outcomes

There were very different findings on health outcomes between different SLT products in different regions. Most data were from AMEA and were less likely to be rigorous than those from Europe and the US. Nevertheless, there is sufficient evidence to show that SLT products in AMEA are associated with harmful health outcomes including: higher mortality; strongly for overall, cancer, CHD; less so for respiratory mortality and not shown to increase overall CVD mortality; increased CVD morbidity, with strong associations for IHD and stroke, and mixed evidence for hypertension and dyslipidaemia.

Different SLT products, even within the same region, have hugely varied strengths of association with oral cancer. Although many were rated as of poor quality and without accounting for cigarette smoking, studies showed markedly high associations of SLT product use with oral cancer with odds ratios ranging from 29 to 39 for shammah; 23 for naswar, 11 for supari, 5.5 gutkha, 8.5 for chewing tobacco and 3.8 for tokomak dipping compared to non-use. All types of SLT products used in AMEA seem to be associated with head and neck cancers albeit with lower odds than for oral cancer, of up to 3.2 in this review.

Several poor-rated studies reported other health impacts from SLT product use in AMEA region including reductions in risk of lung disease, no impact on mental health, and harms to oral health, self-reported chronic health, obstetric and neonatal health. Due to the study flaws, and in particular a failure to adequately account for smoking, these findings would need to be further evaluated.

Several studies showed a strong dose effect from both duration and quantity of use of SLT products in AMEA region.

In stark contrast, there were sparse but higher quality studies in Europe, predominantly in Sweden. Snus and other SLT products used in Sweden and other parts of Europe have not been shown to cause higher mortality or morbidity overall or from overall mortality, CVD or cancers. Two high quality meta-analyses showed no excess mortality, although one smaller cohort study contradicted this finding. Five meta-analyses found no excess IHD risk, and four found no excess stroke risk. Global data showed no excess oral or head and neck cancers in European data. Swedish studies showed no increase in pancreatic or colon cancer but raised risk of rectal cancer in snus users.62 The differences in detrimental health outcomes seen between snus users in Sweden and other parts of Europe compared to elsewhere may in part be attributable to the different chemical content.67 There was robust evidence from a review of pooled studies rated as ‘good’ for a protective effect of snus for the development of Parkinson’s disease (by more than 50%).64 A single cross-sectional study reported harms to respiratory disease from snus use.65

Studies from the US showed more mixed results from SLT product use with some evidence of harmful health outcomes. Meta-analyses and longitudinal studies showed mixed results for overall mortality, and mortality due to CHD, overall cancer and smoking-related cancers but no excess risk of respiratory or CVD mortality. Risk of non-fatal CVD were also mixed but the study with the highest level of evidence and rates as good reported elevated risk for both IHD and stroke.55 A single cross-sectional study reported lower rates of hypertension in SLT product users. There were also mixed results for oral and head and neck cancers ranging from no excess risk to a pooled odds ratio of 1.8 for risk.57

Newer products such as tobacco-free nicotine pouches have not been captured in this review and warrant further investigation as they may pose different health risks. Of the 53 studies included, none reported on the health impact of switching from cigarettes to SLT products.
Levels of evidence, quality and study design
No studies were rated above 2A for level of evidence. There were no meta-analyses or pooled studies of interventional studies, and there were no interventional studies, which perhaps reflects the difficulty of conducting such studies in real world settings. Meta-analyses comprised the most common type of study at 21 studies out of 53. Whilst many meta-analyses were very large, including over 30 individual studies21,68 and 350,000 participants or more,64-63 the size did not reflect the quality of the studies, with only five being rated as good.17-19,28,55,64 Particularly problematic themes in the meta-analyses were the pooling of different SLT products, failing to account for heterogeneity of studies, pooling studies despite variation in sampling methodologies eg different measurement of exposures and outcomes, and failing to report on country-specific results where available.

Case-control and cross-sectional studies also made up a majority of study designs, both are which are problematic in terms of being unable to account for biases. In the case of cross sectional studies, failing to account for temporality of the exposure and outcome, as well as former smoking status, mean that such study findings are inadequate for causal inferences.

Included studies that were global (66%) and from AMEA region (53%) were predominantly rated as being of poor quality. Studies that were exclusively from Europe (100%) and US (66%) had predominantly good or fair-ratings. All studies of exclusively European data were from Sweden.

Definitions of exposures
Studies with poor definitions of exposure failed to account for or report on quantity and duration of SLT product use, dual and former use of cigarettes and SLT products, and in former smokers, duration since quitting. Standard definitions exist for smoking that consider both quantity and duration69 and similar approaches should be used for SLT products. Furthermore, a strong dose response effect has been demonstrated in several studies for both the quantity and duration of SLT product use in AMEA which should form part of the measurement of exposure.

Accounting for smoking status
Indian SLT product users often smoke concurrently70,71 and it is essential for both dual and former cigarette use to be accounted for when investigating health outcomes. Of snus use in Sweden, 82% were former or dual users of cigarettes.72 Overall in our review, only nine studies accounted for both former and current smoking, four out of 11 studies in US and Europe and six out of 49 studies from global and AMEA regions. Future studies must apply far more rigour in investigating sole use of SLT products in never-smokers in order to ascertain its true health impact.

Publication Bias
Many of the meta-analyses and pooled analyses found no formal evidence for publication bias. However, the small number of studies investigating SLT products in Sweden, Europe and US suggests that this is a heavily under-researched topic and the preponderance of reporting on negative outcomes could indicate the presence of publication bias.

Role of SLT products in reducing smoking rates
The prevalence of SLT product use in India is 30% in men and 13% in women, much higher than use of cigarettes (7% men, 0.6% women) and bidis (14% men, 1.2% women) and represents two-thirds of all global smokeless tobacco use.73

There are also schools of thought that snus in Sweden has led to low smoking prevalence rates through a “reverse gateway” effect.74 In addition, use of snus by smokers has been associated with decreased cigarette smoking and increased abstinence of smoking.74,75,76,77,78,79,80 Other studies
do not support some of these findings.\textsuperscript{81,82,83} The low prevalence of smoking in favour of snus use in Sweden compared to the rest of Europe may contribute to its lower rates of tobacco-attributable deaths and cancer-specific deaths. For example, recent data from the Global Burden of Disease (GBD) Study suggest the tobacco-attributable age-standardised death rate in men in 2019 was 72 per 100,000 (versus an average of 128 per 100,000 for the rest of the EU).\textsuperscript{84} Similarly, the tobacco-attributable death rate from smoking-related cancers in Swedish men is dramatically lower at 14 per 100,000 than the EU average of 36 per 100,000. This strengthens the argument for safer forms of SLT products such as Swedish snus to be used as a form of tobacco harm reduction on the pathway to stopping smoking. Indeed, data from Swedish longitudinal studies show that in primary smokers who started secondary snus use, 10.6% reduced to occasional smoking and 76.3% stopped smoking altogether.\textsuperscript{5} Furthermore, studies following up secondary snus users up to seven years show that between 40-50% later also quit snus use.\textsuperscript{5,85} Furthermore, modelling has suggested that switching from smoking to Swedish snus is likely to result in net health gains.\textsuperscript{86} The efficacy of using snus as means to eventually stopping tobacco use will need further investigation as a public health intervention in wider settings and with comparison to alternatives, such as electronic nicotine delivery systems.

**Informing Policy**

The findings of our review have implications for policy makers. SLT products are subjected to various regulations with regard to sales restrictions, advertising, packaging and labelling.\textsuperscript{87} SLT product sales are banned in Hong Kong, Thailand, Singapore, New Zealand, Australia, Uganda and Saudi Arabia. Advertising is banned or restricted in many countries such as the US, where advertisements for SLT products may not contain “low risk” claims unless they have received a product-specific authorization as is the case for only a small number of Swedish snus products.\textsuperscript{88}

The Tobacco Products Directive (TPD) in the European Union has set SLT product rules that are in complete opposition with the findings of the current study or previous scientific evidence with a total ban on Swedish snus whilst allowing South-East Asian SLT products.\textsuperscript{89} Sweden is exempted from that ban and post-Brexit UK may also be exempt in the future. The future of the snus ban in EU countries other than Sweden remains a matter of conflicting views. Sweden has demonstrated what can be achieved through strong regulation of composition of their SLT products; SLT product-related harm has not only been reduced significantly, but snus is now used to reduce harm from smoking.\textsuperscript{90} The findings of this review, together with growing evidence of their role in reducing smoking rates, do not support the continuation of a ban on Swedish snus and other tobacco harm reduction products as a safer alternative to cigarette smoking.

**Strengths and limitations**

As noted in one of the meta-analyses included in this review,\textsuperscript{20} it is a challenge to estimate the risk of disease attributable to such a heterogeneous risk factor such as SLT products. Any review involving SLT products will be limited by these issues, unless a single product is studied such as the European snus or the Asian naswar.\textsuperscript{20} The output of our systematic review is also limited due to the reliance on studies which have reported on heterogenous SLT products. Furthermore, a meta-analysis of the included studies could not be undertaken due to the methodological flaws and vast heterogeneity between studies as discussed earlier.

We sought to identify only those articles where the main research question was on health outcomes from use of SLT products. The key health outcomes under investigation were mortality, CVD, respiratory and cancer as these make up the major health concerns from SLT products. We also searched for general health outcomes to identify the breadth of health outcomes being reported.
Conclusion
Our review found that studies on SLT product use focus predominantly on negative health impacts and no studies were identified that reported on the health impact from switching from cigarettes to SLT products. The strength of evidence and quality of the published studies are generally poor, particularly for global studies and those from SE Asia, Middle East and Africa.

Our review found large differences on the impact on health outcomes between different SLT products in different regions. The majority of studies on SLT products in the SE Asia, Middle East and Africa region were not of high quality, but there is sufficient evidence to show they are associated with harmful health outcomes including higher overall and cancer mortality, CVD morbidity, and greatly increased morbidity from most smoking-related cancers, in particular oral cancer.

In stark contrast, SLT products used in Sweden and other parts of Europe such as snus have not been shown on the whole to cause higher mortality or morbidity from CVD or most cancers with evidence for a protective effect against the development of Parkinson’s disease. SLT product use in the US shows more mixed results for mortality, CVD and cancer outcomes with a higher risk than for Europe but substantially lower than those from SE Asia, Middle East and Africa.

Respiratory and mental health outcomes have not been studied adequately to form a conclusion on impact from SLT product use.

Further studies are required to investigate health outcomes from switching from cigarettes to SLT products and to investigate the full breadth of health outcomes. Furthermore, in order to determine the net health impact of SLT products, the benefits of quitting smoking must be weighed against any health impact (from the use of SLT products). The wider impacts from SLT product use on society, such as new uptake in never smokers and nicotine addiction as must also be factored in; these were outside of the scope of this review.

Considering the widespread and increasing use of SLT products in certain parts of the world, there is far less evidence base for their impact on health outcomes compared with cigarette smoking, which is in part due to their predominant use in developing countries. However, the emergence of SLT products as a driver for reduced smoking rates in Sweden and other parts of Europe warrant further clarification of risk from specific and novel SLT products.
Author Contributions
CH, ES and RP designed the study, conducted data extraction, analysis and review. CH and ES wrote the manuscript; LR, SS and RP reviewed and edited the manuscript. The authors would like to acknowledge Mr Hesham Nasr for his help in retrieving articles and compiling the study.

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Declaration of interests:
CH received reimbursement from ECLAT for research conducted on tobacco harm reduction (2019–2020) including this article; she has served as a paid member of the advisory panel for the Tobacco Transformation Index (contracted by Sustainability, Sept 2019–April 2020); she is a paid consultant to TEVA pharmaceuticals on work related to multiple chronic conditions (2017 to present). ES received reimbursement from ECLAT for research conducted on tobacco harm reduction (2019–2020) including this article. LR has no conflict of interest to declare. SS has no conflict of interest to declare. RP is full-time employee of the University of Catania, Italy. In relation to his work in the area of tobacco control and respiratory diseases, RP has received lecture fees and research funding from Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, MSD, Boehringer Ingelheim, Novartis, Duska Therapeutics, and Forest Laboratories. He has also served as a consultant for Pfizer, Global Health Alliance for treatment of tobacco dependence, CV Therapeutics, NeuroSearch A/S, Boehringer Ingelheim, Novartis, Duska Therapeutics, Alfa-Wassermann, Forest Laboratories, ECITA (Electronic Cigarette Industry Trade Association, in the UK), Arbi Group Srl., and Health Diplomats. RP is the Founder of the Center of Excellence for the acceleration of Harm Reduction at the University of Catania (CoEHAR), which has received a grant from Foundation for a Smoke Free World to develop and carry out eight research projects. RP is also currently involved in the following pro bono activities: scientific advisor for LIAF, Lega Italiana Anti Fumo (Italian acronym for Italian Anti-Smoking League) and Chair of the European Technical Committee for standardization on "Requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437; WG4). SS has no conflict of interest to declare, and has never accepted funding from any tobacco or nicotine commercial or charitable interest, including the FSFW.
APPENDIX 1

Search Terms
Search terms for SLT: Smokeless tobacco; SLT, Chewing tobacco; Reduced risk tobacco; Non-cigarette tobacco; Snus; Snuff

Search terms for health outcomes: Health outcome; Morbidity; Mortality; Cancer; Cardiovascular disease; Chronic obstruct pulmonary disease; COPD; CVD; Acute myocardial infarction; Stroke; Cardiovascular; Cerebrovascular; Health effects; Adverse; effects; Respiratory.

APPENDIX 2

Abbreviations:
AMEA: Asia, Eastern Mediterranean and Africa
AMR: Americas Region
BMI: Body mass index
CAD: Coronary artery disease
CHD: Coronary heart disease
COPD: Chronic obstructive pulmonary disease
CVD: Cardiovascular disease
DALYs: Disability-adjusted life years
DBP: Diastolic blood pressure
EUR: European Region
HNC: Head and neck cancer
IHD: Ischemic heart disease
MI: Myocardial infarction
SBP: Systolic blood pressure
SEAR: Southeast Asian Region
SLT: Smokeless tobacco
APPENDIX 3

Table 4. Description of Studies, Level of Evidence and Quality for Health Outcomes from SLT (see attachment).
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