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RESEARCH ARTICLE

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Global burden of disease due to smokeless tobacco consumption in adults: an updated analysis of data from 127 countries



Kamran Siddiqi^{1,2*}, Scheherazade Husain¹, Aishwarya Vidyasagar¹, Anne Readshaw¹, Masuma Pervin Mishu¹ and Aziz Sheikh³

Abstract

Background: Smokeless tobacco (ST) is consumed by more than 300 million people worldwide. The distribution, determinants and health risks of ST differ from that of smoking; hence, there is a need to highlight its distinct health impact. We present the latest estimates of the global burden of disease due to ST use.

Methods: The ST-related disease burden was estimated for all countries reporting its use among adults. Using systematic searches, we first identified country-specific prevalence of ST use in men and women. We then revised our previously published disease risk estimates for oral, pharyngeal and oesophageal cancers and cardiovascular diseases by updating our systematic reviews and meta-analyses of observational studies. The updated country-specific prevalence of ST and disease risk estimates, including data up to 2019, allowed us to revise the population attributable fraction (PAF) for ST for each country. Finally, we estimated the disease burden attributable to ST for each country as a proportion of the DALYs lost and deaths reported in the 2017 Global Burden of Disease study.

Results: ST use in adults was reported in 127 countries; the highest rates of consumption were in South and Southeast Asia. The risk estimates for cancers were also highest in this region. In 2017, at least 2.5 million DALYs and 90,791 lives were lost across the globe due to oral, pharyngeal and oesophageal cancers that can be attributed to ST. Based on risk estimates obtained from the INTERHEART study, over 6 million DALYs and 258,006 lives were lost from ischaemic heart disease that can be attributed to ST. Three-quarters of the ST-related disease burden was among men. Geographically, > 85% of the ST-related burden was in South and Southeast Asia, India accounting for 70%, Pakistan for 7% and Bangladesh for 5% DALYs lost.

Conclusions: ST is used across the globe and poses a major public health threat predominantly in South and Southeast Asia. While our disease risk estimates are based on a limited evidence of modest quality, the likely ST-related disease burden is substantial. In high-burden countries, ST use needs to be regulated through comprehensive implementation of the World Health Organization Framework Convention for Tobacco Control.

Keywords: Cancer, Chewing, Ischaemic heart disease, Mouth, Oral, Oesophagus, Pharynx, Smokeless tobacco

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Background

Smokeless tobacco (ST) refers to various tobacco-containing products that are consumed by chewing, keeping in the mouth or sniffing, rather than smoking [1]. ST products of many different sorts are used by people in every inhabited continent of the world (Table 1) [1]. For example, in Africa, *toombak* and snuff are commonly used, while in South America, *chimó* is the product of choice. In Australia, indigenous people use *pituri* or *mingkulpa* [2], and in Central Asia, *nasvay* consumption is very common. In North America, plug or snuff are favoured, and even in Western Europe, where ST products are largely banned, there are exemptions allowing people in Nordic countries to use *snus* [3]. All the above products vary in their preparation methods, composition and associated health risks (Table 1), but it is in South and South-east Asia where the greatest diversity of ST products exists, accompanied by the highest prevalence of use [4]. Here, the level of cultural acceptability is such that ST products are often served like confectionery at weddings and other social occasions.

ST products contain nicotine and are highly addictive. Often, they also contain carcinogens, such as tobacco-specific nitrosamines (TSNA), arsenic, beryllium, cadmium, nickel, chromium, nitrite and nitrate, in varying levels depending on the product [5, 6]. The pH of the products also varies widely, with some (e.g. *khaini*, *zarda*) listing slaked lime among their ingredients [7]. Raising the pH in this way increases the absorption of nicotine and enhances the experience of using the ST product, increasing the likelihood of dependence. The elevated pH also increases the absorption of carcinogens, leading to higher toxicity and greater risk of harm [7].

The harmful nature of many ST products, and the fact that 300 million people around the world use ST [8], make ST consumption a global public health issue. Many ST products lead to different types of head and neck cancers [9, 10]. An increased risk of cardiovascular deaths has been reported [11], and its use in pregnancy is associated with stillbirths and low birth weight [12, 13].

Because of the diversity described above, ST should not be considered as a single product, but rather as groups of products with differences in their toxicity and addictiveness, depending on their composition. As a consequence, it is difficult to estimate the global risks of ST to human health and to agree on international policies for ST prevention and control. Several country-specific studies [14, 15] have been carried out, and in 2015, we published an estimate of the global burden of disease associated with ST use [16]. We used a novel approach, whereby we classified ST products according to their availability in different geographical regions of the world. For example, ST products in South Asia pose a much greater risk to health than those available in

Nordic countries, where the manufacturing process removes many of the toxins from the finished product [6, 17]. Using this approach, we estimated the worldwide burden of disease attributable to ST consumption, measured in terms of disability adjusted life years (DALYs) lost and the numbers of deaths in 2010 [16]. Here, we update this estimate to include data up to 2019, providing an indication of how the global ST arena has changed in the intervening years.

Methods

Our methods for updating the estimates of ST disease burden were broadly the same as those used in our earlier publication; these are well described elsewhere [16]. Here, we will summarise these methods and explain any modification made, particularly in relation to the revised timelines. We assessed disease burden for individual countries by varying their populations' exposure to ST, using the comparative risk assessment method [15]. These individual estimates were then summarised for 14 World Health Organization (WHO) sub-regions (Additional file 1: Appendix 1) as well as for the world.

We first searched the literature to identify the latest point prevalence of ST use among adults ≥ 15 years in men and women for each country (see Additional file 1: Appendix 2 for detailed methods). We searched for the latest estimates for x countries included in our previous study as well as those additional y countries where estimates have been made available since 2014 for the first time. We derived single estimates for each country preferring nationally representative surveys using internationally comparable methods over non-standardised national or sub-national surveys.

We also updated risk estimates for individual diseases caused by ST; however, we kept to the original list of conditions, i.e. cancers of the oral cavity, pharynx and oesophagus, ischemic heart disease and stroke. We only searched for papers published since our last literature search; our updated search strategies can be found in Additional file 1: Appendix 3. As before, all searches and data extraction were independently scrutinised by a second researcher and any discrepancies were arbitrated by a third researcher. All case definitions for diseases and exposure (ST use) used in the retrieved articles were checked for accuracy and consistency and all analyses undertaken in these studies were assessed to see if they controlled for key confounders (mainly smoking and alcohol). We assessed study quality using the Newcastle-Ottawa Scale for assessing non-randomised studies in meta-analysis [24]. For all new studies, we log transformed their risk estimates and 95% confidence intervals to effect sizes and standard errors and added these to the rerun of our random-effects meta-analyses to estimate pooled risk estimates for individual conditions.

Table 1 Smokeless tobacco products consumed most commonly across the world

| Smokeless tobacco products | Regions (WHO) | Countries (highest consumption) | Other ingredients | Preparation and use | pH ^a | Nicotine ^a (mg/g) | Total TSNA ^a (ng/g) |
|--------------------------------|--|---|---|---|-----------------|------------------------------|--------------------------------|
| Snus (Swedish) | Europe (region A) | Nordic countries (Denmark, Finland, Iceland, Norway, Sweden) | Water, sodium carbonate, sodium chloride, moisturisers, flavouring | A heat treatment process; placed between the gum and upper lip | 6.6–7.2 | 7.8–15.2 | 601–723 |
| Plug, Snuff (US), Snus (US) | Americas (regions A and B) | The USA, Canada, Mexico | Sweeteners, liquorice | Plug: air cured Dry or moist snuff; finely ground and fire cured Snus: steam cured Snuff; kept between lip and gum, dry snuff can be inhaled too | 4.7–7.8 | 3.9–40.1 | 313–76,500 |
| Chimó | Americas (region B) | Venezuela, Colombia | Sodium bicarbonate, brown sugar, Mamo'n tree ashes | Tobacco paste made from tobacco leaves; placed between the lip or cheek and gum and left there for some time | 6.9–9.4 | 5.3–30.1 | 9390 |
| Nass (Naswar) | Europe (region B) and Eastern Mediterranean (region D) | Uzbekistan, Kyrgyzstan, Tajikistan, Afghanistan, Pakistan, Iran | Lime, ash, flavourings (cardamom), indigo | Sundried and powdered; placed between lip or cheek and gum | 8.4–9.1 | 8.9–14.2 | 478–1380 |
| Toombak | Eastern Mediterranean (region D) and Africa (region D) | Sudan, Chad | Mixed with moist sodium bicarbonate | Fermented and ground; placed and kept in mouth | 7.3–10.1 | 9.6–28.2 | 295,000–992,000 |
| Snuff (North and West African) | Africa (region D) | Nigeria, Ghana, Algeria, Cameroon, Chad, Senegal | Dried tobacco leaves mixed with potassium nitrate and other salts | Dry snuff; finely ground and inhaled as a pinch Moist snuff is placed in mouth | 9.0–9.4 | 2.5–7.4 | 1520–2420 |
| Snuff (South African) | Africa (region E) | South Africa | Dried tobacco leaves mixed with ash | Dry snuff; finely ground and inhaled as a pinch | 6.5–10.1 | 1.2–17.2 | 1710–20,500 |
| Khaini | South East Asia (regions B and D); Western Pacific (region B), Eastern Mediterranean (region D), and Europe (region A) | India, Bangladesh, Nepal, Bhutan | Slaked lime, menthol, flavourings, areca nut | Shredded; kept in mouth between lips and gum | 9.6–9.8 | 2.5–4.8 | 21,600–23,900 |
| Zarda | South East Asia (regions B and D); Western Pacific (region B), Eastern Mediterranean (region D), and Europe (region A) | Bangladesh, India, Pakistan, Myanmar, Thailand, Indonesia, Nepal, Maldives, Sri Lanka, UK | Served wrapped in a betel leaf with lime, catechu, areca nuts | Shredded tobacco leaves are boiled with lime and saffron; the mixture is dried then chewed and spat | 5.2–6.5 | 9.5–30.4 | 5490–53,700 |
| Gutkha | Eastern Mediterranean (region B) | India, Pakistan, Bangladesh, Nepal, Myanmar, Sri Lanka, UK | Betel nut, catechu, flavourings, sweeteners | Commercially manufactured; sucked, chewed, and spat | 7.4–8.9 | 0.2–4.2 | 83–23,900 |
| Afzal | Eastern Mediterranean (region B) | Oman | Dried tobacco mixed with various additives | Fermented; kept in mouth between lips and gums, users suck the juice, and spit out the rest | 10.4 | 48.7 | 3573 |
| Iqimik | Americas (region A) | The USA | Tobacco combined with fungus or plant ash | Involves a burning process to make fungus ash; chewed | 11.0 | 35.0–43.0 | 15–4910 |
| Rapé | Americas (region B) | Brazil | Tobacco mixed with finely ground plant materials (tonka bean, cinnamon, clove buds, etc.) or alkaline ashes | Nasal snuff; air cured or heated, then pulverised, finely sifted, and mixed | 5.2–10.2 | 6.3–47.6 | 88–24,200 |
| Pituri/Mingkulpa | Western Pacific (region B) | Australia | Tobacco mixed with wood ash | Chewed as quid, kept in mouth and/or held against skin | 5.47–11.6 | 4.8 | 15,280 |

WHO World Health Organization, TSMA tobacco-specific nitrosamines

^aFigures are adapted from [1, 2, 18–23]

Where possible, we pooled effect sizes to obtain country-specific risk estimates. For all outcomes in the meta-analyses, we conducted a GRADE assessment to assess the quality of evidence. We also pooled these effect sizes to obtain non-specific global risk estimates. Given that the risk varies from country to country, depending upon which products are locally popular, we used country-specific risk estimates where possible. In countries with no estimates, we used estimates of those countries where similar ST products were consumed. For other countries without estimates that consumed ST products known to contain high levels of TSNA, we applied non-specific global estimates. Where no information was available on the composition of ST, we did not apply any estimates. Details on how these statistically significant estimates were applied to each WHO sub-region can be found in web Additional file 1: Appendix 4.

Based on the extent to which the included studies adjusted for potential confounders, we categorised them as 'best-adjusted' and 'others'. We carried out a sensitivity analysis for all risks and attributable disease burden estimates including only 'best-adjusted' studies. A sensitivity analysis was also carried out by estimating risk estimates separating out cohort from case-control studies.

For each country, we used their point prevalence of ST use and the allocated risk estimate for each condition to estimate its population attributable fraction (PAF) as below:

$$\text{PAF} = P_e(\text{RR}_e - 1) / [1 + P_e(\text{RR}_e - 1)]$$

P_e = Prevalence RR_e = Relative risk

Using the 2017 Global Burden of Disease (GBD) Study, we also extracted the total disease burden (B) in terms of number of deaths and DALYs lost due to the conditions associated with ST use for both men and women. The attributable burden (AB) due to ST was then estimated in deaths and DALYs lost for these conditions for both men and women using the following equation.

$$\text{AB} = \text{PAF} \times B$$

Results

ST consumption was reported in 127 countries (Fig. 1). These estimates were extracted from nationally representative cross-sectional surveys conducted either as part of international (97/127) or national (30/127) health and tobacco surveillance (Additional file 1: Appendix 5a). A variety of age ranges (as young as 15 or as old as 89, including no upper age limit) were used to define adults.

ST consumption was more common among males than females in 95 countries (Table 2). Among males, Myanmar (62.2%), Nepal (31.3%), India (29.6%), Bhutan

(26.5%) and Sri Lanka (26.0%) had the highest consumption rates. Among females, Mauritania (28.3%), Timor Leste (26.8%), Bangladesh (24.8%), Myanmar (24.1%) and Madagascar (19.6%) had the highest consumption rates. Within Europe, Sweden (25.0% males, 7.0% females) and Norway (20.1% males, 6.0% females) had the highest ST (snus) consumption rates.

Our post-2014 systematic literature search identified an additional four studies demonstrating a causal association between ST and oral cancer; these included two Pakistan-based and one India-based case-control studies and one US-based cohort study (Table 3). No new studies were found for pharyngeal and oesophageal cancers. PRISMA flow diagrams describing the selection process of the studies identified in the literature searches are provided in Additional file 1: Appendix 5b,c. By adding the new studies to the list of studies selected in our first estimates and revising the meta-analyses, we found that the pooled estimates were statistically significant for cancers of the mouth (Fig. 2). The non-specific pooled estimate for oral cancers, based on 36 studies, were 3.94 (95% CI 2.70–5.76). The country-specific relative risk for oral cancers for India was higher (RR 5.32, 95% CI 3.53–8.02) than non-specific estimates and for the USA remained statistically insignificant (RR 0.95, 95% CI 0.70–1.28). Since no new studies were added for pharyngeal and oesophageal cancers, their non-specific risk estimates of 2.23 (95% CI 1.55–3.20) and 2.17 (95% CI 1.70–2.78) remained as per our original estimates, respectively. For cardiovascular diseases, we identified another three Swedish studies for ischaemic heart disease and another two (one in Asia and one in Sweden) for stroke (Table 3). In the absence of any new non-Swedish studies on ischaemic heart disease (Fig. 3), we considered the relative risk (adjusted odds ratio 1.57, 95% CI 1.24–1.99) of myocardial infarction due to ST identified in the 52-country INTERHEART study [35] (conducted across nine WHO regions) as a valid estimate. However, the country-specific (Sweden) relative risk for ischaemic heart disease (RR 0.94, 95% CI 0.87–1.03) and both country-specific (RR 1.02, 95% CI 0.93–1.13 [Sweden]) and non-specific relative risks for stroke (RR 1.03, 95% CI 0.94–1.14) remained statistically insignificant. The GRADE assessment was moderate for oral, pharyngeal and oesophageal cancers and low for IHD (see Additional file 1: Appendix 7).

We found that most of the included studies adjusted for potential confounders (35/38 for oral, 10/10 for pharyngeal and 15/16 for oesophageal cancers; and 13/16 for IHD) and classified as providing 'best adjusted' estimates. According to a sensitivity analysis restricted to only 'best-adjusted' studies, the overall risk estimates (RR/OR) for oral cancer increased from 3.94 to 4.46 and for oesophageal cancer from 2.17 to 2.22 (see Additional

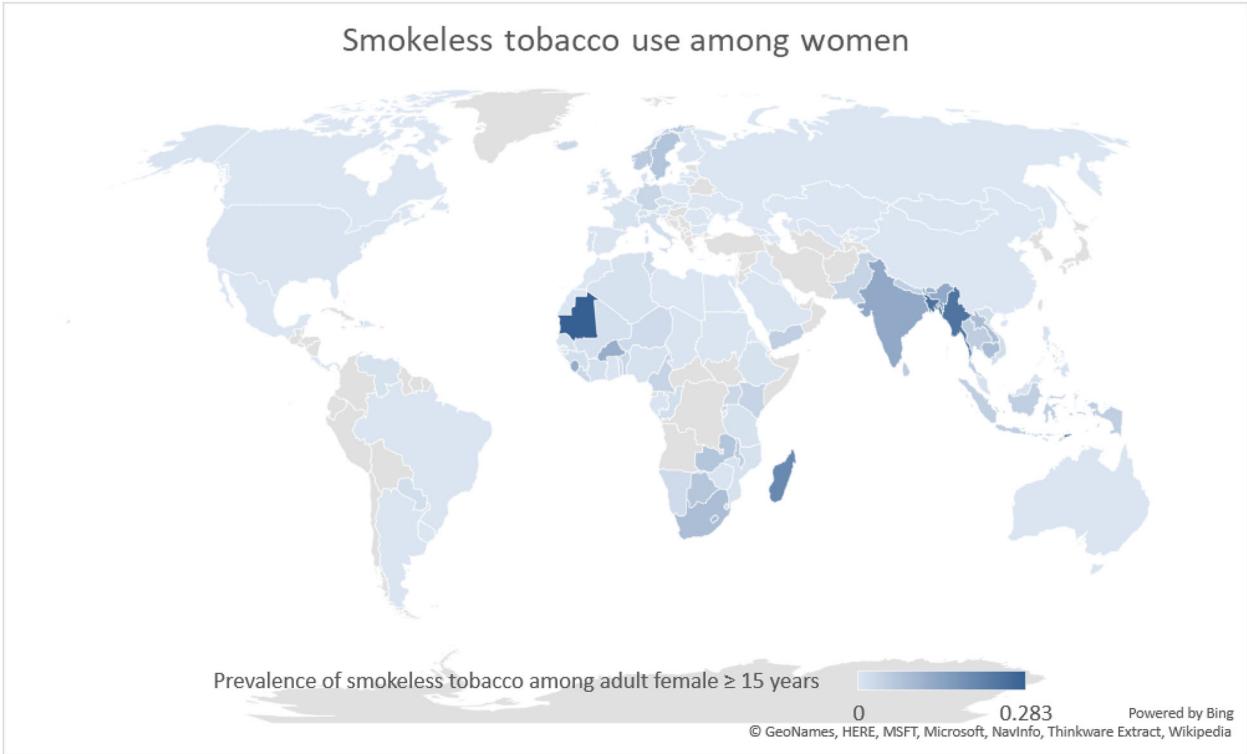
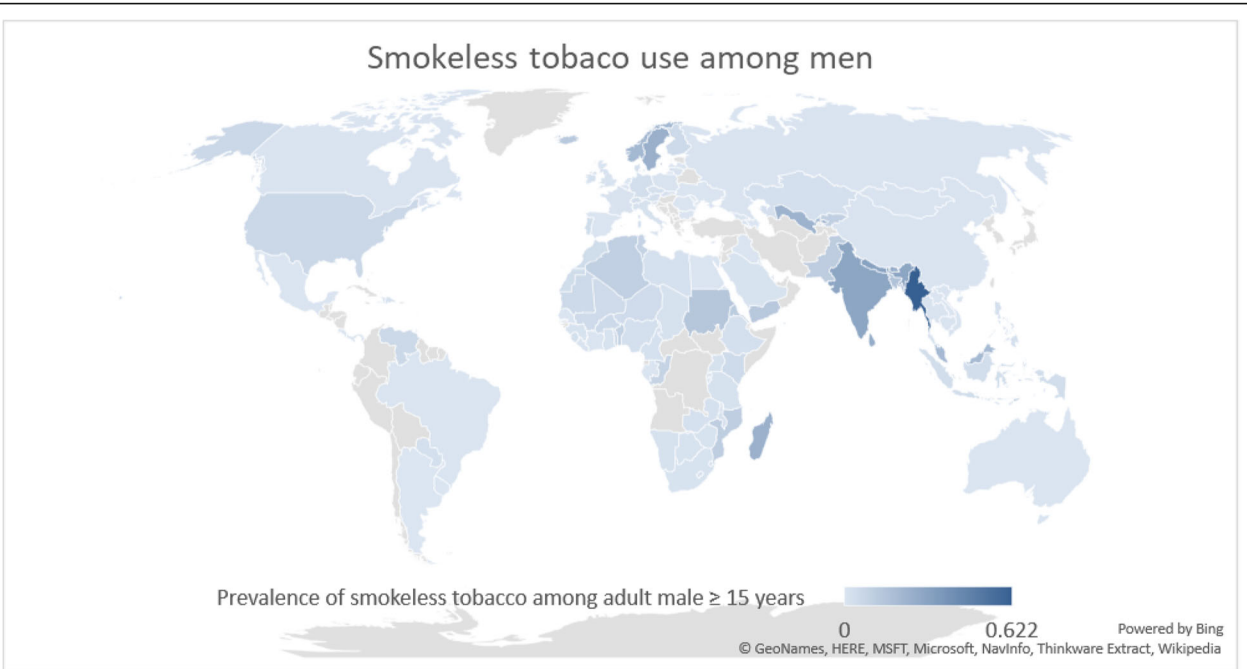


Fig. 1 Smokeless tobacco prevalence among men and women

Table 2 Prevalence of smokeless tobacco use (%) in different countries of the world according to WHO sub-regional classification

| WHO sub-regions | Country | M | F | Source | Year |
|----------------------------|---------------------|-------|------------|---|---------|
| Africa (region D) | Algeria* | 10 | 0.8 | Algeria Adult Tobacco Survey [25] | 2010 |
| | Benin* | 9 | 3 | STEPS [26] | 2015 |
| | Burkina Faso* | 5.6 | 11.6 | STEPS [26] | 2013 |
| | Cameroon* | 2.2 | 3.8 | GATS [27] | 2013 |
| | Cape Verde | 3.5 | 5.8 | STEPS [26] | 2007* |
| | Chad | 1.9 | 0.4 | STEPS [26] | 2008 |
| | Comoros | 7.72 | 2.99 | DHS [28] | 2012 |
| | Gabon | 0.48 | 0.34 | DHS [28] | 2012 |
| | Gambia | 0.8 | 1.4 | STEPS [26] | 2010 * |
| | Ghana | 1.33 | 0.2 | DHS [28] | 2008 |
| | Guinea | 1.4 | 1.5 | STEPS [26] | 2009 |
| | Liberia* | 1.1 | 3.1 | STEPS [26] | 2011 |
| | Madagascar | 24.66 | 19.6 | DHS [28] | 2009 |
| | Mali | 5 | 1.2 | STEPS [26] | 2007 |
| | Mauritania | 5.7 | 28.3 | STEPS [26] | 2006 |
| | Niger | 4.55 | 2.3 | DHS [29] | 2012 |
| | Nigeria* | 2.9 | 0.9 | GATS [27] | 2012 |
| | Sao Tome & Principe | 3.8 | 1.9 | STEPS [26] | 2009 |
| | Senegal* | 0.3 | 1 | GATS [27] | 2015 |
| | Seychelles** | 0.3 | 0.4 | The Seychelles Heart Study IV [25] | 2013–14 |
| Sierra Leone | 2.9 | 12.1 | STEPS [26] | 2009 | |
| Togo | 5.1 | 2.2 | STEPS [26] | 2010 | |
| Africa (region E) | *Botswana* | 1.5 | 6.5 | STEPS [26] | 2014 |
| | *Burundi | 0.03 | 0.31 | DHS [28] | 2011 |
| | Congo (Brazzaville) | 8.3 | 1.54 | DHS [28] | 2012 |
| | Congo (Republic) | 8.67 | 3.22 | DHS [28] | 2013 |
| | Côte d'Ivoire | 0.61 | 1.27 | DHS [28] | 2012 |
| | Eritrea* | 11.6 | 0.1 | STEPS [26] | 2011 |
| | Ethiopia* | 2.6 | 0.8 | GATS [27] | 2016 |
| | Kenya* | 5.3 | 3.8 | GATS [27] | 2014 |
| | *Lesotho | 1.3 | 9.1 | DHS [29] | 2009 |
| | *Malawi | 1.9 | 5 | STEPS [26] | 2009 |
| | Mozambique | 10.94 | 0.82 | DHS [28] | 2011 |
| | Namibia | 1.8 | 2.3 | DHS [29] | 2006–07 |
| | Rwanda* | 0.6 | 3.3 | STEPS [26] | 2012 |
| | *South Africa* | 1.4 | 8.4 | South African Social Attitude Survey [25] | 2007 |
| | Swaziland* | 2.7 | 1.8 | STEPS [26] | 2014 * |
| | *Tanzania | 2.03 | 0.83 | DHS [28] | 2010 |
| | Uganda* | 1.7 | 3 | GATS [27] | 2013 |
| | Zambia* | 2.2 | 6.8 | STEPS [26] | 2017 |
| Zimbabwe | 1.6 | 0.4 | DHS [30] | 2011 | |
| Americas (region A) | *Canada* | 0.8 | – | CTADS [31] | 2015* |
| | USA | 6.5 | 0.4 | ICS [30] | 2010 |

Table 2 Prevalence of smokeless tobacco use (%) in different countries of the world according to WHO sub-regional classification (Continued)

| WHO sub-regions | Country | M | F | Source | Year |
|---|-------------------------------|------|--|---|----------|
| Americas (region B) | Argentina | 0.1 | 0.2 | GATS [27] | 2012 |
| | Barbados | 0 | 0.6 | STEPS [26] | 2007* |
| | *Brazil | 0.6 | 0.3 | GATS [27] | 2008 |
| | Costa Rica** | 0.1 | 0 | GATS [27] | 2015 |
| | Dominican Republic | 1.9 | 0.3 | DHS [29] | 2007* |
| | Grenada | 2.2 | 0.3 | STEPS [26] | 2011 |
| | Mexico* | 0.4 | 0 | GATS [27] | 2015 |
| | Panama** | 1 | 0.5 | GATS [27] | 2013 |
| | Paraguay | 3 | 1.6 | STEPS [25] | 2011 |
| | St Kitts & Nevis ⁹ | 0.3 | 0.1 | STEPS [26] | 2007 |
| | St Lucia** | 1.3 | 0.2 | STEPS [26] | 2012* |
| | Trinidad & Tobago | 0.5 | 0.3 | STEPS [26] | 2011 |
| | *Uruguay** | 0.3 | – | GATS [27] | 2009 |
| | Venezuela | 6.2 | 0.9 | National Survey of Drugs in the General Population [25] | 2011 |
| Americas (region D) | Haiti | – | 2.5 | DHS [29] | 2005–06* |
| Eastern Mediterranean (region B) | Kuwait** | 0.5 | 0 | STEPS [26] | 2014 |
| | Libya | 2.2 | 0.1 | STEPS [26] | 2009 |
| | Qatar** | 1.3 | 0 | GATS [27] | 2013 |
| | Saudi Arabia* | 1.5 | 0.3 | Saudi Health Information Survey [25] | 2014 |
| | Tunisia | 8.6 | 2.2 | ICS [30] | 2005–06 |
| Eastern Mediterranean (region D) | Egypt* | 0.4 | 0 | STEPS [26] | 2017 |
| | Iraq* | 0.4 | 0.02 | STEPS [26] | 2015 |
| | Morocco** | 4.4 | – | STEPS [26] | 2017 |
| | Pakistan* | 11.4 | 3.7 | GATS [27] | 2014 |
| | Sudan* | 14.3 | 0.2 | STEPS [26] | 2016 |
| | Yemen | 13.7 | 4.8 | National Health and Demographic Survey [25] | 2013 |
| Europe (region A) | Austria* | 2.8 | 0.5 | Representative Survey on Substance Abuse [32] | 2015 |
| | Belgium | 1.1 | 0.6 | SEBS [33] | 2012 |
| | Cyprus | 2.1 | 0.4 | SEBS [33] | 2012 |
| | Czech Republic* | 2.2 | 1.2 | The use of tobacco in the Czech Republic [25] | 2015 |
| | Denmark* | 2.3 | 0.9 | Monitoring Smoking Habits in the Danish Population [25] | 2015 |
| | Finland* | 5.6 | 0.4 | Health Behaviour and Health among the Finnish Adult Population [25] | 2014 |
| | France | 1.2 | 0.6 | SEBS [33] | 2012 |
| | Germany | 3.4 | 3.4 | SEBS [33] | 2012 |
| | Iceland* | 13 | 3 | May–December Household Surveys done by Gallup [25] | 2015 |
| | Ireland | 2.2 | 0.9 | SEBS [33] | 2012 |
| | Italy | 1.8 | 1.5 | SEBS [33] | 2012 |
| | Luxembourg | 1.8 | 1 | SEBS [33] | 2012 |
| | Malta | 5.5 | 1.5 | SEBS [33] | 2012 |
| | Netherlands | 0.3 | 0.1 | The Dutch Continuous Survey of Smoking Habits [25] | 2011 |
| Norway* | 21 | 6 | Statistics Norway Smoking Habits Survey [25] | 2015 | |

Table 2 Prevalence of smokeless tobacco use (%) in different countries of the world according to WHO sub-regional classification (Continued)

| WHO sub-regions | Country | M | F | Source | Year |
|-----------------------------------|---------------------|------|------|---|---------|
| | Portugal | 4.4 | 1.1 | SEBS [33] | 2012 |
| | Slovenia | 1.8 | 0.4 | SEBS [33] | 2012 |
| | Spain | 0.4 | 0.2 | SEBS [33] | 2012 |
| | Sweden* | 25 | 7 | National Survey of Public Health [25] | 2015 |
| | Switzerland* | 4.2 | 1.2 | Addiction Monitoring survey [25] | 2013 |
| | United Kingdom | 1.6 | 0.5 | SEBS [33] | 2012 |
| Europe (Region B) | Azerbaijan* | 0.2 | 0 | National study of risk factors for non-communicable diseases [25] | 2011 |
| | Armenia | 1.8 | 0 | DHS [29] | 2005 |
| | Bulgaria | 0.3 | 0 | SEBS [33] | 2012 |
| | Georgia | 1 | 0.2 | Survey of Risk Factors of Non-Communicable Diseases [25] | 2010 |
| | *Kazakhstan** | 2.8 | 0 | GATS [27] | 2014 |
| | Kyrgyzstan* | 10.1 | 0.1 | STEPS [26] | 2013 |
| | Poland | 1 | 0.1 | GATS [27] | 2009 |
| | *Romania | 0.4 | 0.2 | GATS [27] | 2011 |
| | Slovakia* | 1.9 | 0.8 | Tobacco and Health Education Survey [25] | 2014 |
| | Uzbekistan* | 23.2 | 0.2 | STEPS [26] | 2014 |
| Europe (region C) | Latvia* | 0.1 | 0 | Health Behaviour among Latvian Adult Population [25] | 2014 |
| | Lithuania | 1.2 | 0.2 | SEBS [33] | 2012 |
| | Moldova* | 0.1 | 0 | DHS [29] | 2013 |
| | Russia* | 0.8 | 0.1 | GATS [27] | 2016 |
| | Ukraine* | 0.4 | 0 | GATS [27] | 2017 |
| South East Asia (region B) | Indonesia* | 3.9 | 4.8 | Basic Health Research [25] | 2013 |
| | Sri Lanka* | 26 | 5.3 | STEPS [26] | 2014 |
| | Thailand | 1.1 | 5.2 | GATS [27] | 2011 |
| South East Asia (region D) | Bangladesh* | 16.2 | 24.8 | GATS [27] | 2017 |
| | Bhutan* | 26.5 | 11 | STEPS [26] | 2014 |
| | India* | 29.6 | 12.8 | GATS [27] | 2017 |
| | Maldives* | 3.9 | 1.4 | STEPS [26] | 2011 |
| | Myanmar* | 62.2 | 24.1 | STEPS [26] | 2014 |
| | Nepal* | 31.3 | 4.8 | STEPS [26] | 2013 |
| | Timor Leste* | 16.1 | 26.8 | National survey for non-communicable disease risk factors and injuries [34] | 2014 |
| Western Pacific (region A) | Australia* | 0.6 | 0.3 | National Drug Strategy Household Survey [25] | 2013 |
| | Brunei Darussalam** | 1.3 | 2.7 | Knowledge, Attitudes and Practices Survey on Non-communicable Diseases [25] | 2014–15 |

Table 2 Prevalence of smokeless tobacco use (%) in different countries of the world according to WHO sub-regional classification (Continued)

| WHO sub-regions | Country | M | F | Source | Year |
|-----------------------------------|-----------------------------------|------|-----|--|------|
| Western Pacific (region B) | Cambodia* | 0.8 | 8.6 | National Adult Tobacco Survey of Cambodia [25] | 2014 |
| | China | 0.7 | 0 | GATS [27] | 2010 |
| | Lao People's Democratic Republic* | 0.5 | 8.6 | National Adult Tobacco Survey [25] | 2015 |
| | Malaysia* | 20.4 | 0.8 | National Health And Morbidity Survey [25] | 2015 |
| | Marshall Islands** | 13.7 | 4 | STEPS [26] | 2002 |
| | Micronesia | 22.4 | 3 | STEPS [26] | 2002 |
| | Mongolia* | 0.8 | 0.2 | STEPS [26] | 2015 |
| | Niue** | 0.3 | 0.2 | STEPS [26] | 2011 |
| | Philippines* | 2.7 | 0.7 | GATS [27] | 2015 |
| | Vietnam* | 0.8 | 2 | GATS [27] | 2015 |

CTADS Canadian Tobacco Alcohol and Drugs Survey, DHS the Demographic and Health Surveys, ICS Individual Country Survey, GATS Global Adult Tobacco Survey, SEBS The Special Europe Barometer Survey, STEPS STEPwise approach to Surveillance, WHO World Health Organization

*Populations of St Kitts and Nevis are tiny and unlikely to affect our estimates

*Countries included in the earlier paper ($n = 55$), but with updated values

**New countries not included in the earlier paper ($n = 12$)

file 1: sensitivity analysis #1). Separate risk estimates for cohort and case-control studies are included in the Additional file 1: sensitivity analysis #2).

The above risk estimates were included in the mathematical model to estimate the population attributable fraction (PAF), as follows (also see Additional file 1, Appendix 4 for detailed justification): For oral, pharyngeal and oesophageal cancers, Sweden- and US-based country-specific risk estimates were applied to Europe A and America A regions, respectively. Similarly, India-based country-specific risk estimates were applied to Southeast Asia B and D and Western Pacific B regions. No risk estimates were applied to Europe C due to the non-existence of any risk estimates or information about the toxicity of ST products. For all other regions, non-specific country estimates were applied. A few exceptions were made to the above assumptions: a Pakistan-based country-specific estimate was applied for oral cancers for Pakistan and an India-based estimate for the other two cancers; for the UK, India-based country specific estimates were applied due to the predominant use of South Asian products in the country. For ischaemic heart disease, the INTERHEART disease estimates were applied to all WHO regions except two, i.e. Europe A due to the availability of Sweden-based country specific estimates and Europe C due to the non-availability of relevant information. As previously stated, an exception was made for the UK and the INTERHEART estimates were applied.

According to our 2017 estimates, 2,556,810 DALYs lost and 90,791 deaths due to oral, pharyngeal and oesophageal cancers can be attributed to ST use across the globe (Table 4). By applying risk estimates obtained from the INTERHEART study, 6,135,017 DALYs lost and 258,006 deaths from ischaemic heart disease can be

attributed to ST use. The overall global disease burden due to ST use amounts to 8,691,827 DALYs lost and 348,798 deaths. The attributable disease burden estimates when restricted to only 'best adjusted' studies, did not change significantly; the DALYs lost attributable to ST increased to 8,698,142 and deaths to 349,222.

Among these figures, three quarters of the total disease burden was among men. Geographically, > 85% of the disease burden was in South and Southeast Asia, India accounting for 70%, Pakistan for 7% and Bangladesh for 5% DALYs lost due to ST use (Additional file 1: Appendix 6).

Discussion

ST consumption is now reported in at least two thirds of all countries; however, health risks and the overall disease burden attributable to ST use vary widely depending on the composition, preparation and consumption of these products. Southeast Asian countries share the highest disease burden not only due to the popularity of ST but also due to the carcinogenic properties of ST products. In countries (e.g. Sweden) where ST products are heavily regulated for their composition and the levels of TSNAs, the risk to the population is minimal.

We found ST prevalence figures in 12 countries that did not previously report ST use; new figures were also obtained for 55 countries included in the previous estimates [16]. Among these 55 countries: 19 reported a reduction in ST use among both men and women (e.g. Bangladesh, India, Nepal), 14 only among men (e.g. Laos, Pakistan) and eight only among women (e.g. Bhutan, Sri Lanka) (Fig. 4a, b). On the other hand, 13 countries showed an incline in ST use among both men and women (e.g. Indonesia, Myanmar, Malaysia, Timor

Table 3 Smokeless tobacco use and risk of cancers, ischaemic heart disease, and stroke—studies included in meta-analysis

| Country | Study period | Study design | Exposure status | Inclusion of cigarette/alcohol users | Outcome | Odds ratio/relative risk (95% CIs) | Comments | Quality assessment (NOS) ^a | Reference |
|----------------|--------------|--------------|---------------------------------------|--------------------------------------|--|--|---|--|-----------|
| Cancers | | | | | | | | | |
| India | 2001–2004 | Case–control | SLT with or without additives | No/no | Oral cancer | 0.49 (0.32–0.75) | Exclusive SLT users | Selection**** Comparability** Exposure* | [36] |
| India | 1996–1999 | Case–control | Ever SLT users | Yes/yes | Oral cancer | 7.31 (3.79–14.1) | Never drinkers adjusted for smoking Never smokers adjusted for alcohol | Selection**** Comparability** Exposure* | [37] |
| India | 1982–1992 | Case–control | Tobacco quid chewing | Yes/no | Oral cancer Pharyngeal cancer Lung cancer | 5.80 (3.60–9.34) 1.20 (0.80–1.80) 0.70 (0.40–1.22) | Adjusted for smoking | Selection*** Comparability* Exposure* | [38] |
| India | Not clear | Case–control | Chewing tobacco | No/no | Oral cancer | 10.75 (6.58–17.56) | Exclusive SLT users | Selection** Comparability* Exposure ⁰ | [39] |
| India | 1990–1997 | Cohort | Current SLT users Former SLT users | No/no | Oral cancer | 5.50 (3.30–9.17) 9.20 (4.60–18.40) | Exclusive SLT users | Selection**** Comparability* Outcome** | [40] |
| India | 1990–1997 | Cohort | Current SLT user Former SLT users | Yes/yes | Oral cancer | 2.40 (1.70–3.39) 2.10 (1.30–3.39) | Adjusted for smoking and alcohol | Selection**** Comparability* Outcome** | [41] |
| India | Not clear | Case–control | Ever SLT users | No/no | Oral cancer Pharyngeal cancer Laryngeal cancer Oesophageal cancer | 4.23 (3.11–5.75) 2.42 (1.74–3.37) 2.80 (2.07–3.79) 1.55 (1.15–2.07) | Exclusive SLT users | Selection*** Comparability** Exposure ⁰ | [42] |
| India | 1968 | Case–control | Tobacco | Yes/no | Oral cancer Pharyngeal cancer Laryngeal cancer Oesophageal cancer | 4.63 (3.50–6.14) 3.09 (2.31–4.13) 2.29 (1.72–3.05) 3.82 (2.84–5.13) | Exclusive chewers and non-chewers data available | Selection*** Comparability** Exposure ⁰ | [43] |
| India | 2005–2006 | Case–control | Tobacco flakes Gutkha Mishiri | Yes/yes | Oral cancer | 7.60 (4.90–11.79) 12.70 (7.00–23.04) 3.00 (1.90–4.74) | Adjusted for smoking and alcohol | Selection**** Comparability** Exposure* | [44] |

Table 3 Smokeless tobacco use and risk of cancers, ischaemic heart disease, and stroke—studies included in meta-analysis (Continued)

| Country | Study period | Study design | Exposure status | Inclusion of cigarette/alcohol users | Outcome | Odds ratio/relative risk (95% CIs) | Comments | Quality assessment (NOS) ^a | Reference |
|----------|--------------|--------------|--------------------------------------|--------------------------------------|--|--|---|--|-----------|
| India | Not clear | Case-control | Chewing tobacco | Yes/yes | Oral cancer | 5.00 (3.60–6.94) | Adjusted for smoking and alcohol | Selection ^{****} Comparability [*] Exposure [*] | [45] |
| India | 1982–1984 | Case-control | Chewing tobacco | Yes/no | Oral cancer | 10.20 (2.60–40.02) | Adjusted for smoking | Selection ^{***} Comparability ^{**} Exposure [*] | [46] |
| India | 1980–1984 | Case-control | SLT users | No/no | Oral cancer | 1.99 (1.41–2.81) | Exclusive SLT users | Selection ^{**} Comparability ^o Exposure [*] | [47] |
| India | 1952–1954 | Case-control | Chewing tobacco | No/no | Oral cancer | 4.85 (2.32–10.14) | Exclusive SLT users | Selection ^{***} Comparability ^{**} Exposure ^o | [48] |
| India | 1983–1984 | Case-control | Snuff (males only) | Yes/yes | Oral cancer | 2.93 (0.98–8.76) | Adjusted for smoking and alcohol; adjusted effect size is only among males | Selection ^{***} Comparability ^o Exposure [*] | [49] |
| India | Not given | Case-control | Tobacco chewing | Yes/yes | Oropharyngeal cancer | 7.98 (4.11–13.58) ^b | Adjusted for smoking and alcohol | Selection ^{***} Comparability ^{**} Exposure ^o | [50] |
| India | 1991–2003 | Case-control | Chewing tobacco | No/no | Oral cancer | 5.88 (3.66–7.93) | Exclusive SLT users | Selection ^{****} Comparability ^{**} Exposure ^{**} | [51] |
| India | 1950–1962 | Case-control | Tobacco with or without paan or lime | Yes/no | Oral and oropharyngeal cancer | 41.90 (34.20–51.33) | Exclusive chewer data available; data of habit was not available for the whole cohort | Selection ^{**} Comparability ^{**} Exposure ^o | [52] |
| Pakistan | 1996–1998 | Case-control | Naswar Paan with tobacco | Yes/yes | Oral cancer | 9.53 (1.73–52.50) 8.42 (2.31–30.69) | Adjusted for smoking and alcohol | Selection ^{***} Comparability ^{**} Exposure [*] | [53] |
| Sweden | 1973–2002 | Cohort | Snus | Yes/yes | Oral and pharyngeal cancer combined | 3.10 (1.50–6.41) | Adjusted for smoking and alcohol | Selection ^{**} Comparability ^{**} Outcome ^{***} | [54] |
| India | 1993–1999 | Case-control | Chewing tobacco | Yes/yes | Oral cancer Pharyngeal cancer Oesophageal cancer | 5.05 (4.26–5.99) 1.83 (1.43–2.34) 2.06 (1.62–2.62) | Adjusted for smoking and alcohol | Selection ^{***} Comparability ^{**} Exposure [*] | [55] |
| Norway | 1966–2001 | Cohort | Chewing tobacco plus oral snuff | No/no | Oral cancer Oesophageal cancer | 1.10 (0.50–2.42) 1.40 (0.61–3.21) | Adjusted for smoking, might be confounded by alcohol use | Selection ^{***} Comparability [*] Outcome ^{***} | [56] |

Table 3 Smokeless tobacco use and risk of cancers, ischaemic heart disease, and stroke—studies included in meta-analysis (Continued)

| Country | Study period | Study design | Exposure status | Inclusion of cigarette/alcohol users | Outcome | Odds ratio/relative risk (95% CIs) | Comments | Quality assessment (NOS) ^a | Reference |
|----------|--------------|--------------|-----------------|--------------------------------------|--------------------|------------------------------------|---|--|-----------|
| Sweden | 1988–1991 | Case–control | Oral snuff | Yes/yes | Pancreatic cancer | 1.67 (1.12–2.49) | | | |
| | | | | | Lung cancer | 0.80 (0.61–1.05) | | | |
| | | | | | Oral cancer | 1.40 (0.80–2.45) | Adjusted for smoking and alcohol | Selection** Comparability** Exposure* | [57] |
| Sweden | 1969–1992 | Cohort | Snus | No/no | Laryngeal cancer | 0.90 (0.50–1.62) | | | |
| | | | | | Oesophageal cancer | 1.20 (0.70–2.06) | | | |
| | | | | | Pharyngeal cancer | 0.70 (0.40–1.22) | | | |
| Sweden | 2000–2004 | Case–control | Oral snuff | Yes/yes | Oral cancer | 0.80 (0.40–1.60) | Exclusive SLT users | Selection*** Comparability* Outcome*** | [58] |
| | | | | | Lung cancer | 0.80 (0.50–1.28) | | | |
| | | | | | Pancreatic cancer | 2.00 (1.20–3.33) | | | |
| Sweden | 1980–1989 | Case–control | Oral snuff | Yes/yes | Oral cancer | 0.70 (0.30–1.63) | Adjusted for smoking and alcohol | Selection*** Comparability** Exposure** | [59] |
| | | | | | Oral cancer | 0.80 (0.50–1.28) | Adjusted for smoking and alcohol | Selection** Comparability** Exposure*** | [60] |
| | | | | | Oral cancer | 0.80 (0.40–1.60) | Not clear if adjusted for smoking and alcohol | Selection** Comparability ^o Exposure* | [61] |
| USA | Not given | Case–control | SLT use | Yes/yes | Oral cancer | 0.90 (0.38–2.13) | Adjusted for smoking and alcohol | Selection*** Comparability** Exposure* | [10] |
| | | | | | Pharyngeal cancer | 1.59 (0.84–3.01) | | | |
| | | | | | Laryngeal cancer | 0.67 (0.19–2.36) | | | |
| India | 2001–2004 | Case–control | Chewing tobacco | No/no | Pharyngeal cancer | 3.18 (1.92–5.27) | Exclusive SLT users | Selection*** Comparability** Exposure* | [62] |
| | | | | | Laryngeal cancer | 0.95 (0.52–1.74) | | | |
| | | | | | Oesophageal cancer | 4.10 (1.30–12.93) | Adjusted for areca nut | Selection*** Comparability** Exposure** | [63] |
| Pakistan | 1998–2002 | Case–control | Snuff dipping | No/no | Oral cancer | 14.20 (6.40–31.50) | | | |
| | | | | | Pharyngeal cancer | 2.88 (2.06–4.03) | Exclusive SLT users | Selection*** Comparability** Exposure** | [64] |
| | | | | | Laryngeal cancer | 2.87 (0.87–9.47) | | | |
| India | 2007–2011 | Case–control | Oral snuff | Yes/yes | Oesophageal cancer | 3.86 (2.46–6.06) | Adjusted for smoking and alcohol | Selection** Comparability** Exposure* | [65] |

Table 3 Smokeless tobacco use and risk of cancers, ischaemic heart disease, and stroke—studies included in meta-analysis (Continued)

| Country | Study period | Study design | Exposure status | Inclusion of cigarette/alcohol users | Outcome | Odds ratio/relative risk (95% CIs) | Comments | Quality assessment (NOS) ^a | Reference |
|----------|------------------|--------------|-------------------------------|--------------------------------------|----------------------------|--|--|---|-----------|
| India | 2011–2012 | Case–control | Chewing tobacco | Yes/yes | Oesophageal cancer | 2.63 (1.53–4.52) | Adjusted for smoking and alcohol | Selection*** Comparability** Exposure* | [66] |
| Sweden | 1995–1997 | Case–control | Oral snuff | Yes/yes | Oesophageal adenocarcinoma | 1.20 (0.70–2.06) | Adjusted for smoking and alcohol | Selection*** Comparability** Exposure* | [67] |
| Sweden | 1969–1993 | Cohort | Oral snuff | Yes/no | Squamous cell carcinoma | 1.40 (0.90–2.18) | | | |
| Sweden | 1974–1985 | Cohort | SLT users | No/NA | Oesophageal adenocarcinoma | 1.30 (0.80–2.11) | Adjusted for smoking | Selection** Comparability* Outcome** | [68] |
| Sweden | 1974–1985 | Cohort | SLT users | No/NA | Squamous cell carcinoma | 1.20 (0.80–1.80) | | | |
| Sweden | 1974–1985 | Cohort | SLT users | No/NA | Lung cancer | 0.90 (0.20–4.05) | Adjusted for age, region of origin | Selection*** Comparability* Outcome** | [69] |
| Morocco | 1996–1998 | Case–control | SLT users | Yes/no | Lung cancer | 1.05 (0.28–3.94) | Adjusted for smoking | Selection** Comparability** Exposure** | [70] |
| USA | 1977–1984 | Case–control | SLT users | Yes/no | Oesophageal cancer | 1.20 (0.10–14.40) | Adjusted for smoking | Selection*** Comparability** Exposure** | [71] |
| USA | 1986–1989 | Case–control | SLT users | Yes/no | Pancreatic cancer | 1.40 (0.50–3.92) | Adjusted for smoking | Selection*** Comparability* Exposure** | [72] |
| USA | 2000–2006 | Case–control | Chewing tobacco Oral snuff | Yes/yes | Pancreatic cancer | 0.60 (0.30–1.20) 0.50 (0.10–2.50) | Adjusted for smoking and alcohol | Selection**** Comparability** Exposure* | [73] |
| Pakistan | 2014–2015 | Case–control | Ever use of naswar | Yes/yes | Oral cancer | 21.20 (8.40–53.8) | Adjusted for smoking, restricted control for alcohol due to cultural sensitivity | Selection**** Comparability** Exposure*** | [74] |
| India | March–July, 2013 | Case–control | Gutkha Chewing tobacco | Yes/yes | Oral cancer | 5.10 (2.00–10.30) 6.00 (2.30–15.70) | Adjusted for smoking and alcohol | Selection*** Comparability* Exposure** | [75] |
| | | | Supari with tobacco | | | 11.40 (3.40–38.20) | | | |
| | | | Quid with tobacco | | | 6.40 (2.60–15.50) | | | |
| Pakistan | 1996–1998 | Case–control | Quid with tobacco | Yes/yes | Oral cancer | 15.68 (3.00–54.90) | Adjusted for smoking and alcohol | Selection** Comparability* Exposure*** | [76] |

Table 3 Smokeless tobacco use and risk of cancers, ischaemic heart disease, and stroke—studies included in meta-analysis (Continued)

| Country | Study period | Study design | Exposure status | Inclusion of cigarette/alcohol users | Outcome | Odds ratio/relative risk (95% CIs) | Comments | Quality assessment (NOS) ^a | Reference |
|---|--------------|--------------|--|--------------------------------------|--|--------------------------------------|---|--|-----------|
| Cardiovascular diseases (ischaemic heart disease and stroke) | | | | | | | | | |
| 52 countries | 1999–2003 | Case–control | Chewing tobacco | Yes/yes | Myocardial infarction | 1.57 (1.24–1.99) | Adjusted for smoking, diet, diabetes, abdominal obesity, exercise, hypertension | Selection**** Comparability** Exposure* | [35] |
| Pakistan | 2005–2011 | Case–control | Dippers (Naswar) Chewers (Paan/Supari/Gutkha) | No/NA | Myocardial infarction | 1.46 (1.21–1.78) 1.71 (1.46–2.00) | Adjusted for age, gender, region, ethnicity, diet, socioeconomic status | Selection**** Comparability** Exposure** | [77] |
| Bangladesh | 2006–2007 | Case–control | Ever SLT users | Yes/NA | Myocardial infarction, angina pectoris | 2.80 (1.10–7.30) | Adjusted for age, gender, smoking, hypertension | Selection** Comparability** Exposure** | [78] |
| Bangladesh | 2010 | Case–control | Ever SLT users | No/NA | Myocardial infarction, angina pectoris | 0.77 (0.52–1.13) | Adjusted for age, gender, area of residence, hypertension, diabetes, stress | Selection*** Comparability** Exposure* | [79] |
| India | 2013 | Case–control | Current SLT users | Yes/yes | Stroke | 1.50 (0.80–2.79) | Adjusted for age, smoking, alcohol, diabetes, hypertension | Selection** Comparability** Exposure* | [80] |
| Sweden | 1989–1991 | Case–control | Current snuff users | No/NA | Myocardial infarction | 0.89 (0.62–1.29) | Adjusted for age | Selection**** Comparability** Exposure* | [81] |
| Sweden | 1991–1993 | Case–control | Current snuff users | No/NA | Myocardial infarction | 0.58 (0.35–0.94) | Adjusted for heredity, education, marital status, hypertension, diabetes, cholesterol | Selection**** Comparability** Exposure** | [82] |
| Sweden | 1985–2000 | Case–control | Current snuff users | No/NA | Stroke | 0.87 (0.41–1.83) | Adjusted for education, marital status, diabetes, hypertension, cholesterol | Selection**** Comparability** Exposure** | [83] |
| Sweden | 1998–2005 | Case–control | Current snuff users Former snuff users | No/NA | Myocardial infarction | 0.73 (0.35–1.50) 1.20 (0.46–3.10) | Adjusted for age, hospital catchment area | Selection*** Comparability** Exposure** | [84] |
| Sweden | 1988–2003 | Cohort | Current use of snuff | No/NA | Ischaemic heart disease Stroke | 0.77 (0.51–1.15) 1.07 (0.65–1.77) | Adjusted for age, socioeconomic status, residential area, self-reported health, longstanding illnesses, physical activity | Selection*** Comparability** Outcome*** | [85] |
| Sweden | 1978–2004 | Cohort | Ever snuff users | No/NA | Myocardial infarction | 0.99 (0.90–1.10) | Adjusted for age, BMI, region of residence | Selection** Comparability** Outcome*** | [86] |
| Sweden | 1985–1999 | Case–control | Current snuff users Former snuff users | No/NA | Myocardial infarction | 0.82 (0.46–1.43) 0.66 (0.32–1.34) | Adjusted for BMI, leisure time, physical activity, education, cholesterol | Selection**** Comparability** Exposure* | [87] |

Table 3 Smokeless tobacco use and risk of cancers, ischaemic heart disease, and stroke—studies included in meta-analysis (Continued)

| Country | Study period | Study design | Exposure status | Inclusion of cigarette/alcohol users | Outcome | Odds ratio/relative risk (95% CIs) | Comments | Quality assessment (NOS) ^a | Reference |
|---------|--------------|--------------|---|--------------------------------------|---------------------------------|--------------------------------------|--|--|-----------|
| Sweden | 1978–2003 | Cohort | Ever snuff users | No/NA | Stroke | 1.02 (0.92–1.13) | Adjusted for age, BMI, region of residence | Selection** Comparability** Outcome*** | [88] |
| Sweden | 1998–2005 | Cohort | Current snuff users Former snuff users | No/NA | Ischaemic heart disease | 0.85 (0.51–1.42) | Adjusted for age, hypertension, diabetes, cholesterol | Selection*** Comparability** Outcome* | [89] |
| | | | Current snuff users Former snuff users | | Stroke | 1.07 (0.56–2.04) 1.18 (0.67–2.08) | | | |
| | | | Former snuff users | | | 1.35 (0.65–2.82) | | | |
| Sweden | 1991–2004 | Cohort | Current snuff users | No/NA | Myocardial infarction Stroke | 0.75 (0.30–1.87) 0.59 (0.20–1.50) | Adjusted for age, marital status, occupation, diabetes, BMI, hypertension, physical activity | Selection*** Comparability** Outcome** | [90] |

BMI body mass index, NA not applicable, MOS Newcastle-Ottawa Scale, SLT smokeless tobacco

^aNOS for assessing the quality of non-randomised studies in meta-analyses based on selection, comparability, and exposure/outcome. Number of stars (*) indicates the number of criteria met for each of these three categories

^bEffect sizes are for oral and pharyngeal cancers combined and were included in the meta-analysis for oral cancer only

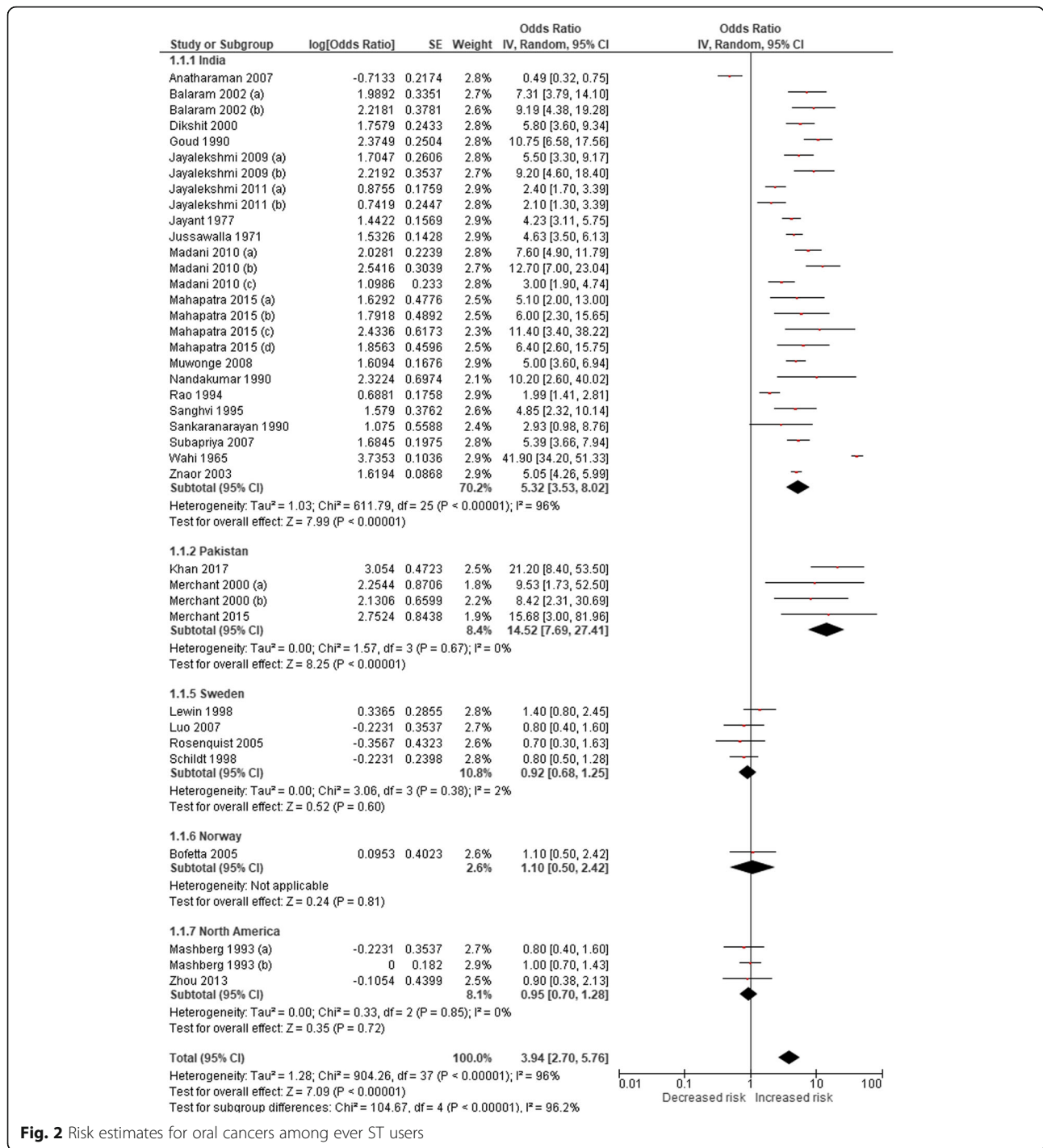
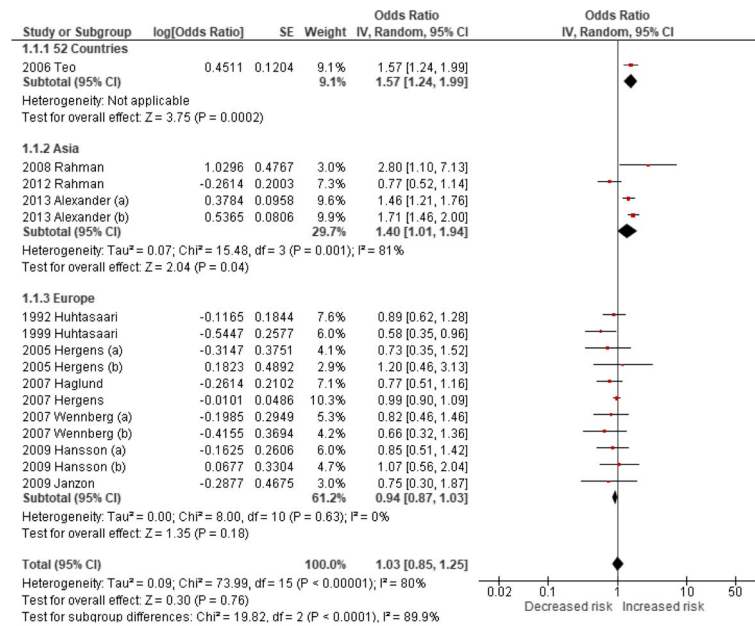


Fig. 2 Risk estimates for oral cancers among ever ST users

Leste) and one country (Sweden) among men only. Overall, our updated ST-related disease burden in 2017 was substantially higher than that for 2010—by approximately 50% for cancers and 25% for ischaemic heart disease. This occurred despite a substantial reduction in ST prevalence in India (constituting 70% of the disease burden) and little change in the disease risk estimates. We are now reporting ST use in 12 more countries;

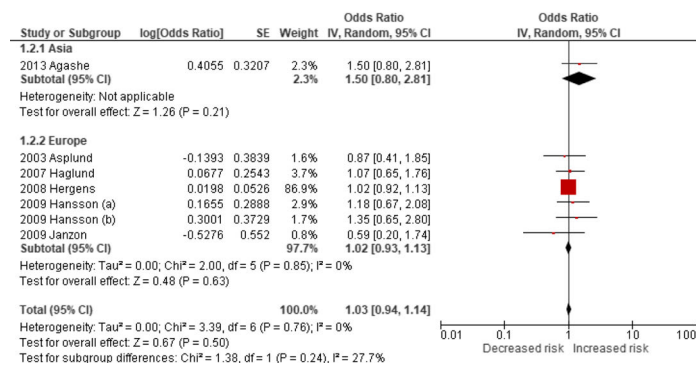
however, the main reason for the increased burden of disease was a global rise in the total mortality and DALYs lost—oral, pharyngeal and oesophageal cancers, in particular. The disease burden due to these cancers lags several decades behind the risk exposure. Therefore, a significant reduction in ST-related disease burden as a result of a reduced prevalence will not become apparent for some time to come. Among other studies estimating

Risk estimates for cardiovascular diseases (Ischaemic heart disease, stroke) among ever ST users
ISCHAEMIC HEART DISEASE



Alexander 2013 (a): Dippers, Alexander 2012 (b): Chewers, Hergens 2005 (a): Current users, Hergens 2005 (b): Former users, Wennberg 2007 (a): Current users, Wennberg 2007 (b): Former users, Hansson 2009 (a): Current users, Hansson 2009 (b): Former users

STROKE



Hansson 2009 (a): Current users, Hansson 2009 (b): Former users

Fig. 3 Risk estimates for cardiovascular diseases (ischaemic heart disease, stroke) among ever ST users

ST-related global disease burden, our mortality estimates were far more conservative than those reported by Sinha et al. (652,494 deaths); however, their methods were different from ours [9]. Moreover, Sinha et al.'s estimates included a number of additional diseases such as cervical cancer, stomach cancer and stroke. None of these risks were substantiated in our systematic reviews and meta-analyses. On the other hand, our estimates of 2,556,810 DALYs lost and 90,791 deaths due to cancers are close to those estimated by the GBD Study for 2017, i.e. 1,890,882 DALYs lost and 75,962 deaths due to cancers [91].

A reason for the slight difference between these two estimates might be that ours included pharyngeal cancers in the estimates while GBD Study only included oral and oesophageal cancers.

Our methods have several limitations. These have been described in detail elsewhere [16] but are summarised here. Our estimates were limited by the availability of reliable data and caveated by several assumptions. The ST use prevalence data were not available for a third of countries despite reports of ST use there. Where prevalence data were available, there were

Table 4 Number of deaths and DALYs lost from SLT use in 2017, by WHO sub-region as defined in Additional file 1: Appendix 1

| WHO sub-regions ^a | Mouth cancer | | | Pharyngeal cancer | | | Oesophageal cancer | | | Ischaemic heart disease | | | All causes | | |
|------------------------------|--------------|---------|-----------|-------------------|---------|---------|--------------------|---------|---------|-------------------------|-----------|-----------|------------|-----------|-----------|
| | M | F | All | M | F | All | M | F | All | M | F | All | M | F | All |
| Deaths | | | | | | | | | | | | | | | |
| Africa D | 184 | 83 | 267 | 120 | 37 | 157 | 294 | 124 | 418 | 3414 | 1497 | 4911 | 4012 | 1741 | 5753 |
| Africa E | 305 | 149 | 454 | 95 | 41 | 136 | 449 | 276 | 725 | 2231 | 1797 | 4027 | 3079 | 2263 | 5343 |
| Americas A | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 10,298 | 565 | 10,863 | 10,298 | 565 | 10,863 |
| Americas B | 1189 | 112 | 1301 | 46 | 4 | 50 | 103 | 12 | 115 | 1275 | 260 | 1535 | 2613 | 389 | 3001 |
| Americas D | 0 | 3 | 3 | 0 | 1 | 1 | 0 | 2 | 2 | 0 | 76 | 76 | 0 | 82 | 82 |
| Eastern Mediterranean B | 27 | 3 | 31 | 21 | 1 | 22 | 13 | 1 | 14 | 818 | 122 | 940 | 879 | 128 | 1007 |
| Eastern Mediterranean D | 5488 | 3756 | 9244 | 611 | 138 | 749 | 752 | 269 | 1021 | 13,062 | 1982 | 15,045 | 19,913 | 6146 | 26,059 |
| Europe A | 69 | 14 | 84 | 30 | 3 | 33 | 246 | 42 | 288 | 0 | 0 | 0 | 346 | 60 | 405 |
| Europe B | 286 | 5 | 291 | 85 | 1 | 86 | 189 | 2 | 192 | 6552 | 163 | 6715 | 7112 | 170 | 7283 |
| Europe C | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Southeast Asia B | 663 | 467 | 1130 | 394 | 148 | 542 | 260 | 123 | 383 | 5014 | 3349 | 8363 | 6330 | 4087 | 10,418 |
| Southeast Asia D | 25,966 | 9829 | 35,795 | 16,378 | 4499 | 20,876 | 9366 | 3493 | 12,859 | 147,065 | 50,509 | 197,573 | 198,774 | 68,329 | 267,103 |
| Western Pacific A | 8 | 2 | 11 | 3 | 1 | 4 | 8 | 2 | 10 | 53 | 23 | 76 | 73 | 27 | 100 |
| Western Pacific B | 781 | 173 | 954 | 611 | 44 | 655 | 1841 | 49 | 1890 | 7084 | 798 | 7883 | 10,317 | 1065 | 11,382 |
| Worldwide | 34,966 | 14,597 | 49,563 | 18,394 | 4918 | 23,312 | 13,519 | 4397 | 17,916 | 196,867 | 61,140 | 258,006 | 263,746 | 85,052 | 348,798 |
| DALYs | | | | | | | | | | | | | | | |
| Africa D | 5350 | 2499 | 7849 | 3823 | 1245 | 5068 | 7860 | 3166 | 11,027 | 78,500 | 31,152 | 109,651 | 95,533 | 38,062 | 133,595 |
| Africa E | 9242 | 4105 | 13,348 | 3174 | 1323 | 4497 | 12,358 | 6590 | 18,948 | 59,082 | 32,930 | 92,012 | 83,856 | 44,948 | 128,804 |
| Americas A | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 180,756 | 6870 | 187,626 | 180,756 | 6870 | 187,626 |
| Americas B | 2283 | 315 | 2598 | 1321 | 104 | 1425 | 2562 | 261 | 2823 | 28,177 | 4397 | 32,575 | 34,344 | 5077 | 39,421 |
| Americas D | 0 | 68 | 68 | 0 | 34 | 34 | 0 | 62 | 62 | 0 | 1745 | 1745 | 0 | 1909 | 1909 |
| Eastern Mediterranean B | 758 | 90 | 848 | 593 | 42 | 634 | 301 | 23 | 324 | 16,420 | 1919 | 18,339 | 18,072 | 2073 | 20,145 |
| Eastern Mediterranean D | 177,353 | 126,901 | 304,254 | 19,303 | 4655 | 23,958 | 20,904 | 7393 | 28,298 | 324,744 | 46,679 | 371,423 | 542,305 | 185,628 | 727,933 |
| Europe A | 1618 | 272 | 1890 | 686 | 76 | 763 | 4959 | 682 | 5641 | 0 | 0 | 0 | 7263 | 1030 | 8293 |
| Europe B | 5714 | 106 | 5820 | 2642 | 30 | 2672 | 4871 | 55 | 4926 | 141,562 | 2177 | 143,740 | 154,789 | 2369 | 157,158 |
| Europe C | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Southeast Asia B | 17,730 | 10,792 | 28,523 | 11,164 | 4319 | 15,484 | 6608 | 2951 | 9558 | 122,177 | 68,896 | 191,073 | 157,679 | 86,958 | 244,637 |
| Southeast Asia D | 767,549 | 258,275 | 1,025,824 | 471,141 | 131,531 | 602,672 | 252,556 | 87,759 | 340,314 | 3,697,819 | 1,114,976 | 4,812,796 | 5,189,065 | 1,592,540 | 6,781,606 |
| Western Pacific A | 201 | 48 | 249 | 78 | 15 | 93 | 166 | 24 | 191 | 809 | 233 | 1042 | 1255 | 320 | 1575 |
| Western Pacific B | 20,556 | 3795 | 24,351 | 18,452 | 1324 | 19,776 | 40,948 | 1055 | 42,003 | 157,624 | 15,371 | 172,995 | 237,580 | 21,545 | 259,124 |
| Worldwide | 1,008,356 | 407,266 | 1,415,621 | 532,378 | 144,696 | 677,074 | 354,093 | 110,021 | 464,114 | 4,807,671 | 1,327,346 | 6,135,017 | 6,702,497 | 1,989,330 | 8,691,827 |

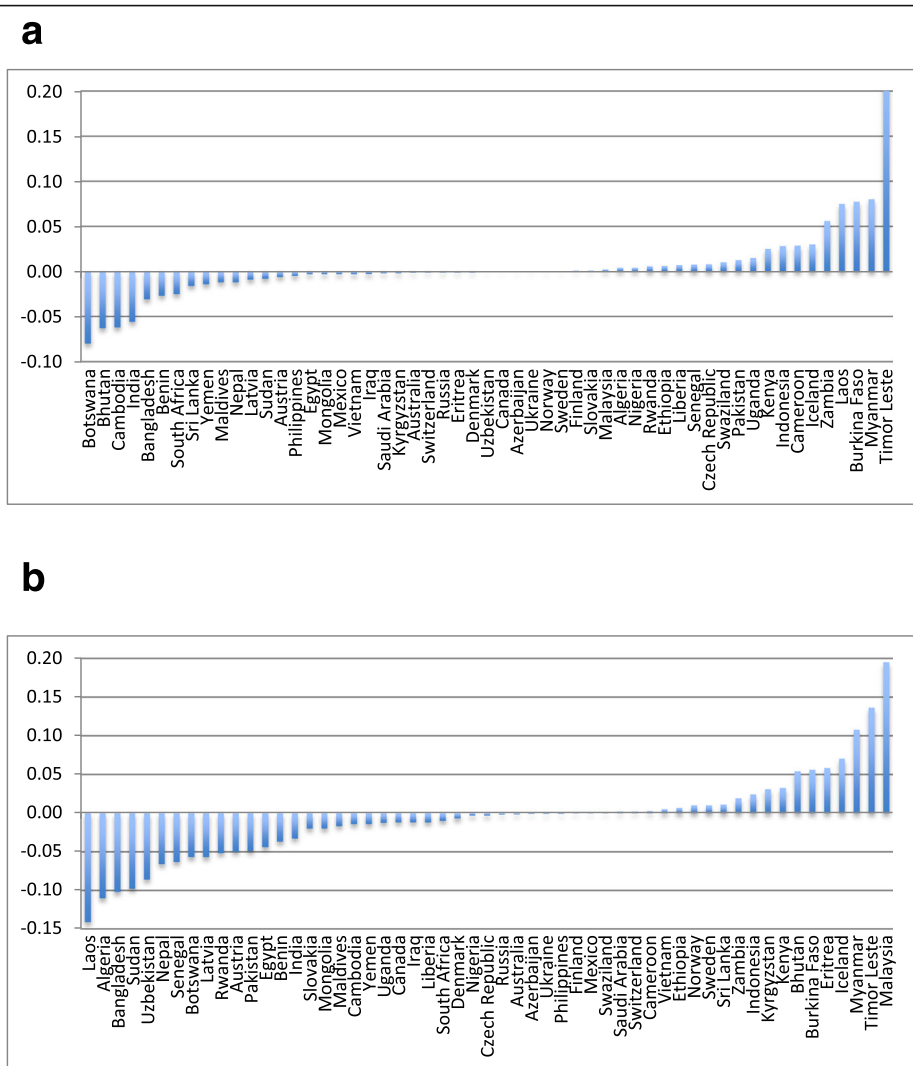


Fig. 4 a Countries with a proportional change in female ST use between 2015 and 2020 estimates. **b** Countries with a proportional change in male ST use between 2015 and 2020 estimates

very few studies providing country-specific disease risks—a particular limitation in Africa and South America. In the absence of country-specific risk estimates, the model relied on assuming that countries that share similar ST products also share similar disease risks. For example, oral cancers risk estimates were only available from five countries (India, Norway, Pakistan, Sweden and the USA). For other countries, the extrapolated risks were based on similarities between ST products sold there and in the above five countries. The estimates for ischemic heart disease must be interpreted with caution, in particular, as the risk estimates for most countries were extrapolated from a single (albeit multi-country) study (INTERHEART). However, we excluded those regions from the above extrapolation where the INTERHEART study was not conducted. As previously noted, the total disease burden observed in 2017 is a

consequence of risk exposure over several decades. Therefore, the attributable risk based on the prevalence figures gathered in the last few years may not be accurate. If ST prevalence has been declining in a country over the last few decades, the disease burden obtained by applying more recent prevalence figures may underestimate attributable disease burden. This may well be the case in India where ST use has declined by 17% between the 2009 and 2017 GATS surveys [92]. On the other hand, if ST use is on the rise (e.g. in Timor Leste), the attributable disease burden for 2017 could be an overestimate. While we found a few more recent ST prevalence surveys and observational studies on the risks associated with ST use, big evidence gaps still remain. The ST surveillance data for many countries are either absent or outdated. The biggest gap is in the lack of observational

studies on the risks associated with various types of ST used both within and between countries. While longitudinal studies take time, global surveillance of ST products, their chemical composition and risk profile can help improve the precision of future estimates. As cancer registries become more established around the globe, their secondary data analysis can also provide opportunities to estimate ST-related risks.

ST is the main form of tobacco consumption by almost a quarter of all tobacco users in the world. Yet, its regulation and control lags behind that of cigarettes. The diversity in the composition and toxicity of ST products and the role of both formal and informal sectors in its production, distribution and sale make ST regulation a particular challenge. In a recent policy review of 180 countries that are signatories to WHO FCTC, we found that only a handful of countries have addressed ST control at par with cigarettes [93]. The regulatory bar is often much lower for ST than cigarettes [94]. Where ST control policies are present, there are gaps in their enforcement [95]. On the other hand, Sweden has demonstrated what can be achieved through strong regulations; ST-related harm has not only been reduced significantly, but snus is now used to reduce harm from smoking. Countries where ST use is popular and poses risks to health need to prioritise ST control and apply WHO FCTC articles comprehensively and evenly across all forms of tobacco.

Conclusions

ST is consumed across the globe and poses a major public health threat predominantly in South and Southeast Asia. While our disease risk estimates are based on a limited number of studies with modest quality, the likely disease burden attributable to ST is substantial. In high-burden countries, ST use needs to be regulated through comprehensive implementation and enforcement of the WHO FCTC.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12916-020-01677-9>.

Additional file 1. Supplementary description of methods and results sections.

Abbreviations

CI: Confidence intervals; DALYs: Disability-adjusted life years; DHS: Demographic and Health Surveys; GATS: Global Adult Tobacco Survey; ICS: Individual Country Survey; PAF: Population attributable fraction; SEBS: Special Europe Barometer Survey; ST: Smokeless tobacco; STEPS: STEPwise Approach to Surveillance; TSNA: Tobacco-specific nitrosamines; WHO: World Health Organization

Authors' contributions

KS jointly developed the study idea, planned the analysis, interpreted the findings, wrote the methods, results and discussion sections and approved

the final manuscript. SH led two literature reviews, interpreted the findings, contributed to the tables and approved the final manuscript. AV led one of the literature reviews, interpreted the findings, drafted several tables and approved the final manuscript. AR contributed to the literature reviews, interpreted the findings, wrote the background section and approved the final manuscript. MM contributed to the literature reviews, interpreted the findings, reviewed the analysis and the tables and approved the final manuscript. AS jointly developed the study idea, interpreted the findings, critically reviewed the write up and approved the final manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information file 1.

Ethics approval and consent to participate

Given that this is a secondary analysis of anonymised data that were already publicly available, ethics approval and consent to participate were not applicable.

Consent for publication

As above, consent for publication was not applicable.

Competing interests

None declared

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