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RESEARCH ARTICLE

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# Global burden of disease due to smokeless tobacco consumption in adults: analysis of data from 113 countries

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## Abstract

**Background:** Smokeless tobacco is consumed in most countries in the world. In view of its widespread use and increasing awareness of the associated risks, there is a need for a detailed assessment of its impact on health. We present the first global estimates of the burden of disease due to consumption of smokeless tobacco by adults.

**Methods:** The burden attributable to smokeless tobacco use in adults was estimated as a proportion of the disability-adjusted life-years (DALYs) lost and deaths reported in the 2010 Global Burden of Disease study. We used the comparative risk assessment method, which evaluates changes in population health that result from modifying a population's exposure to a risk factor. Population exposure was extrapolated from country-specific prevalence of smokeless tobacco consumption, and changes in population health were estimated using disease-specific risk estimates (relative risks/odds ratios) associated with it. Country-specific prevalence estimates were obtained through systematically searching for all relevant studies. Disease-specific risks were estimated by conducting systematic reviews and meta-analyses based on epidemiological studies.

**Results:** We found adult smokeless tobacco consumption figures for 115 countries and estimated burden of disease figures for 113 of these countries. Our estimates indicate that in 2010, smokeless tobacco use led to 1.7 million DALYs lost and 62,283 deaths due to cancers of mouth, pharynx and oesophagus and, based on data from the benchmark 52 country INTERHEART study, 4.7 million DALYs lost and 204,309 deaths from ischaemic heart disease. Over 85 % of this burden was in South-East Asia.

**Conclusions:** Smokeless tobacco results in considerable, potentially preventable, global morbidity and mortality from cancer; estimates in relation to ischaemic heart disease need to be interpreted with more caution, but nonetheless suggest that the likely burden of disease is also substantial. The World Health Organization needs to consider incorporating regulation of smokeless tobacco into its Framework Convention for Tobacco Control.

## Background

Smokeless tobacco (SLT) consists of a number of products containing tobacco, which are consumed—without burning—through the mouth or nose [1]. A diverse range of SLT products are available worldwide, varying in their composition, methods of preparation and consumption, and associated health risks (Table 1) [1]. Its use is most prevalent in South and South-East Asia where one-third of tobacco is consumed in smokeless

form [2, 3]. Wrapped in a betel leaf with areca nut, slaked lime, and catechu, SLT is often served at social occasions in this region. Other products (e.g. gutkha, khaini) contain slaked lime, areca nut, flavourings, and aromatic substances [4]. A number of products based on powdered tobacco (e.g. snus) are also consumed in Nordic countries and North America. In other parts of world, the most commonly used SLT products (Table 1) include Chimó (Venezuela), Nass (Uzbekistan, Kyrgyzstan), Tambook (Sudan, Chad), and Snuff (Nigeria, Ghana, South Africa).

In addition to nicotine, SLT products contain over 30 carcinogens [5] including tobacco-specific nitrosamines

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**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 <sup>a</sup> | Nicotine <sup>a</sup> (mg/g) | Total TSNA <sup>a</sup> (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 (Region A and B)                                    | US, Canada, Mexico  | Sweeteners, liquorice  | Plug; air cured<br>Dry or moist snuff; finely ground and fire cured<br>Snus; steam cured<br>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                       |
| Tambook                        | Eastern Mediterranean (Region D) and Africa (Region D)       | Sudan, Chad   | Mixed with moist sodium bicarbonate                                | Fermented and grounded; placed and kept in mouth  | 7.3–10.1        | 9.6–28.2                     | 302,000–992,000                |
| 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<br>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) | 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                          | Eastern Mediterranean (Region D) 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                         |  | 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                      |

WHO World Health Organization, TSNA tobacco-specific nitrosamines

<sup>a</sup>Figures are adapted from Stanfill et al. [6], Lawler et al. [17], and NIH & CDC 2014 report on smokeless tobacco products [37]

(TSNA), arsenic, beryllium, cadmium, nickel, chromium, nitrite, and nitrate. The level of nicotine and carcinogens vary between products (Table 1) [6]. For example, nicotine content among SLT products varies between 0.2 and 40.1 mg/g, compared to commercial filtered cigarettes which contain 16.3 mg/g of nicotine [7]. Their pH also varies, which, being a key determinant of the level of absorption of nicotine and carcinogens, determines its toxicity: the higher the pH, the higher the absorption and, consequently, the higher the toxicity [6]. Such considerations mean that there are substantial variations between different SLT products in the level of risk posed to human health [4, 8–11]. It is therefore important not to consider SLT as a single product, but rather as groups of products with differences in their toxicity and addictiveness depending upon their carcinogen, nicotine, and pH levels. The diversity in SLT toxicity has been an impediment not only in establishing its global risks to human health, but also in agreeing on international policies for its prevention and control. It is therefore perhaps unsurprising that despite several country-specific studies [12–15] no attempt has hitherto been made to estimate its global disease burden.

To overcome these challenges, we developed a novel approach to estimate the global burden associated with the use of SLT products. The determinants of their toxicity (carcinogens and pH) and addictiveness (nicotine) are dependent on preparation methods, ingredients that are added to SLT products, and consumption behaviours. Given that the SLT preparations and consumption patterns are determined by, and vary with, geography and culture [16], it is possible to group them according to their availability in different parts of the world (Table 1). These groups of SLT products, classified according to different geographical regions, will also be distinguishable from each other on the basis of their toxicity, addictiveness, and associated health risks. Hence, the risks were assumed to be highest in those regions and cultures where products are combined with other ingredients, and are prepared and consumed in a way that makes them very alkaline (i.e. a high pH), and rich in nicotine and TSNA [6, 17]. Building on this assumption, we aimed to estimate the worldwide burden of disease attributable to SLT use, measured in terms of disability adjusted life years (DALYs) lost and number of deaths in 2010.

## Methods

We used the comparative risk assessment method, which evaluates changes in population health (burden of disease) that result from modifying a population's exposure to a risk factor [18, 19]. For this, we used 2010 datasets, which provided the most recent global estimates of burden of disease [20]. The estimates were calculated for individual countries and then grouped into 14 World

Health Organization (WHO) sub-regions (Additional file 1: Appendix 1) [21]. These were generated through estimating the following:

1. The prevalence of SLT consumption
2. Diseases caused by SLT use
3. The relative risks of acquiring these diseases
4. The population attributable fraction (PAF) for each of these diseases
5. The overall burden of these diseases in terms of DALYs lost and deaths
6. Proportion of this burden attributable to SLT use

## Prevalence of smokeless tobacco use

We carried out a systematic literature search (see Additional file 1: Appendix 2 for a detailed description of the methods employed) for the point prevalence (current use) of SLT consumption among all adult ( $\geq 15$  years) populations, and also for men and women separately. Only one prevalence report was included for one country. Latest national prevalence data collected as part of an international or regional survey were preferred over an older isolated national or a sub-national survey. We used data from the Global Adult Tobacco Survey (GATS), where available [22]. In its absence, other international (WHO STEPwise approach to Surveillance, The Demographic and Health Surveys), regional (Special Europe Barometer), national, and/or sub-national surveys were used to extract prevalence data.

## Diseases caused by smokeless tobacco use

A scoping review was carried out to identify associated diseases. A series of focused literature reviews were subsequently carried out to find and assess the evidence of causation between each of these diseases and SLT use. Our search strategies and selection criteria are provided in Additional file 1: Appendix 3. One researcher ran the searches, which were then independently scrutinised by another independent researcher who considered the search results against the pre-specified inclusion and exclusion criteria. Similarly, one researcher extracted data, which were independently crosschecked by another researcher. In particular, we appraised the studies for case definitions for diseases and for assessment methods for measuring exposure to SLT and for investigating the effects of potential confounders. We excluded those diseases (and respective studies) where evidence was not supportive of a causal relationship. Only studies that adequately controlled for smoking and/or alcohol as potential confounders either at the design or the analysis stage were carried forward into the next stage of the analysis (discussed below). Quality was assessed using the Newcastle-Ottawa Scale for assessing the quality of non-randomised studies in meta-analyses [23].

### Assessing risk and meta-analyses

Risk estimates (relative risks/odds ratios) and their confidence intervals (CI) were log transformed to produce effect sizes and standard errors, respectively [24]. We carried out random effects meta-analysis using RevMan version 5 to estimate pooled risk estimates. We first obtained country-specific risk estimates (relative risks/odds ratios) for individual diseases by pooling data from the included studies carried out in respective countries. We then extrapolated non-specific global risk estimates by pooling respective country-specific risk estimates. We were mindful that the risk of acquiring diseases varies between countries owing to differences in SLT products used. Therefore, for each disease where good country-specific risk estimates (pooled estimate from a meta-analysis of three or more studies in respective country) were available, we applied these to respective countries and also to those countries and regions where similar SLT products are used. In the absence of good country-specific risk estimates, we used either one of the following two approaches: (a) In countries and regions that use SLT products with moderate to high pH and TSNA levels, we applied non-specific global estimates (pooled estimate from a meta-analysis of all studies); and (b) in countries and regions where there was either no information available on the SLT products or the information available indicates low levels of pH and TSNA, we did not apply any estimates. Further details on the application of these assumptions across all 14 WHO regions are provided in web Additional file 1: Appendix 4. We only used those pooled relative risks (country or non-specific) that were found to be statistically significant.

Where associations were presented for more than one SLT product in the same paper, we considered these as separate studies for the purpose of meta-analysis. Similarly, where risks were given separately for former and current SLT users, these were also treated as separate studies. We did not attempt to group risks according to gender because very few studies had such sub-group analysis.

### Population attributable fraction

PAF is the proportional reduction in disease or mortality that would occur if exposure were reduced to zero [25, 26]. PAF was estimated for each disease for each country for both males and females, using the following formula:

$$PAF = P_e(RR_e - 1) / [1 + P_e(RR_e - 1)]$$

$P_e$  = Prevalence

$RR_e$  = Relative Risk

### Overall burden

The overall number of DALYs and deaths for each associated disease for both males and females for each

country were extracted from the 2010 Global Burden of Disease study [27, 28].

### Attributable burden

The attributable burden (AB), in deaths and DALYs, was estimated for each associated disease for each country for both males and females by multiplying PAF by the overall burden of the disease (B):

$$AB = PAF \times B$$

## Results

### Prevalence of smokeless tobacco use

We found adult prevalence figures for SLT consumption in 115 countries (Fig. 1). The definition for 'adult' ranged from 15, 16, 25, or 35 years at one end to 49, 64, 65, 70, 74, 84, 85, 89, or no age limit at the other. The PRISMA diagram describing the selection of the prevalence reports is provided in Additional file 1: Appendix 5a.

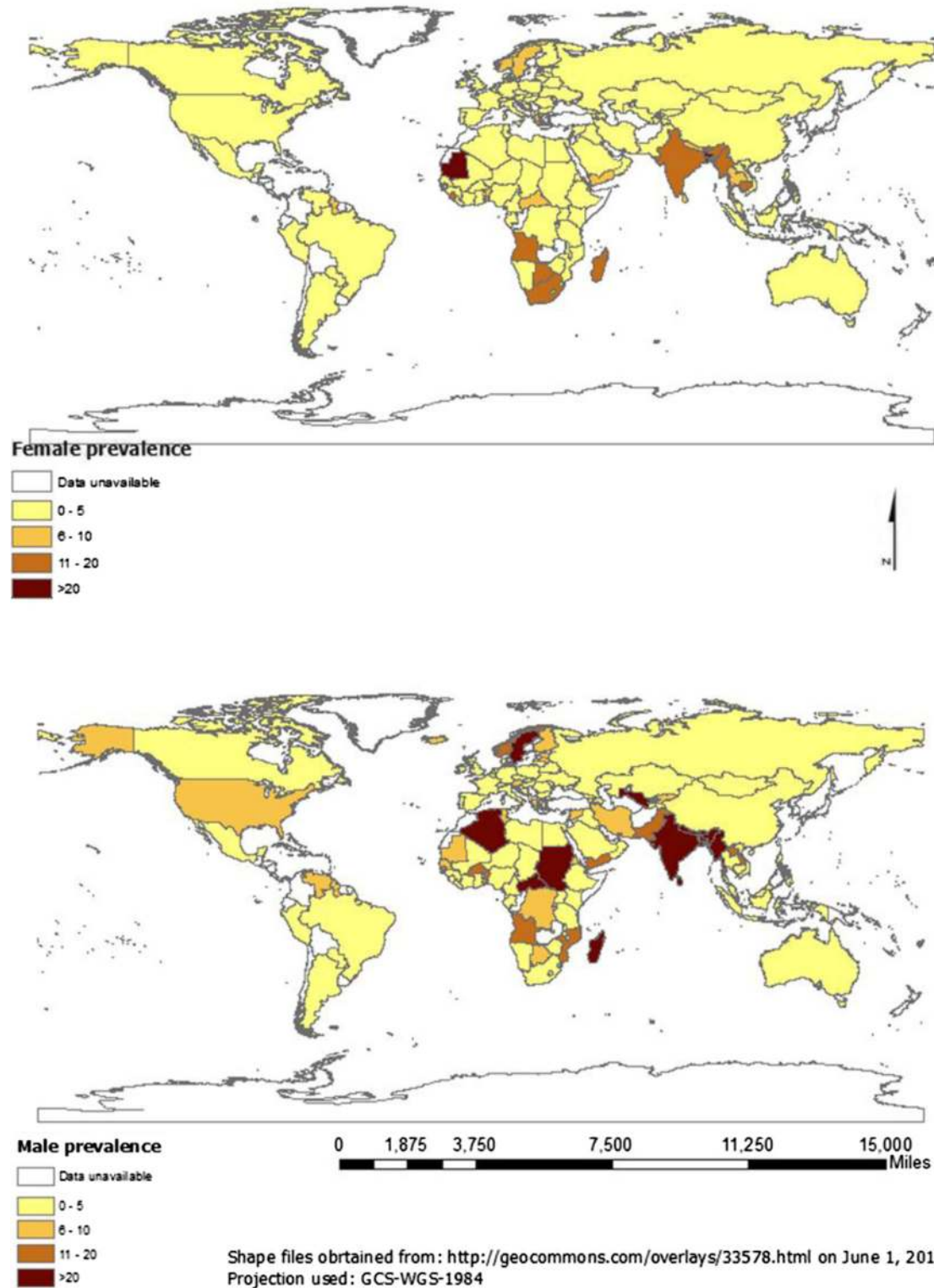
In general, SLT consumption was higher among males than females (Table 2). Mauritania had the highest prevalence of SLT consumption among females (28.3 %), followed by Bangladesh (27.9 %), Madagascar (19.6 %), India (18.4 %), and Bhutan (17.3 %). Among males, Myanmar (51.4 %), Nepal (37.9 %), India (32.9 %), Uzbekistan (31.8 %), and Bangladesh (26.4 %) had the highest consumption rates. Within Europe, SLT (snus) consumption was high in Sweden (24.0 % males, 7.0 % females) and Norway (20.0 % males, 6.0 % females).

### Diseases caused by smokeless tobacco use

The initial scoping review identified a number of associated diseases, including a range of cancers, cardiovascular diseases (ischaemic heart disease and stroke), periodontal conditions, and adverse pregnancy outcomes. The subsequent more focused systematic reviews identified 53 studies (Table 3) reporting association between SLT consumption and cancers of mouth, pharynx, larynx, oesophagus, lung, and pancreas (39 studies); and cardiovascular diseases, such as ischaemic heart disease and stroke (14 studies). PRISMA flow diagrams describing the selection process of the studies identified in the literature searches are provided in Additional file 1: Appendix 5b,c. The pooled non-specific relative risks were statistically significant for cancers of the mouth, pharynx, and oesophagus (Figs. 2, 3, 4, and 5). Only statistically significant relative risks (country-specific or non-specific) were included in the model to estimate attributable risks. For example, the pooled non-specific relative risk for laryngeal cancer was 1.42 (95 % CI 0.77–2.59), and hence excluded (Additional file 1: Appendix 6). Likewise, none of the country-specific estimates for the USA were statistically significant



# Global Prevalence of Smokeless Tobacco Use



**Fig. 1** Smokeless tobacco prevalence among males and females

**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             | 21           | 0.4      | STEPS [38] | 2005       |
|                     | Benin               | 12.7         | 5.7      | STEPS [38] | 2008       |
|                     | Burkina Faso        | –            | 3.86     | DHS [39]   | 2011       |
|                     | Cameroon            | 1.94         | 0.94     | DHS [39]   | 2011       |
|                     | Cape Verde          | 3.5          | 5.8      | STEPS [38] | 2007       |
|                     | Chad                | 1.9          | 0.4      | STEPS [38] | 2008       |
|                     | Comoros             | 7.72         | 2.99     | DHS [39]   | 2012       |
|                     | Gabon               | 0.48         | 0.34     | DHS [39]   | 2012       |
|                     | Gambia              | 0.8          | 1.4      | STEPS [38] | 2010       |
|                     | Ghana               | 1.33         | 0.2      | DHS [39]   | 2008       |
|                     | Guinea              | 1.4          | 1.5      | STEPS [38] | 2009       |
|                     | Liberia             | 2.3          | 2.4      | DHS [40]   | 2007       |
|                     | Madagascar          | 24.66        | 19.6     | DHS [39]   | 2009       |
|                     | Mali                | 5            | 1.2      | STEPS [38] | 2007       |
|                     | Mauritania          | 5.7          | 28.3     | STEPS [38] | 2006       |
|                     | Niger               | 4.55         | 2.3      | DHS [39]   | 2012       |
|                     | Nigeria             | 3.2          | 0.5      | DHS [40]   | 2008       |
|                     | Sao Tome & Principe | 3.8          | 1.9      | STEPS [38] | 2009       |
|                     | Senegal             | 6.63         | 0.23     | DHS [39]   | 2011       |
|                     | Africa (Region E)   | Sierra Leone | 3        | 12         | STEPS [38] |
| Togo                |                     | 5.1          | 2.2      | STEPS [38] | 2010       |
| Botswana            |                     | 7.2          | 14.5     | STEPS [38] | 2007       |
| Burundi             |                     | 0.03         | 0.31     | DHS [39]   | 2011       |
| Congo (Brazzaville) |                     | 8.3          | 1.54     | DHS [39]   | 2012       |
| Congo (Republic)    |                     | 8.67         | 3.22     | DHS [39]   | 2013       |
| Cote d'Ivoire       |                     | 0.61         | 1.27     | DHS [39]   | 2012       |
| Eritrea             |                     | 5.8          | 0.2      | STEPS [38] | 2004       |
| Ethiopia            |                     | 1.94         | 0.2      | DHS [39]   | 2011       |
| Kenya               |                     | 2.05         | 1.29     | DHS [39]   | 2008       |
| Lesotho             |                     | 1.3          | 9.1      | DHS [40]   | 2009       |
| Malawi              |                     | 1.9          | 5        | STEPS [38] | 2009       |
| Mozambique          |                     | 10.94        | 0.82     | DHS [39]   | 2011       |
| Namibia             |                     | 1.8          | 2.3      | DHS [40]   | 2006–07    |
| Rwanda              |                     | 5.8          | 2.73     | DHS [39]   | 2011       |
| South Africa        |                     | 2.4          | 10.9     | DHS [41]   | 2003       |
| Swaziland           |                     | 2.6          | 0.8      | STEPS [38] | 2007       |
| Tanzania            |                     | 2.03         | 0.83     | DHS [39]   | 2010       |
| Uganda              |                     | 2.94         | 1.5      | DHS [39]   | 2011       |
| Zambia              |                     | 0.3          | 1.2      | DHS [39]   | 2007       |
| Zimbabwe            | 1.6                 | 0.4          | DHS [41] | 2011       |            |
| Americas (Region A) | Canada              | 2            | –        | ICS [41]   | 2011       |
|                     | USA                 | 6.5          | 0.4      | ICS [41]   | 2010       |

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

|                                  |                               |      |           |            |         |
|----------------------------------|-------------------------------|------|-----------|------------|---------|
| Americas (Region B)              | Argentina                     | 0.1  | 0.2       | GATS [42]  | 2012    |
|                                  | Barbados                      | 0    | 0.6       | STEPS [38] | 2007    |
|                                  | Brazil                        | 0.6  | 0.3       | GATS [42]  | 2010    |
|                                  | Dominican Republic            | 1.9  | 0.3       | DHS [40]   | 2007    |
|                                  | Grenada                       | 2.2  | 0.3       | STEPS [38] | 2011    |
|                                  | Mexico                        | 0.3  | 0.3       | GATS [42]  | 2009    |
|                                  | Paraguay                      | 3    | 1.6       | ICS [41]   | 2011    |
|                                  | St Kitts & Nevis <sup>a</sup> | 0.3  | 0.1       | STEPS [38] | 2007    |
|                                  | Trinidad & Tobago             | 0.5  | 0.3       | STEPS [38] | 2011    |
|                                  | Venezuela                     | 6.2  | 0.9       | ICS [41]   | 2011    |
| Americas (Region D)              | Haiti                         | –    | 2.5       | DHS [40]   | 2005–06 |
| Eastern Mediterranean (Region B) | Libya                         | 2.2  | 0.1       | STEPS [38] | 2009    |
|                                  | Saudi Arabia                  | 1.3  | 0.5       | STEPS [38] | 2004    |
|                                  | Tunisia                       | 8.6  | 2.2       | ICS [41]   | 2005–06 |
| Eastern Mediterranean (Region D) | Egypt                         | 4.8  | 0.3       | GATS [42]  | 2009    |
|                                  | Iraq                          | 1.6  | 0.3       | STEPS [38] | 2006    |
|                                  | Pakistan                      | 16.3 | 2.44      | DHS [43]   | 2012–13 |
|                                  | Sudan                         | 24.1 | 1         | STEPS [38] | 2005    |
|                                  | Yemen                         | 15.1 | 6.2       | ICS [41]   | 2003    |
| Europe (Region A)                | Austria                       | 7.8  | 1.1       | SEBS [44]  | 2012    |
|                                  | Belgium                       | 1.1  | 0.6       | SEBS [44]  | 2012    |
|                                  | Cyprus                        | 2.1  | 0.4       | SEBS [44]  | 2012    |
|                                  | Czech Republic                | 2.5  | 0.4       | SEBS [44]  | 2012    |
|                                  | Denmark                       | 3    | 1         | ICS [41]   | 2010    |
|                                  | Finland                       | 5.5  | 0.3       | ICS [41]   | 2011    |
|                                  | France                        | 1.2  | 0.6       | SEBS [44]  | 2012    |
|                                  | Germany                       | 3.4  | 3.4       | SEBS [44]  | 2012    |
|                                  | Iceland                       | 5.97 | –         | ICS [41]   | 2008    |
|                                  | Ireland                       | 2.2  | 0.9       | SEBS [44]  | 2012    |
|                                  | Italy                         | 1.8  | 1.5       | SEBS [44]  | 2012    |
|                                  | Luxembourg                    | 1.8  | 1         | SEBS [44]  | 2012    |
|                                  | Malta                         | 5.5  | 1.5       | SEBS [44]  | 2012    |
|                                  | Netherlands                   | 0.3  | 0.1       | ICS [41]   | 2011    |
|                                  | Norway                        | 20   | 6         | ICS [41]   | 2011    |
|                                  | Portugal                      | 4.4  | 1.1       | SEBS [44]  | 2012    |
|                                  | Slovenia                      | 1.8  | 0.4       | SEBS [44]  | 2012    |
|                                  | Spain                         | 0.4  | 0.2       | SEBS [44]  | 2012    |
|                                  | Sweden                        | 24   | 7         | ICS [41]   | 2011    |
|                                  | Switzerland                   | 4    | 1.3       | ICS [41]   | 2011    |
| United Kingdom                   | 1.6                           | 0.5  | SEBS [44] | 2012       |         |
| Europe (Region B)                | Azerbaijan                    | 0.3  | 0         | DHS [40]   | 2006    |
|                                  | Armenia                       | 1.8  | 0         | DHS [40]   | 2005    |
|                                  | Bulgaria                      | 0.3  | 0         | SEBS [44]  | 2012    |
|                                  | Georgia                       | 1    | 0.2       | ICS [41]   | 2010    |



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

|                            |                                  |      |      |            |         |
|----------------------------|----------------------------------|------|------|------------|---------|
|                            | Kyrgyzstan                       | 7    | 0.3  | ICS [41]   | 2006    |
|                            | Poland                           | 1    | 0.1  | GATS [42]  | 2009    |
|                            | Romania                          | 0.4  | 0.2  | GATS [42]  | 2011    |
|                            | Slovakia                         | 3.9  | 0.7  | SEBS [44]  | 2012    |
|                            | Uzbekistan                       | 31.8 | 0.2  | DHS [40]   | 2002    |
| Europe (Region C)          | Latvia                           | 5.8  | 0.9  | ICS [41]   | 2010    |
|                            | Lithuania                        | 1.2  | 0.2  | SEBS [44]  | 2012    |
|                            | Moldova                          | 0.1  | 0    | DHS [40]   | 2005    |
|                            | Russia                           | 1    | 0.2  | GATS [42]  | 2009    |
|                            | Ukraine                          | 0.5  | 0    | GATS [42]  | 2010    |
| South East Asia (Region B) | Indonesia                        | 1.5  | 2    | GATS [42]  | 2011    |
|                            | Sri Lanka                        | 24.9 | 6.9  | STEPS [38] | 2006    |
|                            | Thailand                         | 1.1  | 5.2  | GATS [42]  | 2011    |
| South East Asia (Region D) | Bangladesh                       | 26.4 | 27.9 | GATS [42]  | 2009    |
|                            | Bhutan                           | 21.1 | 17.3 | STEPS [38] | 2007    |
|                            | India                            | 32.9 | 18.4 | GATS [42]  | 2009    |
|                            | Maldives                         | 5.6  | 2.6  | STEPS [38] | 2011    |
|                            | Myanmar                          | 51.4 | 16.1 | STEPS [38] | 2009    |
|                            | Nepal                            | 37.9 | 6    | DHS [41]   | 2011    |
|                            | Timor Leste                      | 2.48 | 1.93 | DHS [43]   | 2009–10 |
| Western Pacific (Region A) | Australia                        | 0.75 | 0.41 | ICS [45]   | 2004    |
| Western Pacific (Region B) | Cambodia                         | 2.2  | 14.8 | STEPS [38] | 2010    |
|                            | China                            | 0.7  | 0    | GATS [42]  | 2010    |
|                            | Lao People's Democratic Republic | 14.6 | 1.1  | STEPS [38] | 2008    |
|                            | Malaysia                         | 0.9  | 0.6  | GATS [42]  | 2011    |
|                            | Micronesia                       | 22.4 | 3    | STEPS [38] | 2002    |
|                            | Mongolia                         | 2.8  | 0.5  | STEPS [38] | 2009    |
|                            | Philippines                      | 2.8  | 1.2  | GATS [42]  | 2009    |
|                            | Vietnam                          | 0.3  | 2.3  | GATS [42]  | 2010    |

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

<sup>a</sup>Populations of St Kitts and Nevis are tiny and unlikely to affect our estimates

(Additional file 1: Appendix 4). Based on the above reviews, we assumed that a causal association exists between some SLT products and cancers of the mouth, pharynx, and oesophagus, and ischaemic heart disease.

### Relative risks

Based on 32 studies, the estimated pooled non-specific relative risk for mouth (oral cavity, tongue, and lip) cancers was 3.43 (95 % CI 2.26–5.19) (Fig. 2). Studies from South-East Asia indicated an increased risk of oral cancer for SLT use whereas results from studies pertaining to Europe and the Americas did not substantiate such an association. For cancers of the pharynx, pooled non-specific relative risk was 2.23 (95 % CI 1.55–3.20), based

on ten studies (Fig. 3). For oesophageal cancers, no clear increased risk was present in studies in the USA, whereas a pooled estimate reported a relative risk of 2.17 (95 % CI 1.70–2.78) (Fig. 4). For ischaemic heart disease, no good country-specific risk estimates were available (Fig. 5). However, we found one large case-control study (INTERHEART study) [29] conducted in 52 countries from all regions showing a statistically significant risk of ischaemic heart disease (adjusted odds ratio 1.57, 95 % CI 1.24–1.99) among SLT users.

### Applying risk estimates

For cancers in general, pooled country-specific risk estimates obtained from Sweden and the USA were applied

**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 ratios/relative risks (95 % confidence intervals)                       | Comments  | Quality assessment (NOS) <sup>a</sup>                            | Reference                        |
|---------|--------------|--------------|---|--------------------------------------|--|--|---|--|----------------------------------|
| CANCERS |              |              |   |                                      |  |  |   |  |                                  |
| India   | 2001–2004    | Case–control | Smokeless tobacco with or without additives | No/No                                | Oral cancer  | 0.49 (0.32–0.75)   | Exclusive SLT users   | Selection****<br>Comparability**<br>Exposure/Outcome*            | Anantharaman et al. 2007 [46]    |
| India   | 1996–1999    | Case–control | Ever SLT users                              | Yes/Yes                              | Oral cancer  | 7.31 (3.79–14.1)<br>9.19 (4.38–19.28)  | Never drinkers adjusted for smoking<br>Never smokers adjusted for alcohol | Selection****<br>Comparability**<br>Exposure/Outcome*            | Balaram et al. 2002 [47]         |
| India   | 1982–1992    | Case–control | Tobacco quid chewing                        | Yes/No                               | Oral cancer<br>Pharyngeal cancer<br>Lung cancer                            | 5.8 (3.6–9.34)<br>1.2 (0.8–1.8)<br>0.7 (0.4–1.22)                            | Adjusted for smoking  | Selection***<br>Comparability*<br>Exposure/Outcome*              | Dikshit & Kanhere 2000 [48]      |
| India   | Unclear      | Case–control | Chewing tobacco                             | No/No                                | Oral cancer  | 10.75 (6.58–17.56)   | Exclusive SLT users   | Selection**<br>Comparability*<br>Exposure/Outcome <sup>0</sup>   | Goud et al. 1990 [49]            |
| India   | 1990–1997    | Cohort       | Current SLT users<br>Former SLT users       | No/No                                | Oral cancer  | 5.5 (3.3–9.17)<br>9.2 (4.6–18.40)  | Exclusive SLT users   | Selection****<br>Comparability*<br>Exposure/Outcome**            | Jayalekshmi et al. 2009 [50]     |
| India   | 1990–1997    | Cohort       | Current SLT user<br>Former SLT users        | Yes/Yes                              | Oral cancer  | 2.4 (1.7–3.39)<br>2.1 (1.3–3.39)   | Adjusted for smoking and alcohol  | Selection****<br>Comparability*<br>Exposure/Outcome***           | Jayalekshmi et al. 2010 [51]     |
| India   | May 2005     | Case–control | Ever SLT users                              | No/No                                | Oral cancer<br>Pharyngeal cancer<br>Laryngeal cancer<br>Oesophageal cancer | 4.23 (3.11–5.75)<br>2.42 (1.74–3.37)<br>2.8 (2.07–3.79)<br>1.55 (1.15–2.07)  | Exclusive SLT users   | Selection***<br>Comparability**<br>Exposure/Outcome <sup>0</sup> | Jayant et al. 1977 [52]          |
| India   | 1968         | Case–control | Tobacco                                     | Yes/No                               | Oral cancer<br>Pharyngeal cancer<br>Laryngeal cancer<br>Oesophageal cancer | 4.63 (3.50–6.14)<br>3.09 (2.31–4.13)<br>2.29 (1.72–3.05)<br>3.82 (2.84–5.13) | Exclusive chewers and non-chewers data available                          | Selection***<br>Comparability**<br>Exposure/Outcome <sup>0</sup> | Jussawalla & Deshpande 1971 [53] |
| India   | 2005–2006    | Case–control | Tobacco flakes<br>Gutkha<br>Mishiri         | Yes/Yes                              | Oral cancer  | 7.6 (4.9–11.79)<br>12.7 (7–23.04)<br>3.0 (1.9–4.74)                          | Adjusted for smoking and alcohol  | Selection****<br>Comparability**<br>Exposure/Outcome*            | Madani et al. 2010 [54]          |

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

|          |           |              |                                      |         |  |   |   |  |                                 |
|----------|-----------|--------------|--------------------------------------|---------|--|---|---|--|---------------------------------|
| India    | Unclear   | Case-control | Chewing tobacco                      | Yes/Yes | Oral cancer  | 5.0 (3.6–6.94)  | Adjusted for smoking and alcohol  | Selection****<br>Comparability*<br>Exposure/Outcome*             | Muwonge et al. 2008 [55]        |
| India    | 1982–1984 | Case-control | Chewing tobacco                      | Yes/No  | Oral cancer  | 10.2 (2.6–40.02)  | Adjusted for smoking  | Selection***<br>Comparability**<br>Exposure/Outcome*             | Nandakumar et al. 1990 [56]     |
| India    | 1980–1984 | Case-control | SLT users                            | No/No   | Oral cancer  | 1.99 (1.41–2.81)  | Exclusive SLT users   | Selection**<br>Comparability <sup>0</sup><br>Exposure/Outcome*   | Rao et al. 1994 [57]            |
| India    | 1952–1954 | Case-control | Chewing tobacco                      | No/No   | Oral cancer<br>Pharyngeal cancer<br>Laryngeal cancer | 4.85 (2.32–10.14)<br>2.02 (0.94–4.33)<br>0.76 (0.37–1.56) | Exclusive SLT users   | Selection***<br>Comparability**<br>Exposure/Outcome <sup>0</sup> | Sanghvi et al. 1955 [58]        |
| 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***<br>Comparability <sup>0</sup><br>Exposure/Outcome*  | Sankaranarayan et al. 1990 [59] |
| India    | Not given | Case-control | Tobacco chewing                      | Yes/Yes | Oropharyngeal cancer                                 | 7.98 (4.11–13.58) <sup>b</sup>                            | Adjusted for smoking and alcohol  | Selection***<br>Comparability**<br>Exposure/Outcome <sup>0</sup> | Wasnik et al. 1998 [60]         |
| India    | 1991–2003 | Case-control | Chewing tobacco                      | No/No   | Oral cancer  | 5.88 (3.66–7.93)  | Exclusive SLT users   | Selection****<br>Comparability**<br>Exposure/Outcome**           | Subapriya e al. 2007 [61]       |
| 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<br>Note: data of habit was not available for the whole cohort | Selection**<br>Comparability**<br>Exposure/Outcome <sup>0</sup>  | Wahi et al. 1965 [62]           |
| Pakistan | 1996–1998 | Case-control | Naswar<br>Paan with tobacco          | Yes/Yes | Oral cancer  | 9.53 (1.73–52.50)<br>8.42 (2.31–30.69)                    | Adjusted for smoking and alcohol  | Selection***<br>Comparability**<br>Exposure/Outcome*             | Merchant et al. 2000 [63]       |
| Sweden   | 1973–2002 | Cohort       | Snus                                 | Yes/Yes | Oral and pharyngeal combined                         | 3.10 (1.50–6.41)  | Adjusted for smoking and alcohol  | Selection**<br>Comparability**<br>Outcome***                     | Roosar et al. 2008 [64]         |

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

|          |           |              |                                    |         |                    |                  |  |                            |                             |
|----------|-----------|--------------|------------------------------------|---------|--------------------|------------------|--|----------------------------|-----------------------------|
| India    | 1993–1999 | Case–control | Chewing tobacco                    | Yes/Yes | Oral cancer        | 5.05 (4.26–5.99) | Adjusted for smoking and alcohol                         | Selection***               | Znaor et al. 2003 [65]      |
|          |           |              |                                    |         | Pharynx            | 1.83 (1.43–2.34) |  | Comparability**            |                             |
|          |           |              |                                    |         | Oesophagus         | 2.06 (1.62–2.62) |  | Exposure/Outcome*          |                             |
| Norway   | 1966–2001 | Cohort       | Chewing tobacco plus oral snuff    | No/No   | Oral cancer        | 1.1 (0.5–2.42)   | Adjusted for smoking, might be confounded by alcohol use | Selection***               | Bofetta et al. 2005 [66]    |
|          |           |              |                                    |         | Oesophageal cancer | 1.4 (0.61–3.21)  |  | Comparability*             |                             |
|          |           |              |                                    |         | Pancreatic cancer  | 1.67 (1.12–2.49) |  | Exposure/Outcome***        |                             |
|          |           |              |                                    |         | Lung cancer        | 0.80 (0.61–1.05) |  |                            |                             |
| Sweden   | 1988–1991 | Case–control | Oral snuff                         | Yes/Yes | Oral cancer        | 1.4 (0.8–2.45)   | Adjusted for smoking and alcohol                         | Selection**                | Lewin et al. 1998 [67]      |
|          |           |              |                                    |         | Larynx             | 0.9 (0.5–1.62)   |  | Comparability**            |                             |
|          |           |              |                                    |         | Oesophagus         | 1.2 (0.7–2.06)   |  | Exposure/Outcome*          |                             |
|          |           |              |                                    |         | Pharynx            | 0.7 (0.4–1.22)   |  |                            |                             |
| Sweden   | 1969–1992 | Cohort       | Snus                               | No/No   | Oral cancer        | 0.8 (0.4–1.60)   | Exclusive SLT users                                      | Selection***               | Luo et al. 2007 [68]        |
|          |           |              |                                    |         | Lung cancer        | 0.8 (0.5–1.28)   |  | Comparability*             |                             |
|          |           |              |                                    |         | Pancreatic cancer  | 2 (1.20–3.33)    |  | Exposure/Outcome***        |                             |
| Sweden   | 2000–2004 | Case–control | Oral snuff                         | Yes/Yes | Oral               | 0.70 (0.3–1.63)  | Adjusted for smoking and alcohol                         | Selection***               | Rosenquist et al. 2005 [69] |
|          |           |              |                                    |         |                    |                  |  | Comparability**            |                             |
|          |           |              |                                    |         |                    |                  |  | Exposure/Outcome**         |                             |
| Sweden   | 1980–1989 | Case–control | Oral snuff                         | Yes/Yes | Oral cancer        | 0.8 (0.5–1.28)   | Adjusted for smoking and alcohol                         | Selection**                | Schildt et al. 1998 [70]    |
|          |           |              |                                    |         |                    |                  |  | Comparability**            |                             |
|          |           |              |                                    |         |                    |                  |  | Exposure/Outcome***        |                             |
| USA      | 1972–1983 | Case–control | Oral snuff<br>Chewing tobacco      | Yes/Yes | Oral cancer        | 0.8 (0.4–1.60)   | Not clear if adjusted for smoking and alcohol            | Selection**                | Mashberg et al. 1993 [71]   |
|          |           |              |                                    |         |                    | 1 (0.7–1.43)     |  | Comparability <sup>0</sup> |                             |
|          |           |              |                                    |         |                    |                  |  | Exposure/Outcome*          |                             |
| USA      | Not given | Case–control | SLT use                            | Yes/Yes | Oral cancer        | 0.90 (0.38–2.13) | Adjusted for smoking and alcohol                         | Selection***               | Zhou et al. 2013 [15]       |
|          |           |              |                                    |         | Pharyngeal cancer  | 1.59 (0.84–3.01) |  | Comparability**            |                             |
|          |           |              |                                    |         | Laryngeal cancer   | 0.67 (0.19–2.36) |  | Exposure/Outcome*          |                             |
| India    | 2001–2004 | Case–control | Chewing tobacco                    | No/No   | Pharyngeal cancer  | 3.18 (1.92–5.27) | Exclusive SLT users                                      | Selection***               | Sapkota et al. 2007 [72]    |
|          |           |              |                                    |         | Laryngeal cancer   | 0.95 (0.52–1.74) |  | Comparability**            |                             |
|          |           |              |                                    |         |                    |                  |  | Exposure/Outcome*          |                             |
| Pakistan | 1998–2002 | Case–control | Snuff dipping<br>Quid with tobacco | No/No   | Oesophageal cancer | 4.1 (1.3–12.93)  | Adjusted for areca nut                                   | Selection***               | Akhtar et al. 2012 [73]     |
|          |           |              |                                    |         |                    | 14.2 (6.4–31.50) |  | Comparability**            |                             |
|          |           |              |                                    |         |                    |                  |  | Exposure/Outcome**         |                             |

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

|         |           |              |                                |         |  |                                      |                                    |   |                                |
|---------|-----------|--------------|--------------------------------|---------|--|--------------------------------------|------------------------------------|---|--------------------------------|
| India   | 2008–2012 | Case-control | Nass chewing<br>Gutkha chewing | No/No   | Oesophageal cancer   | 2.88 (2.06–4.03)<br>2.87 (0.87–9.47) | Exclusive SLT users                | Selection***<br>Comparability**<br>Exposure/Outcome** | Dar et al.<br>2012 [74]        |
| India   | 2007–2011 | Case-control | Oral snuff                     | Yes/Yes | Oesophageal cancer   | 3.86 (2.46–6.06)                     | Adjusted for smoking and alcohol   | Selection**<br>Comparability**<br>Exposure/Outcome*   | Sehgal et al.<br>2012 [75]     |
| India   | 2011–2012 | Case-control | Chewing tobacco                | Yes/Yes | Oesophageal cancer   | 2.63 (1.53–4.52)                     | Adjusted for smoking and alcohol   | Selection***<br>Comparability**<br>Exposure/Outcome*  | Talukdar et al.<br>2013 [76]   |
| Sweden  | 1995–1997 | Case-control | Oral snuff                     | Yes/Yes | Oesophageal cancer (adenocarcinoma)<br>(Squamous cell carcinoma) | 1.2 (0.7–2.06)<br>1.4 (0.9–2.18)     | Adjusted for smoking and alcohol   | Selection***<br>Comparability**<br>Exposure/Outcome*  | Lagergren et al.<br>2000 [77]  |
| Sweden  | 1969–1993 | Cohort       | Oral snuff                     | Yes/No  | Oesophageal cancer (Adenocarcinoma)<br>(Squamous cell carcinoma) | 1.3 (0.8–2.11)<br>1.2 (0.8–1.80)     | Adjusted for smoking               | Selection**<br>Comparability*<br>Exposure/Outcome**   | Zendehdel et al.<br>2008 [78]  |
| Sweden  | 1974–1985 | Cohort       | SLT users                      | No/NA   | Lung cancer  | 0.90 (0.20– 4.05)                    | Adjusted for age, region of origin | Selection***<br>Comparability*<br>Outcome**           | Bolinder et al.<br>1994 [79]   |
| Morocco | 1996–1998 | Case-control | SLT users                      | Yes/No  | Lung cancer  | 1.05 (0.28–3.94)                     | Adjusted for smoking               | Selection**<br>Comparability**<br>Exposure/Outcome**  | Sasco et al.<br>2002 [80]      |
| USA     | 1977–1984 | Case-control | SLT users                      | Yes/No  | Oesophageal cancer   | 1.2 (0.1–14.40)                      | Adjusted for smoking               | Selection***<br>Comparability**<br>Exposure/Outcome** | Brown et al.<br>1988 [81]      |
| USA     | 1986–1989 | Case-control | SLT users                      | Yes/No  | Pancreatic cancer  | 1.4 (0.5–3.92)                       | Adjusted for smoking               | Selection***<br>Comparability*<br>Exposure/Outcome**  | Alguacil & Silverman 2004 [82] |
| USA     | 2000–2006 | Case-control | Chewing tobacco<br>Oral snuff  | Yes/Yes | Pancreatic cancer  | 0.6 (0.3–1.20)<br>0.5 (0.1–2.5)      | Adjusted for smoking and alcohol   | Selection****<br>Comparability**<br>Exposure/Outcome* | Hassan et al.<br>2007 [83]     |

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

| CARDIOVASCULAR DISEASES (ischaemic heart disease and stroke) |           |              |  |        |  |                                      |   |  |                             |
|--|-----------|--------------|--|--------|--|--------------------------------------|---|--|-----------------------------|
| 52 countries   | 1999–2003 | Case-control | Chewing tobacco  | No/Yes | Myocardial infarction                  | 1.57 (1.24–1.99)                     | Adjusted for diabetes, abdominal obesity, hypertension, exercise, diet      | Selection****<br>Comparability**<br>Exposure/Outcome*  | Teo et al. 2006 [29]        |
| Pakistan   | 2005–2011 | Case-control | Dippers only (Naswar)<br>Chewers only (Paan/ Supari/ Gutkha) | No/NA  | Myocardial infarction                  | 1.46 (1.20–1.77)<br>1.71 (1.46–2.00) | Adjusted for age, sex, region, ethnicity                                    | Selection****<br>Comparability**<br>Exposure/Outcome** | Alexander 2013 [84]         |
| Bangladesh   | 2006–2007 | Case-control | Ever SLT users   | No/NA  | Myocardial infarction, Angina pectoris | 2.8 (1.1–7.13)                       | Adjusted for age, sex, hypertension   | Selection***<br>Comparability**<br>Exposure/Outcome*   | Rahman & Zaman 2008 [85]    |
| Bangladesh   | 2010      | Case-control | Ever SLT users   | No/NA  | Myocardial infarction, Angina pectoris | 0.77 (0.52–1.14)                     | Adjusted for age, hypertension, diabetes, acute psycho-social stress        | Selection****<br>Comparability**<br>Exposure/Outcome*  | Rahman et al. 2012 [86]     |
| Sweden   | 1998–2005 | Case-control | Current SLT users<br>Former SLT users                        | No/NA  | Myocardial infarction                  | 0.73 (0.35–1.52)<br>1.2 (0.46–3.13)  | Exclusive SLT users   | Selection***<br>Comparability**<br>Exposure/Outcome**  | Hergens et al. 2005 [87]    |
| Sweden   | 1978–2004 | Cohort       | Ever SLT users   | No/NA  | Myocardial infarction                  | 0.99 (0.90–1.10)                     | Adjusted for age, BMI, region of residence                                  | Selection**<br>Comparability**<br>Exposure/Outcome***  | Hergens et al. 2007 [88]    |
| Sweden   | 1989–1991 | Case-control | Regular SLT users  | Yes/NA | Myocardial infarction                  | 1.01 (0.66–1.55) <sup>c</sup>        | Adjusted for age, education, smoking  | Selection***<br>Comparability**<br>Exposure/Outcome*   | Huhtasaari et al. 1992 [89] |
| Sweden   | 1991–1993 | Case-control | Former SLT users   | No/NA  | Myocardial infarction                  | 1.23 (0.54–2.82)                     | Exclusive SLT users   | Selection****<br>Comparability**<br>Exposure/Outcome** | Huhtasaari et al. 1999 [90] |
| Sweden   | 1988–2000 | Cohort       | Daily SLT users  | No/NA  | Ischaemic heart disease                | 1.41 (0.61–3.28)                     | Adjusted for BMI, physical activity, diabetes, hypertension                 | Selection****<br>Comparability**<br>Exposure/Outcome** | Johansson et al. 2005 [91]  |
| Sweden   | 1985–1999 | Case-control | Current SLT users<br>Former SLT users                        | No/NA  | Myocardial infarction                  | 0.82 (0.46–1.46)<br>0.66 (0.32–1.36) | Adjusted for BMI, physical activity, education, cholesterol                 | Selection****<br>Comparability**<br>Exposure/Outcome** | Wennberg et al. 2007 [92]   |
| Sweden   | 1985–2000 | Case-control | Regular SLT users  | No/NA  | Stroke                                 | 0.87 (0.41–1.83)                     | Adjusted for diabetes, hypertension, education, marital status, cholesterol | Selection****<br>Comparability**<br>Exposure/Outcome** | Asplund et al. 2003 [93]    |



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

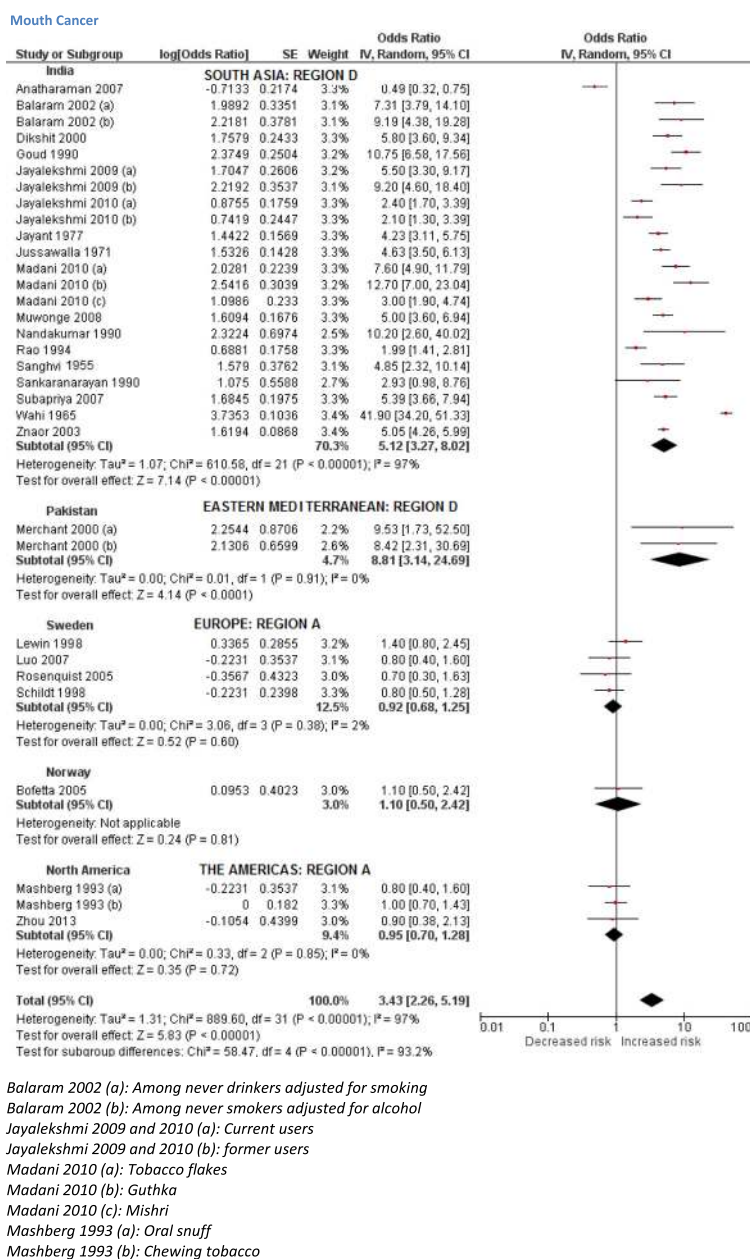
|        |           |        |                   |       |                         |                                      |  |   |                          |
|--------|-----------|--------|-------------------|-------|-------------------------|--------------------------------------|--|---|--------------------------|
| Sweden | 1978–2003 | Cohort | Ever SLT users    | No/NA | Stroke                  | 1.02 (0.92–1.13)                     | Adjusted for age, BMI, region of residence   | Selection**<br>Comparability**<br>Exposure/Outcome*** | Hergens et al. 2008 [94] |
| Sweden | 1998–2005 | Cohort | Current SLT users | No/NA | Ischaemic heart disease | 0.85 (0.51–1.42)                     | Adjusted for age, hypertension, diabetes, cholesterol  | Selection***<br>Comparability**<br>Exposure/Outcome** | Hansson et al. 2009 [95] |
|        |           |        | Former SLT users  |       | Stroke                  | 1.07 (0.56–2.04)                     |  |   |                          |
|        |           |        |                   |       |                         | 1.18 (0.67–2.08)<br>1.35 (0.65–2.82) |  |   |                          |
| Sweden | 1991–2004 | Cohort | SLT users         | No/NA | Myocardial infarction   | 0.75 (0.3–1.87)                      | Adjusted for age, diabetes, occupation, hypertension, physical activity, BMI, marital status | Selection***<br>Comparability**<br>Exposure/Outcome** | Janzon et al. 2009 [96]  |
|        |           |        |                   |       | Stroke                  | 0.59 (0.2–1.5)                       |  |   |                          |

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

<sup>a</sup>NOS 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 [23]

<sup>b</sup>Effect sizes are for oral and pharyngeal cancers combined and were included in the meta-analysis for oral cancer only

<sup>c</sup>Based on parameter estimate and standard error reported in paper



**Fig. 2** Random effects model showing relative risk for mouth cancer for smokeless tobacco use

to Europe A and Americas A, respectively. For South-East Asia B and D and Western Pacific B regions, country-specific estimates from India were applied. There were a few exceptions to this rule, because some countries (UK, Mexico, Pakistan, China, Mongolia) differed in their SLT consumption patterns from their respective regions (see Additional file 1: Appendix 4 for details). In short, country-specific risk estimates for cancers could only be fully applied to five regions. For the remaining nine regions, our findings were imputed either by applying statistically significant non-specific risk estimates or none at all (Additional file 1: Appendix 4). In

case of ischaemic heart disease, Sweden was the only country with a pooled country-specific relative risk (0.98, 95% CI 0.90–1.07) obtained from a good number (more than three) of studies. For 11 out of 14 regions, we used a large multi-country study (INTERHEART)—conducted in 52 countries—to apply and deduce risk estimates. The three regions (Europe A and C and Americas D) were excluded, as these were not among those regions included in the INTERHEART study (Additional file 1: Appendix 4). There was one exception (UK) where INTERHEART study estimates were applied because SLT products consumed in the UK commonly originate from South Asia.

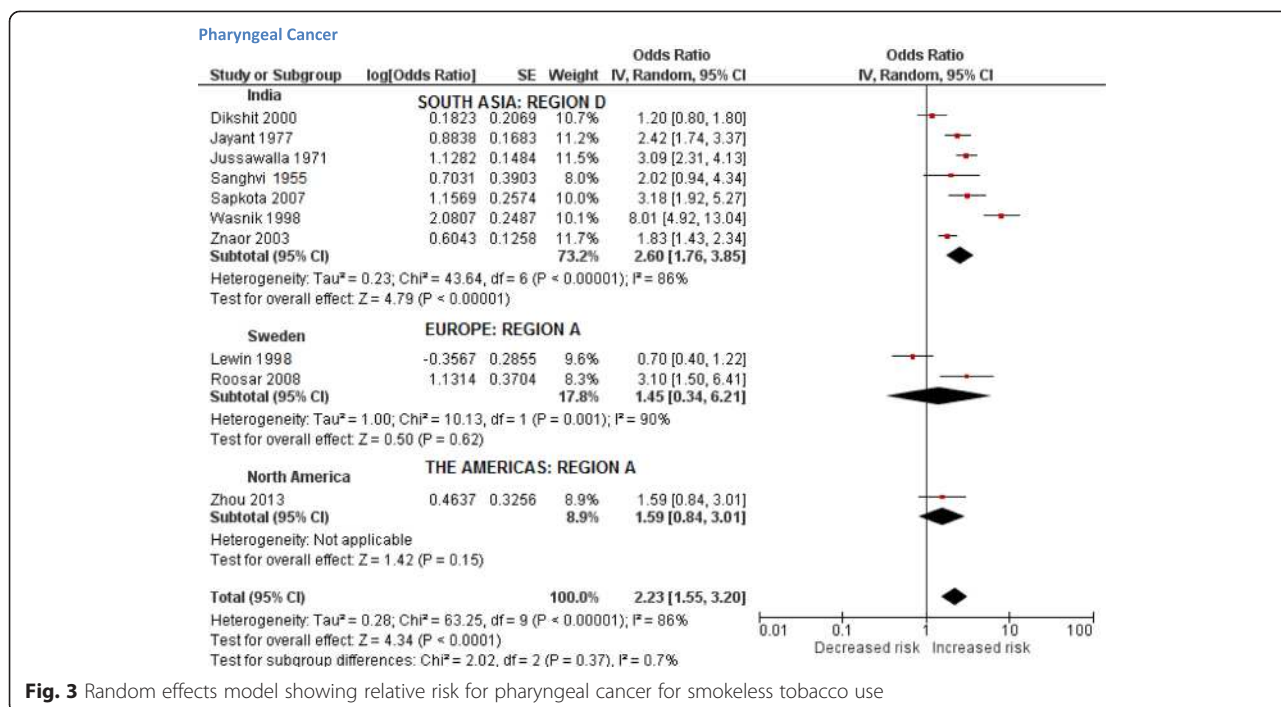


Fig. 3 Random effects model showing relative risk for pharyngeal cancer for smokeless tobacco use

**Attributable burden**

The attributable burden of SLT use is outlined in Table 4. Our estimates indicate that in 2010, SLT use led to 1,711,539 DALYs lost and 62,283 deaths due to cancers of mouth, pharynx, and oesophagus, and, based on data from the benchmark 52 country INTERHEART study, 4,725,381 DALYs lost and 204,309 deaths from ischaemic heart disease. In total, SLT use caused the loss of 6,436,920 DALYs and 266,592 deaths. The figures show that three-quarters of these deaths and loss of DALYs were among males. This disease burden was found to be distributed across all WHO sub-regions. However, nearly 85 % of the total burden attributable to SLT use was in South-East Asia, with India alone accounting for 74 % of the global burden, followed by Bangladesh (5 %).

**Discussion**

We have found that SLT is consumed worldwide and that its use results in substantial, potentially avoidable, morbidity and mortality. However, owing to marked differences in the types of products available, patterns of consumption, and associated risks, there are substantial differences in the attributable burden between regions and countries. In particular, SLT consumption in South-East Asia leads to a much greater burden of disease than in Sweden, despite its use being equally prevalent. This is due to the much lower levels of TSNA and pH in SLT products in Sweden compared to those found in SLT in South-East Asia [6]. Similarly, SLT products used in the

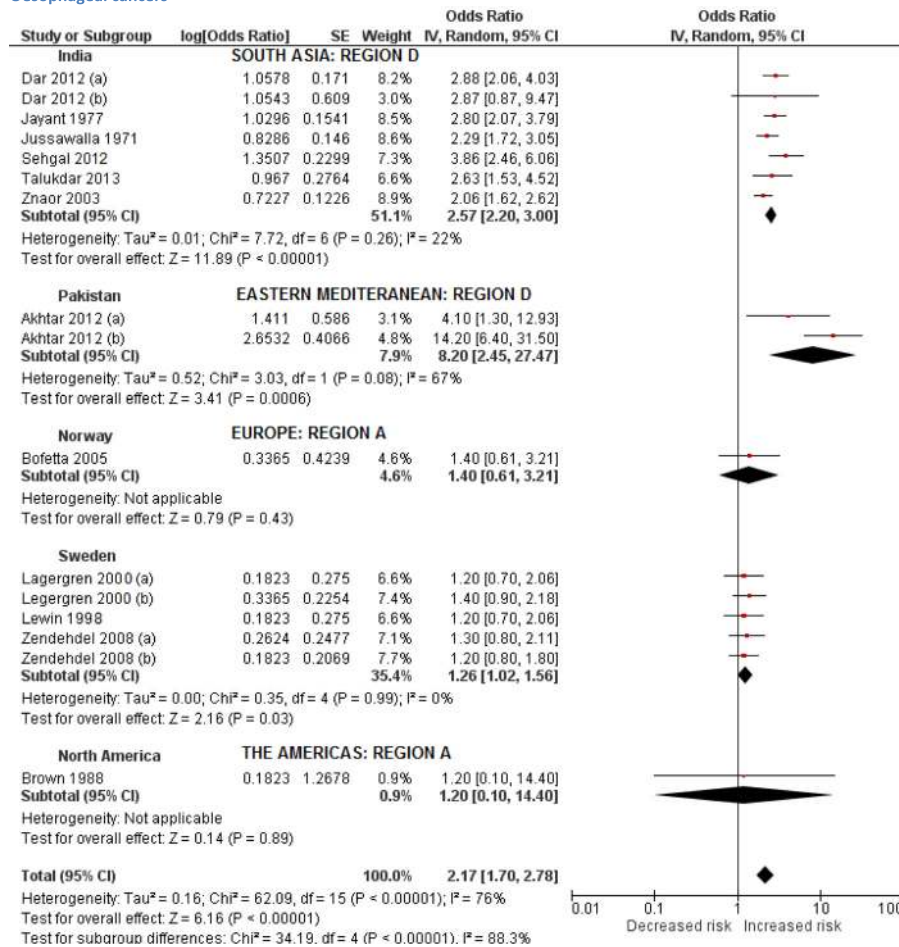
USA have lower risk estimates than for those used in South-East Asia.

We found that more than six million DALYs were lost and over a quarter of a million deaths occurred in 2010 owing to SLT consumption. However, our estimates require cautious interpretation because of a number of potential limitations.

First, our analysis was limited to those countries and diseases for which reliable prevalence and risk data were available, respectively. Most global tobacco surveys that reported on SLT consumption did not include all countries in the world. While global figures on smoking prevalence were available, we did not find any SLT prevalence figures for almost half of all countries. Where SLT prevalence figures were available, two countries (Micronesia and Saint Kitts & Nevis) were excluded from the final estimates owing to an absence of data for cancers in the 2010 Global Burden of Disease study. Moreover, for certain disease outcomes, e.g. adverse reproductive and oral health effects, poor quality as well as limited quantity of evidence precluded their inclusion.

Second, lack of country-specific risk estimates leads to considerable uncertainty. Despite several countries reporting SLT consumption, most did not have any reliable information on the types of SLT products used and on their associated health risks. For example, studies from several African countries reported high SLT consumption (Table 2), but provided little information on their hazard profile. There is some evidence, mainly

Oesophageal cancers

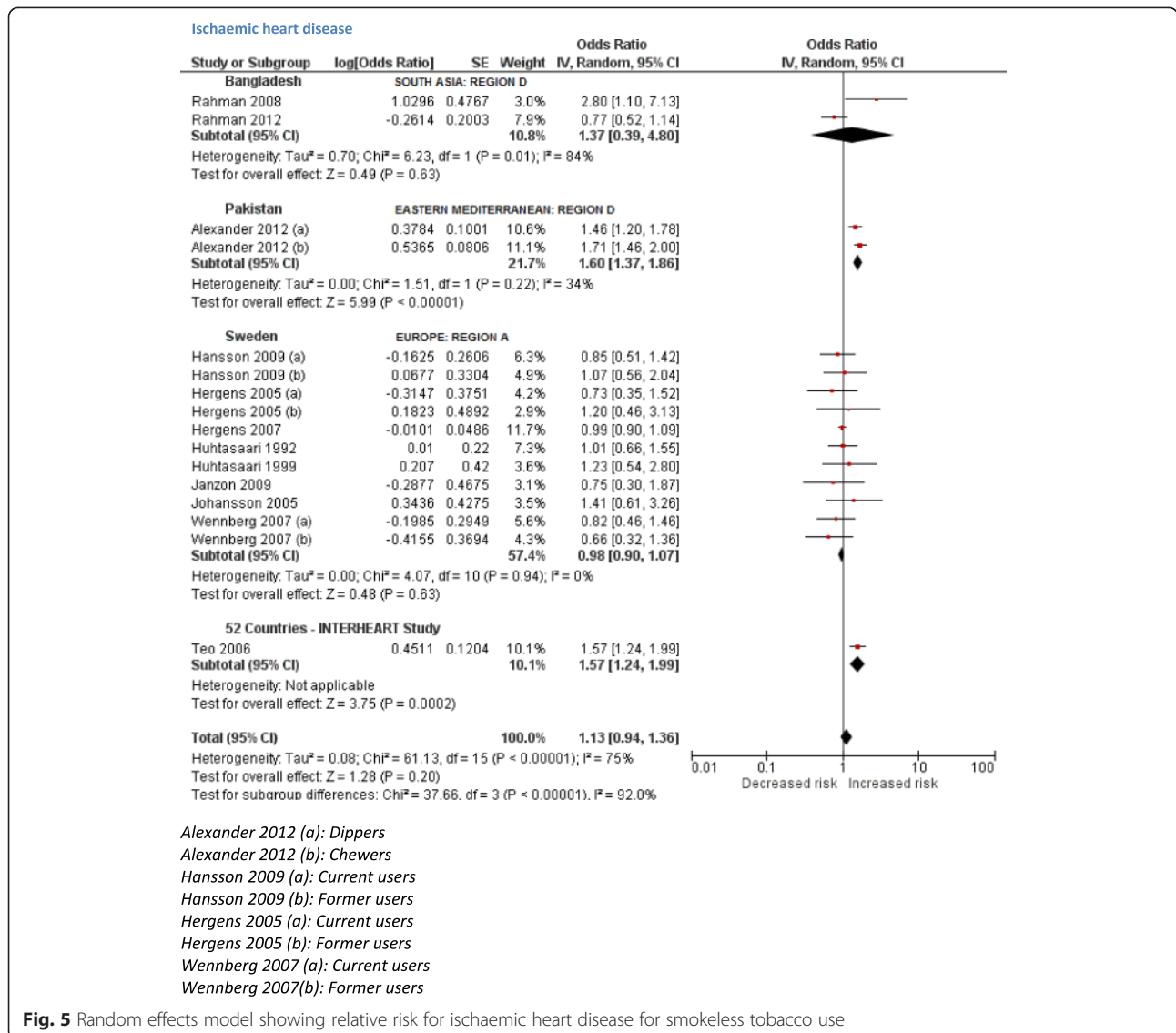


- Akhtar 2012 (a) Quid tobacco chewers
- Akhtar 2012 (b) Snuff dipping users
- Lagergren 2000 (a) Esophageal adenocarcinoma
- Lagergren 2000 (b) Esophageal squamous cell carcinoma
- Zendeudel 2008 (a) Esophageal adenocarcinoma
- Zendeudel 2008 (b) Esophageal squamous cell carcinoma
- Mashberg 1993 (a): Oral snuff
- Mashberg 1993 (b): Chewing tobacco

Fig. 4 Random effects model showing relative risk for oesophageal cancer for smokeless tobacco use

from Sudan [30], that products used in Africa tend to have a higher pH than those used in Europe or in the USA. However, we did not find any data on the risks associated with widespread SLT use in southern parts of Africa. Likewise, various forms of SLT have been used in parts of South America (Brazilian rapê or Venezuelan chimó) for many years, yet there are no studies on the health effects of such products. In the absence of country-specific risk estimates, we assumed that in general those populations that consume similar SLT products are likely to share similar health risks and susceptibilities. We extrapolated and applied risk estimates to most countries included in our analysis on that

basis (Additional file 1: Appendix 4). For cancer, our extrapolation was based on estimates obtained from several studies; for ischaemic heart diseases, extrapolations were mostly based on a single although large multi-country study (INTERHEART). As a result, almost three-quarters of the estimated SLT disease burden, which is attributed to ischaemic heart disease, is uncertain. Therefore, a cautious interpretation would be to exclude ischaemic heart disease burden figures from our estimates. However, in estimating these figures we had already excluded those regions and their respective countries that were not included in INTERHEART study. As a pointer on future research, our study



highlights the need to study risk of SLT consumption on ischaemic heart diseases across the spectrum of SLT products and consumption behaviours. In time, this will produce more country-specific risk estimates, which would undoubtedly improve the reliability of our estimates presented here.

Third, the disease burden observed in 2010 is unlikely to be a consequence of SLT consumption in recent years. Therefore, our prevalence figures, obtained in surveys carried out in the last decade and used in the estimates, could be problematic. However, we assumed that the SLT consumption rates have remained stable over the last 30–40 years in these countries. We consider this as a safe assumption given that SLT use is not a new trend and historically embedded in culture and tradition in many countries, most remarkably in South Asia [31]. Consumption trends based on repeated youth surveys in

India and Bangladesh suggest that SLT use has remained stable over the last decade [32]. Evidence from Sweden suggests that while more people are using snus now than 25 years ago, the consumption trends, compared to cigarette use, have essentially remained stable in this period [33, 34].

Finally, the age range of the adult sampling frames used in different SLT prevalence surveys varied, which could also increase uncertainty. The main difference between two of the key categories used was in the adult range starting from either ≥15 years or ≥25 years. Given that the risk of cancers and ischemic heart disease accumulates after many years of use well beyond young adult age, it may not have made much of a difference to our burden of disease estimates.

For the seven countries in South-East Asia region D, we estimated that 55,060 deaths caused by cancers of

**Table 4** Number of DALYs lost and deaths from SLT use in 2010, by WHO sub-region as defined in Additional file 1: Appendix 1

| WHO sub-regions <sup>a</sup> | 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                     | 86           | 36      | 123     | 15                | 2       | 17      | 157                | 77      | 233     | 2323                    | 751       | 3074      | 2581       | 866       | 3448      |
| Africa E                     | 155          | 85      | 240     | 19                | 12      | 31      | 389                | 252     | 641     | 1202                    | 923       | 2125      | 1765       | 1272      | 3037      |
| Americas A                   | 0            | 0       | 0       | 0                 | 0       | 0       | 0                  | 0       | 0       | 10,240                  | 649       | 10,889    | 10,240     | 649       | 10,889    |
| Americas B                   | 90           | 11      | 102     | 28                | 3       | 31      | 74                 | 9       | 83      | 1030                    | 291       | 1321      | 1222       | 314       | 1536      |
| Americas D                   | 0            | 0       | 0       | 0                 | 0       | 0       | 0                  | 0       | 0       | 0                       | 0         | 0         | 0          | 0         | 0         |
| Eastern Mediterranean B      | 11           | 1       | 12      | 1                 | 0       | 2       | 4                  | 1       | 5       | 441                     | 74        | 515       | 457        | 76        | 534       |
| Eastern Mediterranean D      | 933          | 254     | 1187    | 604               | 59      | 663     | 1012               | 129     | 1141    | 7401                    | 926       | 8327      | 9950       | 1368      | 11,318    |
| Europe A                     | 66           | 13      | 78      | 16                | 2       | 18      | 244                | 38      | 282     | 539                     | 145       | 684       | 865        | 197       | 1062      |
| Europe B                     | 146          | 3       | 148     | 57                | 1       | 58      | 260                | 2       | 262     | 5506                    | 156       | 5662      | 5969       | 162       | 6130      |
| Europe C                     | 0            | 0       | 0       | 0                 | 0       | 0       | 0                  | 0       | 0       | 0                       | 0         | 0         | 0          | 0         | 0         |
| South-East Asia B            | 438          | 396     | 835     | 129               | 58      | 187     | 243                | 139     | 382     | 3205                    | 1852      | 5057      | 4016       | 2445      | 6461      |
| South-East Asia D            | 11,527       | 6459    | 17,987  | 12,715            | 3485    | 16,200  | 15,247             | 5625    | 20,873  | 117,523                 | 45,047    | 162,570   | 157,013    | 60,617    | 217,630   |
| Western Pacific A            | 0            | 0       | 0       | 0                 | 0       | 0       | 0                  | 0       | 0       | 69                      | 36        | 104       | 69         | 36        | 104       |
| Western Pacific B            | 134          | 159     | 293     | 22                | 34      | 56      | 51                 | 63      | 114     | 3167                    | 814       | 3981      | 3374       | 1070      | 4443      |
| Worldwide                    | 13,586       | 7418    | 21,003  | 13,608            | 3656    | 17,264  | 17,680             | 6336    | 24,016  | 152,647                 | 51,662    | 204,309   | 197,520    | 69,072    | 266,592   |
| DALYs                        |              |         |         |                   |         |         |                    |         |         |                         |           |           |            |           |           |
| Africa D                     | 2516         | 1046    | 3562    | 452               | 65      | 517     | 4119               | 1906    | 6024    | 64,043                  | 19,116    | 83,159    | 71,130     | 22,132    | 93,262    |
| Africa E                     | 4926         | 2293    | 7220    | 573               | 349     | 922     | 10,159             | 6290    | 16,449  | 33,502                  | 21,109    | 54,610    | 49,159     | 30,042    | 79,201    |
| Americas A                   | 0            | 0       | 0       | 0                 | 0       | 0       | 0                  | 0       | 0       | 172,206                 | 7213      | 179,419   | 172,206    | 7213      | 179,419   |
| Americas B                   | 2311         | 230     | 2541    | 734               | 63      | 797     | 1717               | 176     | 1893    | 22,252                  | 4728      | 26,980    | 27,014     | 5197      | 32,210    |
| Americas D                   | 0            | 0       | 0       | 0                 | 0       | 0       | 0                  | 0       | 0       | 0                       | 0         | 0         | 0          | 0         | 0         |
| Eastern Mediterranean B      | 285          | 36      | 321     | 33                | 9       | 43      | 86                 | 20      | 106     | 9841                    | 1383      | 11,224    | 10,246     | 1448      | 11,694    |
| Eastern Mediterranean D      | 29,240       | 7669    | 36,909  | 16,446            | 1800    | 18,247  | 27,777             | 3613    | 31,390  | 187,394                 | 21,544    | 208,938   | 260,857    | 34,627    | 295,483   |
| Europe A                     | 1514         | 224     | 1738    | 369               | 45      | 414     | 4949               | 545     | 5494    | 8397                    | 1491      | 9888      | 15,230     | 2304      | 17,534    |
| Europe B                     | 4439         | 60      | 4499    | 1704              | 20      | 1724    | 6460               | 56      | 6517    | 115,640                 | 1991      | 117,631   | 128,243    | 2128      | 130,371   |
| Europe C                     | 0            | 0       | 0       | 0                 | 0       | 0       | 0                  | 0       | 0       | 0                       | 0         | 0         | 0          | 0         | 0         |
| South-East Asia B            | 10,968       | 7741    | 18,709  | 3217              | 1487    | 4704    | 5608               | 2983    | 8591    | 66,969                  | 29,913    | 96,881    | 86,762     | 42,124    | 128,886   |
| South-East Asia D            | 351,752      | 179,051 | 530,803 | 338,976           | 107,041 | 446,017 | 400,770            | 143,146 | 543,916 | 290,6993                | 938,528   | 3,845,521 | 3,998,491  | 1,367,766 | 5,366,257 |
| Western Pacific A            | 0            | 0       | 0       | 0                 | 0       | 0       | 0                  | 0       | 0       | 1024                    | 340       | 1364      | 1024       | 340       | 1364      |
| Western Pacific B            | 3700         | 3567    | 7267    | 615               | 794     | 1409    | 1313               | 1485    | 2797    | 72,936                  | 16,830    | 89,766    | 78,564     | 22,675    | 101,239   |
| Worldwide                    | 411,652      | 201,918 | 613,569 | 363,120           | 111,673 | 474,793 | 462,957            | 160,219 | 623,177 | 3,661,195               | 1,064,186 | 4,725,381 | 4,898,924  | 1,537,996 | 6,436,920 |



mouth, pharynx, and oesophagus, could be attributed to SLT in 2010. This is a little higher than the estimates from a recent study in which 50,000 deaths were attributed to SLT in eight South Asian countries [4]. This discrepancy may be explained by the fact that we used the most recent, updated prevalence and burden of disease figures.

Our estimate does not include economic impact. However, given the nature of the associated diseases, it is likely that the SLT use imposes a huge economic burden on weak health systems and poor economies. Moreover, owing to higher consumption of SLT among people of lower socio-economic status and inequitable access to health care in low-income and middle-income countries, its use is likely to contribute to driving disadvantaged sections of these societies into further poverty. A disproportionate impact on the male population (more than 70 % of disease burden due to SLT is in males) is also likely to have a disproportionate economic impact on societies in terms of reduced workforce contributions by men. On the other hand, effective legislation, policy, and preventive programmes could avert this burden due to SLT.

The signatories of the WHO's Framework Convention on Tobacco Control should, in addition to the focus on reducing smoking consumption and related harm, now also consider the need to regulate production, marketing, and labelling of SLT products. This is particularly necessary in those countries where prevalence is high and SLT products are manufactured at a large scale without any checks on the carcinogenic level of their ingredients [35]. In countries where its use is largely limited to immigrant populations (such as in the UK) [36], strict regulation and taxation policies should be enforced which prevent import of SLT products and sale by local shops.

SLT is an important health issue, applying to a large part of the world. The data presented here are the most comprehensive gathered and brought together thus far. However, considerable uncertainties remain pertaining to risk estimation of different diseases associated with SLT use. Therefore more research is needed to investigate the newly established and previously known adverse health outcomes pertaining to SLT, particularly within countries where prevalence is high but no research evidence of risk estimation is available. Moreover, more descriptive questions about the type of SLT products and the pattern of use should be introduced into national surveys and publications of such findings encompassing all the regions.

## Conclusions

Our study, a first attempt to assess global burden of disease due to SLT, estimates that more than six million

DALYs are lost and over a quarter of a million deaths occur each year owing to its consumption. There is a need to build on the insights obtained from efforts to reduce cigarette smoking-related harm and to investigate strategies to reduce use of SLT and decrease the substantial associated burden of harm.

## Additional file

**Additional file 1: Supplementary description of methods and results sections.** (DOCX 281 kb)

## 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; SLT: Smokeless tobacco; STEPS: STEPwise Approach to Surveillance; TSNA: Tobacco-specific nitrosamines; WHO: World Health Organization.

## Competing interests

KS, SS, SA, AV, MJ, and OD declare that they have no competing interests. AS reports grants from The Commonwealth Fund, outside the submitted work but no other conflict of interest.

## Authors' contributions

KS: Developed the protocol, data analysis, data interpretation, drafting and approval of the manuscript. SS: Data collection, data analysis, data interpretation, contribution to and approval of the manuscript. SA: Co-drafted the protocol, data collection, data analysis, contribution to and approval of the manuscript. AV: Data collection, data analysis, data interpretation, contribution to and approval of the manuscript. MJ: Data collection, data interpretation, contribution to and approval of the manuscript. OD: Contribution to the protocol, data interpretation, contribution to and approval of the manuscript. AS: Conceived the idea, contribution to the protocol, data interpretation, contribution to and approval of the manuscript.

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## Ethics approval

No ethics approval was required for this study.

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