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Oral Cancer Risk Assessment for Different Type of Smokeless Tobacco Products Sold Worldwide: A Review of Reviews and Meta-analyses

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Abstract

Smokeless tobacco (SLT) use is a significant cause of lip and oral cavity cancers. Globally, oral cancer (OC) prevalence is strongly linked to the types of tobacco products used, their chemical composition, and their pattern of use. Except snus, all SLT products sold in different WHO regions are strongly associated with OC incidence. Shammah showed the highest association odds ratio (OR) with 95% confidence intervals (CI) (OR 38.74, 95% CI 19.50-76.96), followed by oral snuff (OR 11.80, 95% CI 8.45-16.49), gutkha (OR 8.67, 95% CI 3.59-20.93), tobacco with betel quid (OR 7.74, 95% CI 5.38-11.13), toombak (OR 4.72, 95% CI 2.88-7.73) and unspecified chewing tobacco (OR 4.72, 95% CI 3.13-7.11). Most SLT products containing high levels of carcinogenic tobacco-specific nitrosamines (TSNAs) exhibit a high risk of oral cancer. There is an urgent need to frame and implement international policies for OC prevention through legal control of the TSNA levels in all SLT product types.

Prevention Relevance Statement

Most smokeless tobacco products sold worldwide, mainly shammah, toombak, gutkha, betel quid with tobacco, and dry snuff, are associated with a high risk of oral cancer. A high concentration of tobacco-specific nitrosamines in SLT products is the major causative factor for oral cancer development.

Introduction

Oral cancer (OC) is a highly lethal disease and one of the most debilitating and disfiguring malignancies globally. Head and neck cancers represent the sixth most common cancer worldwide and OC accounts for ~37% of head and neck cancers with more than 500,000 cases worldwide and are predicted to rise by 62% to 856,000 cases by 2035 (1). According to global cancer statistics, Globocan 2020, cancers of the lip and oral cavity pose an enormous global challenge, with 377,713 new cases and 177,757 deaths accounting for about 3.8% of all cancer cases and 3.6% of cancer deaths globally (2).

OC is most likely caused by a combination of extrinsic and intrinsic factors acting in concert over a period of time (3,4). Major risk factors implicated in the aetiology of OCs are tobacco use (5), areca nut use (6) alcohol consumption (7), ultraviolet radiation (UVR), and human papillomavirus (HPV) infection (8). Other factors include poor oral hygiene, low socioeconomic status and genetic factors, occupational exposure (9), weakened immune system, deficiencies in dietary intake, or lack of healthy eating (10). Gender, age, physical activity and environmental factors may also play a crucial role in the progression of the disease (11,12). Tobacco and alcohol use are two of the most common risk factors for oral cavity and oropharyngeal cancers (13). As dual use of tobacco products and alcohol act synergistically, and account for 3 out of 4 oral cavity cancer cases globally (14,15).

Smokeless Tobacco (SLT) includes a large variety of commercial or non-commercial tobacco preparations used orally or nasally, without combustion. Chewing tobacco, moist snuff, and dry snuff are the three most common types of SLT products used worldwide . The chewing tobacco products mainly include betel quid with tobacco, khaini, zarda and gutkha. Non-chewing products include oral snuff, nasal snuff, and snus. Snuffedtobacco products are used in either wet or dry form. Use of wet snuff is more common in the Western world, while nasal snuff in dry powder form is used in the South East Asia and Eastern Mediterranean regions (16).

The WHO South-East Asia Region (SEAR), notably the Indian subcontinent, contains 90% of the world's 250 million SLT consumers and accounts for nearly one-third of all cancers (17,18). SLT use is culturally widely acceptable due to its association with socialisation and family tradition in various parts of the world (19). SLT products may be premade (ready-to-use) or custom-made. Premade products range from large factory manufactured products to small cottage industry products, while custom made are assembled by the user or a vendor in market stalls or shops according to one's preferences. Due to thevast heterogeneity and lack of standardization, the chemical formulation or composition of SLT products show great complexity. Factors for the high prevalence of SLT are its addictive properties, easy accessibility, low cost and lack of prohibitive legislation (20). This could be the reason that the US, Food and Drug Administration's (FDA) nicotine reduction strategy which

greatly improved the health consequences of tobacco dependence in smokers, could not be applied to SLT products.

SLT causes cancers of all parts of the oral cavity including the lip, tongue, palate, gum, cheek, buccal gingivae and floor of the mouth (21), along with oesophageal and pancreatic cancer, etc. (22). More than 180,000 cases of OC occur every year in SEAR with approximately 90% of which are due to tobacco use (23). The odds of developing OC in SEAR were more than four times higher among SLT users than non-tobacco users (24,25). India has one of the highest incidences of OC and accounts for about 30% of all new cases annually due to the high prevalence of SLT use and betel-quid chewing (26). Population-based studies from 13 countries showed that the OC incidence rate is increasing, especially among the younger population (27). Other than HPV, increased incidence of early-onset oral carcinoma in the United States (US) has been associated with SLT use, mainly chewing tobacco and snuff (28).

Due to increasing awareness about smoking-related harms and growing regulatory pressures on cigarettes, the global prevalence of smoking is showing a downward trend in the last two decades (29). A systematic analysis of the global burden of disease study results in 204 countries and territories between 1990–2019 indicated that the global age-standardised prevalence of smoking had decreased significantly during this period, while the use of SLT products continued unabated during this period (30). Such a trend could be one of the reasons that the incidence of nasopharyngeal cancers has decreased dramatically (estimated annual percentage change (EAPC) -1.5, 95% CI -1.7 to -1.3) from 1990 to 2017, while the global incidence for lip and oral cavity cancers has shown a substantial increase from 1990 to 2017 (EAPC 0.26, 95% CI 0.16–0.37). Globally, the absolute number of lip and oral cavity cancers incidence increased from around 186,000 in 1990 to 389,800 in 2017, which is about a 109% increase over 28 years (31).

Great diversity in the preparation and composition of SLT products makes their regulation a big challenge. For example, gutkha is chewing tobacco mixed with areca nut and slaked lime (32), often marketed as a mouth freshener due to added flavours (33). Shammah is a traditional form of fermented chewing tobacco popular in the Middle East (34) while toombak, a homemade oral snuff mainly used in Sudan, is prepared from the tobacco leaves of *Nicotiana rustica* species having high nicotine content (35). Weak enforcement of regulatory policies and aggressive marketing of SLT products by the tobacco industry worsens the situation (36,37).

Broadly, reports quantifying the promotion of all types of SLT, as a harm reduction strategy and as a safer alternative to cigarettes, have shown no apparent health benefits at a population level (38). On the other hand, this has caused an increase in the sale of SLT. Because nicotine content in a cigarette stick varies from 0.8 to 13.0 mg/g, while it ranges from 0.8 to 76.0 mg/g in SLT products (39), SLT

users absorb two to three times the amount of nicotine as those who smoke cigarettes (40). This is due to the high alkaline nature of most SLT products providing free nicotine at a high concentration in a short time. Excessive high nicotine concentration makes SLT products highly addictive, and nicotine is also a precursor of carcinogenic tobacco-specific N-nitrosamines (TSNAs) (41,42).

Nicotine and Tobacco Specific Nitrosamine (TSNA) levels

TSNAs are chemically stable compounds under physiological conditions and are found to be associated with carcinogenicity in humans and experimental animals (43). TSNAs mainly N'-nitrosonornicotine (NNN) and nicotine-derived nitrosamine ketone (NNK)are listed as group 1 human carcinogens by IARC (3).They are shown to disrupt DNA repair and molecular processes and are the prime cause of OC in SLT users (44–46).

Addictiveness and health hazards of SLT across the globe are largely dependent upon product's chemical composition and its use pattern (47). Globally, the magnitude of cancer risk due to SLT use shows disparity and is highly correlated with the variation in the levels of NNN and NNK present in diverse SLT products sold worldwide (48,49). Seeing the carcinogenicity of NNN and NNK in humans, the WHO Study Group on Tobacco Product Regulation in 2010 recommended a regulatory limit for maximal total concentration of NNN and NNK as less than 2 μg/g dry weight of tobacco (48) However, the levels of NNN and NNK, per unit dose, in SLT products are much higher as compared to cigarette smoke. While on an average mainstream cigarette smoke contains NNK and NNN in the range of 0.006-1.74 μg/g and 0.004–2.83 μg/g, respectively, SLT products sold across the world showed NNK levels between 0.019 to 7870 μg/g and NNN levels between 0.080 to 3080 μg/g against the WHO permissible limit of less than 2 μg/g.

Swedish Match, the principal manufacturer of Swedish moist snuff, adopted a voluntary standard for TSNAs levels, called the *GothiaTek* standard. (50).Table 1 represents comparative data on the type of SLT sold across the world, its preparation process and use, country/ WHO region, levels of nicotine, total TSNAs, NNN and NNK. SLT products viz. shammah gutkha, toombak, betel quid with tobacco, chewing tobacco (unspecified) along with dry snuff and moist snuff (snus) were found to contain high levels of carcinogenic TSNAs, mainly NNN and NNK in them.

Many research articles in the previous years have indicated the link between SLT and OC but the present systematic review, for the first time, describes the levels of risk estimates of OC associated with the major individual type of SLT products sold across the five world health organisation (WHO) regions. It also reports the WHO region-wise OC risk estimates associated with different SLT products and compiles data on the global pattern of different types of SLT product use and the concentration of nicotine, total TSNAs, NNN and NNK in them.

Materials and Methods

Electronic Searches

An electronic search was conducted on PubMed and Google Scholar for articles published between Jan 1, 2010, to Aug 5, 2021 using the key phrases “oral cancer”, “oral squamous cell carcinoma” “smokeless tobacco”, “chewing tobacco”, “betel quid”, “snuff”, “snus”, “gutkha/gutka”, “toombak” and “shammah”. The references of relevant articles were manually searched for additional eligible citations. This comprehensive review presents pooled data from the different studies.

Selection of Studies

Author, AKG extracted data through this literature search and identified studies. Duplicate records were removed, and the reference lists of the selected articles were screened for additional relevant articles. Titles and abstracts of papers identified through the search strategy were reviewed and relevant articles, potentially fulfilling the inclusion criteria, were retrieved in full text. A second reviewer (RM) screened the titles and abstracts of the retrieved articles to identify the relevance of the articles to the objectives of this review. Two authors, AKG and MK, independently assessed the eligibility of the selected data to assure quality and minimise biases. **Figure 1** provides the detailed strategy of the study selection process using PRISMA guidelines.

Inclusion Criteria -

- Oral cancer had to be one of the outcomes of smokeless tobacco use in the adult population.
- Articles presented only as reviews, systematic reviews and meta-analyses.
- Studies providing odds ratio (OR)/risk ratio (RR) estimates with corresponding 95% confidence intervals (CI).
- Articles published in English.

Exclusion Criteria

- Studies not designed to investigate SLT association with OC.
- Articles published before year 2010.
- Articles published in languages other than English.

Data Extraction

For articles meeting the eligibility criteria, the following information was extracted: the study authors with the date of publication, region of the study, the type of smokeless tobacco, period of study, OR/RR estimates and corresponding 95% CI. Information was extracted by one author AKG and checked by another author, MK. (Supplementary Table 1)

The region of the study was classified as global or as one of the WHO regions, namely, the American Region (AMR), Eastern Mediterranean Region (EMR) including Pakistan, European Region (EUR), African Region (AFR) and South-East Asian Region (SEAR). The type of tobacco was classified as: any type of smokeless tobacco, if not explicitly specified which type, shammah (Arabian chewing

tobacco), toombak (Sudanese dipping tobacco), gutkha (Indian chewing tobacco), betel quid with tobacco, chewing tobacco (unspecified), dry snuff and moist snuff (snus). If a review article had been updated, then the updated review estimates were used and if two reviews cite the same source, then the one reporting pooled estimates was used.

Data Analysis

We used forest plot graphs to represent the OR/RR estimates and 95% CI. Results were stratified by WHO region and by tobacco type. No overall pooled analysis was conducted. If a previous review reported individual studies without pooling the results, these were pooled if the estimates were provided together with 95% CI or other information to enable pooling the results. All studies were systematic reviews with meta-analysis except one study on toombak where the combined OR estimates were not reported and thus were calculated (see supplementary method).

Ethics Statement

Article does not contain any studies involving human or animal participants.

Data Availability Statement

The data generated in this study are available upon request from the first author AKG.

Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/)

Results

Articles, published in the last decade, i.e., from 2010 to 2021 and reporting the OC risk estimates in the association of the SLT product, were selected for the present review. After removing duplicate records, titles and abstracts of 74 records were retrieved through the selected databases. The reference lists of the included articles were screened for 4 additional articles. All 78 articles were reviewed thoroughly. After removing 52 irrelevant articles, 26 were selected for the full-text study, of which, 17 which did not meet the selection criteria, were excluded. **Figure 1** demonstrates the flow-chart of the study selection process for smokeless tobacco use and oral cancer risk using PRISMA guidelines. Oral potentially malignant disorders are abbreviated as OPMD in fig 1).

Nine studies fulfilling all the eligibility criteria for inclusion were finally included in the current review. Of these, three reviews evaluated the risk of OC with the use of all types of SLT products combined (51–53). Three reported OR estimates for betel quid with tobacco (51,54,55). Dry snuff was evaluated for high risk of OC in three studies (51,56,57). Two studies mentioned chewing tobacco (without specifying the type) (51,56), while one study each was found on shammah (58), gutkha (51), toombak (59) and snus (51). All the selected studies are systematic reviews with meta-analysis and OR estimates were adjusted for confounding factors mainly smoking except for one study (59). (Supplementary Table 1)

Data analysis of all included studies together indicated that the individual product that showed the highest association (OR 38.74, 95% CI 19.50-76.96) was shammah, followed by oral snuff (OR 11.80, 95% CI 8.45-16.49), gutkha (OR 8.67, 95% CI 3.59-20.93), tobacco with betel quid (OR 7.74, 95% CI 5.3-11.13), toombak (calculated OR 4.72, 95% CI 2.88-7.73, please see supplementary method) and unspecified chewing tobacco (OR 4.72, 95% CI 3.13-7.11). Overall, all selected SLT product types, except snus, were found to have a strong association with OC incidence across the globe. **Figure 2** represents a forest plot of the included studies showing odds ratios and 95% confidence intervals (CI) for the association between the types of SLT products and the risk of OC. Region-wise analysis of SLT products showed that the overall global OR for OC for all SLT types combined, ranged from 3.53 (95% CI 2.76-4.52) to 3.94 (95% CI 2.70-5.75). In general, region-wise OC risk estimates, for all types combined, were highest for EMR with OR ranging from 1.28 (95% CI 1.05-1.57) to 14.52 (95% CI 7.69-27.41), followed by SEAR with OR 4.44 (95% CI 3.51-5.61) to 5.67 (95% CI 3.83-8.40) and for AMR, OR 0.95 (95% CI 0.71-1.25) to 4.72 (95% CI 0.66-33.69), while it was not statistically significant for EUR with OR 0.94 (95% CI 0.71-1.25). For further details, see **figure 3** which represents a forest plot of included studies by the WHO region.

A strong positive association of betel quid with tobacco and OC was seen globally OR 7.18 (95% CI 5.489.41) (51) while for Asian studies risk estimates for betel quid with tobacco range from OR 7.10 (95% CI 4.49–11.22) to 7.74 (5.38-11.13) (54,55), toombak and shammah use for EMR, showed highest OC risk estimate with OR 4.72 (95% CI 2.88-7.73) (56) and OR 38.74 (95% CI 19.50-76.96) respectively (58). Risk estimates for snuff-type products vary significantly among various WHO regions. In EUR and AMR, dry snuff and snus are more prevalent. Global OC risk estimates for oral snuff showed OR 4.18 (95% CI 2.37-7.38) (51) while for AMR, OR was 3.01 (95% CI 1.63-5.55) (56). Naswar, used in EMR was shown to have a high OR value of 11.80 (95% CI 8.45-16.49) (57). Globally, chewing tobacco, is shown to have a high OC risk with OR 4.37 (95% CI 3.27-5.84) as compared to non-chewing SLT products with OR 1.56 (95% CI 1.04- 2.35) (51). **Figure 3**

The level of TSNAs in SLT products plays a significant role in carcinogen exposure levels. Thus the difference in the magnitude of OC risks can be correlated with the variation in the levels of NNN and NNK present in SLT products (49). TSNA levels varies from 0.08 µg/g to as high as 992 µg/g in the selected SLT products. **Figure 4** indicates that high levels of TSNAs are present in SLT products with a high-risk ratio for OC. Fig 4 (a) presents TSNAs values on the log scale while the original TSNAs levels in µg/g are presented on the right-hand side of the y-axis. (b) OR and corresponding 95% CIs estimates are based on review studies from the same region that the SLT product TSNAs values are based. The OR estimates for zarda and khaini are not product specific but those for all types of chewing tobacco from SEAR (54). For gutkha, dry snuff and snus the OR estimates are

based on global pooled estimates (51), whereas for naswar (a nasal snuff) these are based on EMR estimates only (57).

Discussion

Global Pattern of Oral Cancer Risk Estimates for different SLT Products

According to a recent study, published in Lancet Public Health, out of the total 273·9 million tobacco chewers (age 15 and above) in the world, about 228·2 million lived in SEAR (30). Over the past several decades, it has been seen that SLT use has increased by nearly 50% in low-and-middle-income countries (LMIC) while declining in high-income countries (60). Tobacco chewing and betel quid with tobacco are the two most prevalent forms of SLT use in Asia (61). In India, the majority of SLT users consume chewing tobacco (11.6% khaini, 8.2% gutkha preparations, 6.2% betel quid with tobacco, 4.7% oral snuff and 4.4% other SLT products) (51). Gutkha use has been gaining popularity in Europe and US in the last two decades due to its easy availability, low cost and extensive marketing (62). In the US, the sale of SLT products increased by 5.8% between 2011 and 2016, but declined by 3.9% from 2016 to 2019; however, the sale of snus consistently increased while the sale of chewing tobacco, dry snuff, and dissolvable decreased during this period (63).

A recent CDC report indicated that the incidence of cancers of the oral cavity and pharynx (all sites), not associated with HPV, increased in the US during 2007–2016 (64). In 2018, an estimated 120,000 new OC patients were diagnosed with 72,000 deaths in India alone (65). Studies revealed that a higher risk of OC was observed for SLT products sold before 1990 (OR 6.6, 95% CI 5.3-8.2) as compared to that sold after 1990 (OR 3.0, 95% CI 2.3-3.9) (17). Dry snuff sold in the US and Western Europe, before 2000, was shown to have higher relative risks for OCs (RR 8, 95% CI 2.7-20.0) (66). This is due to improvement in the quality of manufactured tobacco products. Most SLT products sold in the US after 1990, achieved TSNAs levels below 20 ppm as compared to generally high TSNAs levels (above 100 ppm) in earlier SLT products, sold before 1990 (67). Previous studies showed that snus had an association with an increased risk of oral or pancreatic cancer as compared to non-tobacco users (68,69). However, the current prevalence statistics and epidemiological data on snus use, in the European population, do not indicate an increased risk of OC compared to cigarettes (70).

More than 50% of OCs are attributable to using SLT products in Sudan and India compared to about 4% in US men (65). Literature studies show that toombak has a major role in the aetiology of oral/oropharyngeal cancer in Sudan (71,72) and sub-Saharan Africa (73). OC occurrence is about 3 to 6 times higher in North-East Nigeria than reported for the US and Europe -mainly due to the use of dry snuff (OR 10, 95% CI 4.1-4.3) (74,75). Oral cancer is the third most common malignancy in Saudi Arabia mainly due to the use of shammah, the traditional form of chewing tobacco prevalent in

the Middle East, Yemen and Sudan (76). A review of studies by Awan and Patil showed that in the SEAR, the OC risk estimates (OR) for betel quid varied from 3.1 to 15.7 (95% CI 11.0-22.1) and from 1.2 (95% CI 1.0-1.4) to 12.9 (95% CI 7.5-22.3) for chewing tobacco (43).

The frequency of SLT use was also seen to vary substantially across countries and by sex, age, ethnic origin, and socioeconomic characteristics within a country (77). A linear dose-response association was observed between OC and chewing tobacco regarding age at initiation, duration, and frequency of chewing per day (78).

Most SLT users have limited awareness of its association with OC due to a lack of knowledge of its harmful constituents and high use due to cultural traditions/ religious norms (79). According to the Global Adult Tobacco Survey in India (GATS, 2016-17), the prevalence of SLT use is very high, especially in females, which could be due to a lack of awareness and knowledge about the health hazards of the SLT product used (80). In the Indian subcontinent, betel quid chewing, with added tobacco has a much higher risk ratio in women (OR 14.6, 95% CI 7.6-27.8) (55). Globally, gender-wise sub-group analysis showed a higher risk for females with (OR 5.8, 95% CI 2.9-11.6), as compared to males (OR 2.7, 95% CI 1.7-4.3) (51).

High Levels of Nicotine and Tobacco-specific Nitrosamines (TSNAs) in Smokeless Tobacco Products and Oral Cancer

High nicotine content in SLT products is responsible for the increased levels of TSNAs which are primarily formed during tobacco fermentation and storage, especially at elevated temperature and moisture (81). A global surveillance study across 113 countries from five WHO regions over the past 10 years, indicated that diverse SLT products sold worldwide seem to contain high levels of carcinogenic TSNAs (52). Maximum concentrations of NNN and NNK content for toombak products from Sudan were found to be 3085 and 7870 μg/g respectively which were remarkably higher than most of the products sold worldwide (82). Average levels of NNN, in a brand of khaini, marketed as snus, were 22.9 and 2.6 μg/g tobacco respectively (83). Khaini, sold in South Asia, contains alarmingly high levels of NNN (39.4-76.9 μg/g) and NNK (2.34-28.4 μg/g) (84). Snuff sold in America was shown to have TSNAs levels as high as 76.5 μg/g, while NNN (0.37-42.6 μg/g) and NNK (0.38-9.9 μg/g) (85). The literature did not report levels of TSNAs in shammah, showing the highest OR. On average, NNN and NNK levels showed an almost 70-fold variation with NNN concentrations ranging from 0.09 to 76.9 μg/g while NNK levels ranged from 0.04 to 28.4 μg/g in all selected SLT products (6). Fermented SLT products, like toombak, shammah, dry snuff, khaini, gutkha, have been found to contain higher levels of TSNA than pasteurised products like snus (84). Shammah, a highly fermented product with high nicotine content (86), is made under long anaerobic conditions so more nitrite is generated which increases TSNA concentration. However, no study was

found reporting the TSNA levels in shammah (34). The OR of developing OC, for shammah users was 38.7 (95% CI 19.5-77.0) which was nearly 39 times higher than non-shammah users (58). Studies showed that NNN and NNK levels for toombak were about 100 folds higher than most of the products sold worldwide (87,88). OC risk estimate for toombak use was significantly high among users in comparison with controls (OR 3.8, 95% CI 1.7-8.6) (89). A report showed that US snus had high TSNAs with NNN and NNK as high as 42.55 and 9.95 μg/g, respectively (90). Dry snuff, the major factor for tongue carcinoma in the US, is shown to contain high TSNAs levels (91). On the other hand, Swedish snus made with improved manufacturing techniques has low OC risks due to low levels of NNN and NNK (92). Thus, the levels of nicotine and TSNAs showed several hundred-fold variations across different product types and substantial vendor-to-vendor variation within some product categories (93).

Thus, SLT products with higher NNN concentration pose higher cancer risks, so reducing the levels of carcinogenic nitrosamines in finished SLT products could prove a beneficial strategy to reduce OR risk for OC (94,95).

For the protection of public health, FDA has proposed a tobacco product standard rule, which states that the mean level of NNN in any batch of finished SLT product should not exceed 1.0 μg/g of tobacco (on a dry weight basis) at any time through the product's labelled expiration date (96). However, constituent regulation and control of SLT products lag far behind cigarettes, mainly due to non-standardised production and storage methods, greater heterogeneity and the lack of strict legal policies for SLT (39).

Conclusions

The current review is to bring attention to the prevention community to the risks of individual smokeless tobacco product for risk of oral cancer. Most carcinogenic SLT types sold across the various geographic regions worldwide, mainly shammah, toombak, gutkha, betel quid with tobacco, dry snuff were found to be associated with high OC risks. Data analysis indicated that the shammah showed the highest association (OR 38.7, 95% CI 19.5-77.0), followed by oral snuff (OR 11.8, 95% CI 8.4-16.4), gutkha (OR 8.7, 95% CI 3.6-20.9), tobacco with betel quid (OR 7.7, 95% CI 5.3-11.1), toombak (OR 4.7, 95% CI 2.9-7.7) and unspecified chewing tobacco (OR 4.7, 95% CI 3.0-7.1). The difference in the magnitude of OC risks has been found to correlate highly with regional variation in the SLT product type which showed great diversity and heterogeneity in its composition, usage and manufacturing process. A decrease in smoking and the prevalence of lung cancer in the US shows the effectiveness of decades of public education and tobacco control policies (97). However, the rising incidence of OC across the world, primarily associated with SLT use, indicates that the tobacco control policies do not have a more prominent effect on SLT usage. The huge variation in the levels

of carcinogenic TSNAs, especially NNN and NNK, in diverse types of SLT products, hinders the comparability of results from evaluating the global risks estimate of SLT to human health across the globe. It is imperative to develop and effectively implement strategies for monitoring TSNA levels in SLT products. There is a critical need for systematic surveillance of all types of SLT products through legal control of the permissible TSNA levels. Global standards for testing and measuring TSNAs levels in all types of SLT products, with effective measures to minimise the levels of TSNA, can significantly help reduce OC risk associated with individual SLT products.

Road Ahead

The high concentration of TSNAs, mainly NNN and NNK, in diverse types of SLT products is the major causative factor for the development of OC. Applying a grassroots approach to lower the levels of carcinogenic TSNAs at various stages of SLT production, right from its growth, processing, manufacturing, and storage, could prove to be a beneficial strategy. This includes the use of tobacco plant varieties having low levels of nitrate and TSNAs precursors, decreasing the use of nitrate fertilisers and chemical pesticides while growing tobacco, avoiding microbial contamination during tobacco processing, air-curing of leaves instead of fire curing under controlled conditions, use of newer technologies like heat treatment, pasteurisation for tobacco processing and avoiding tobacco fermentation etc. can significantly lower the concentration of carcinogenic TSNAs in the finished SLT products (39).

As the majority of OC are preventable through risk factors intervention, creating awareness about their carcinogenicity among consumers, constituent's disclosure along with their health hazard information on all SLT products may play a key factor in reducing oral cancer incidence in the future. Strict regulatory measures are to be taken for the additives and flavouring agents in SLT products, which make them palatable and more appealing especially amongst youth (98).

For the first time, the World Health Assembly, in 2007, passed a resolution on oral health and oral cancer prevention to be an integral part of national cancer control programs. The WHO global oral health program was launched to work for the capacity building in OC prevention in different countries, inter-country exchange and the development of global surveillance systems for OC and risk factors. With the establishment of more cancer registries across the globe and their secondary data analysis, the surveillance of SLT products should become easier.

Conflict of Interest statement:

The authors declare no potential conflicts of interest.

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680 *Table 1. Global pattern of types of SLT use and nicotine and nitrosamine levels in different SLT products*

S no	SLT type	Preparation and Use	Region	Countries with major consumption	Nicotine* mg/g	Total TSNA* µg/g	NNN*µg/g	NNK* µg/g
1	Snuff	Finely cut or ground air-cured flavoured tobacco dry or moist, placed in the mouth and sucked.	America	USA, Canada, Mexico,	3.9–40.1	0.3–76.5	0.37-42.6	0.38-9.9
2	Snus (Swedish)	Pasteurized finely ground moist tobacco, moisturizers, sodium carbonate, salt, sweeteners	Europe	Sweden, Denmark, Finland, Iceland, Norway,	7.8–15.2	0.6–0.7	0.42-3.28	0.13-1.1
3	Nass (Naswar)	Sun-dried and powdered tobacco; ash, oil, placed in the mouth and sucked	Parts of Europe and Eastern Mediterranean	Uzbekistan, Kyrgyzstan, Tajikistan, Afghanistan, Pakistan, Iran	8.9–14.2	0.5–1.4	0.59-1.3	0.07-0.21
4	Toombak	Fermented and grounded Tobacco, baking soda and water. Oral and nasal use	Parts of Eastern Mediterranean and Africa	Sudan, Chad	9.6–28.2	295–992	115-3085	147-7870
5	Dry Snuff	Finely ground powder, inhaled	Africa	Nigeria, Ghana, Algeria, Cameroon, Chad, South Africa	1.2–17.2	1.7–20.5	2.4-18.1	0.58-6.4
7	Gutkha (Chewing tobacco)	Commercial preparation, finely chopped tobacco with flavourings and sweeteners, Sucked and chewed	SEAR	India, Pakistan, Bangladesh, Nepal, Myanmar, Sri Lanka, UK	0.2–4.2	0.1–23.9	0.1-1.1	0.04-0.43
8	Khaini (Chewing tobacco)	Coarsely cut tobacco leaves mixed with slaked lime, Sun-dried or fermented.	South East Asia, Western Pacific and Eastern Mediterranean Europe	India, Bangladesh, Nepal, Bhutan	2.5–4.8	21.6–23.9	13.2-76.9	0.11-28.4
9	Zarda (Chewing Tobacco)	Shredded tobacco leaves are boiled with lime and saffron; often used with betel quid	SEAR	Bangladesh, India, Pakistan, Myanmar, Thailand, Indonesia, Nepal, Maldives, Sri Lanka, UK	9.5–30.4	5.5–53.7	4.79-19.9	0.22-24.1
10	Betel quid with tobacco	Mixture of betel quid with areca nut, with or without tobacco. May also be mixed with slaked lime ad f tobacco. be mixed with slaked lime, or sweeteners	SEAR	India, Pakistan, Bangladesh, Nepal, Myanmar	6.7-8.4	0.17-2.1	1.2-48.6	0-14.3
11	Shammah (Chewing tobacco)	Powdered tobacco used with slaked lime, oil, flavouring, kept in the mouth and sucked	Middle East	Saudi Arabia, Yemen, Algeria.	37.82-87.56	DNA**	DNA**	DNA**

681

682 Note: List of products is not exhaustive. *Figures are adapted from refs (26, 37, 52, 93 and 99); **DNA: Data not available.

683 **Figure Legends**

684 **Figure 1**: Search strategy flow-chart of study selection process for smokeless tobacco use and oral
685 cancer risk using PRISMA guidelines.

686 **Figure 2**: Forest plot of studies showing oral cancer risks associated with various types of SLT
687 product. Data presented also include: the SLT type, the study reference, region, the odds ratio and
688 corresponding 95% confidence interval, in addition, where available the number of estimates (No.
689 Est) that the pooled estimate is based on are provided.

690 **Figure 3**: Forest plot of studies showing WHO region-wise oral cancer risks associated with various
691 SLT products . Data presented also include: the SLT type, the study reference, the odds ratio and
692 corresponding 95% confidence interval, in addition, where available the number of estimates (No.
693 Est) that the pooled estimate is based on are provided.

694 **Figure 4. T**obacco specific nitrosamines (TSNAs) levels and odds ratio for oral cancer in diverse
695 SLT products. (BQ+ denotes betel quid with tobacco) (a) TSNA values are presented on the log
696 scale; the original TSNAs levels in μg/g are presented on the right hand side y-axis. (b) OR and
697 corresponding 95% CIs estimates are based on review studies from the same region that the SLT
698 product TSNAs values are based. The OR estimates for zarda and khaini are not product specific but
699 those for all types of chewing tobacco from SEAR (ref 54). For gutkha, dry snuff and snus, the OR
700 estimates are based on global pooled estimates (ref 51), whereas for naswar these are based on EMR
701 estimates only (ref 57).
702

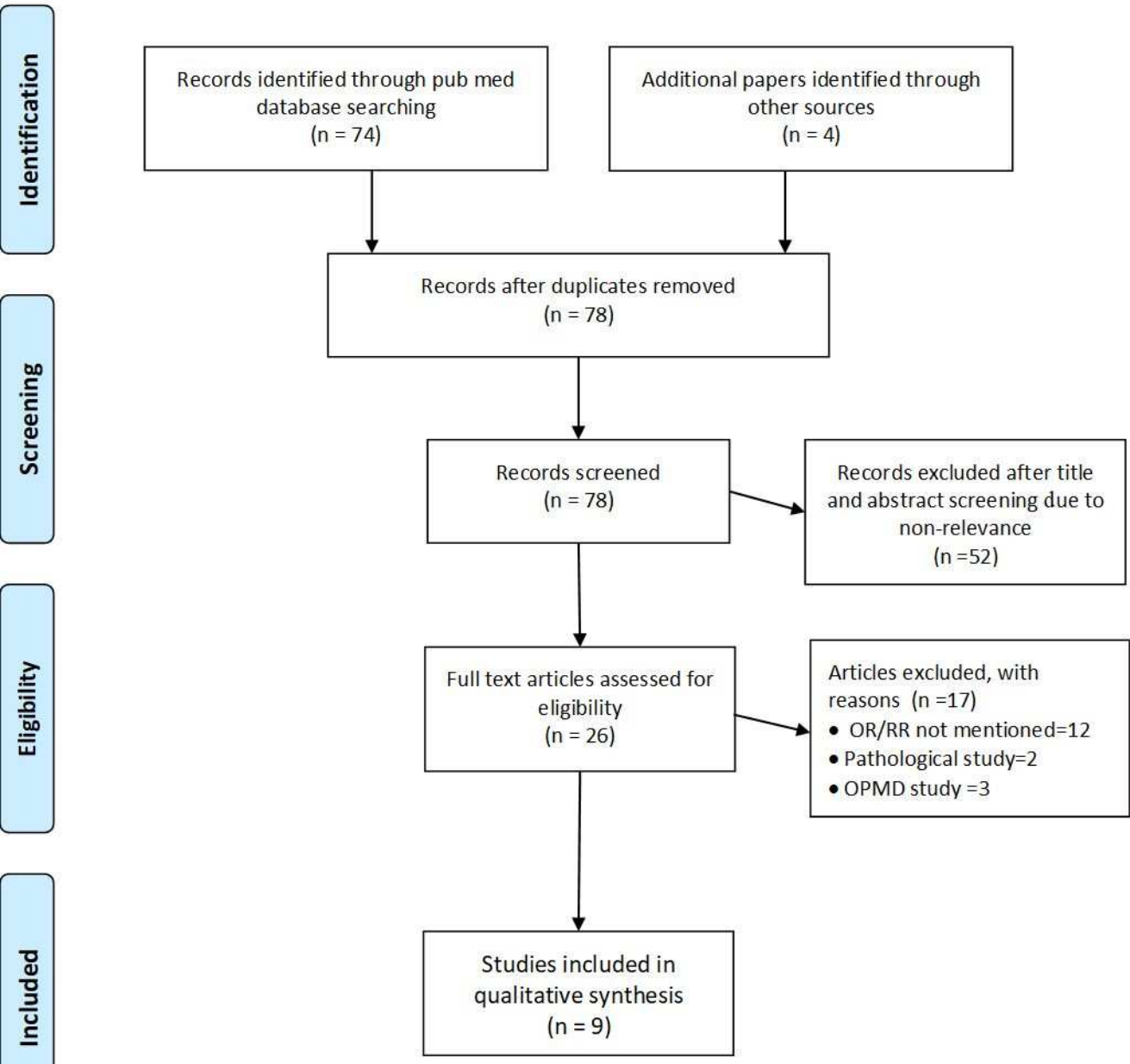
Identification
Screening
Eligibility
Included
Records identified through pub med database searching (n = 74)
Additional papers identified through other sources (n = 4)
Records after duplicates removed (n = 78)
Records screened (n = 78)
Records excluded after title and abstract screening due to non-relevance (n =52)
Full text articles assessed for eligibility (n = 26)
Articles excluded, with reasons (n =17)
• OR/RR not mentioned=12
• Pathological study=2
• OPMD study =3
Studies included in qualitative synthesis (n = 9)

Figure 1

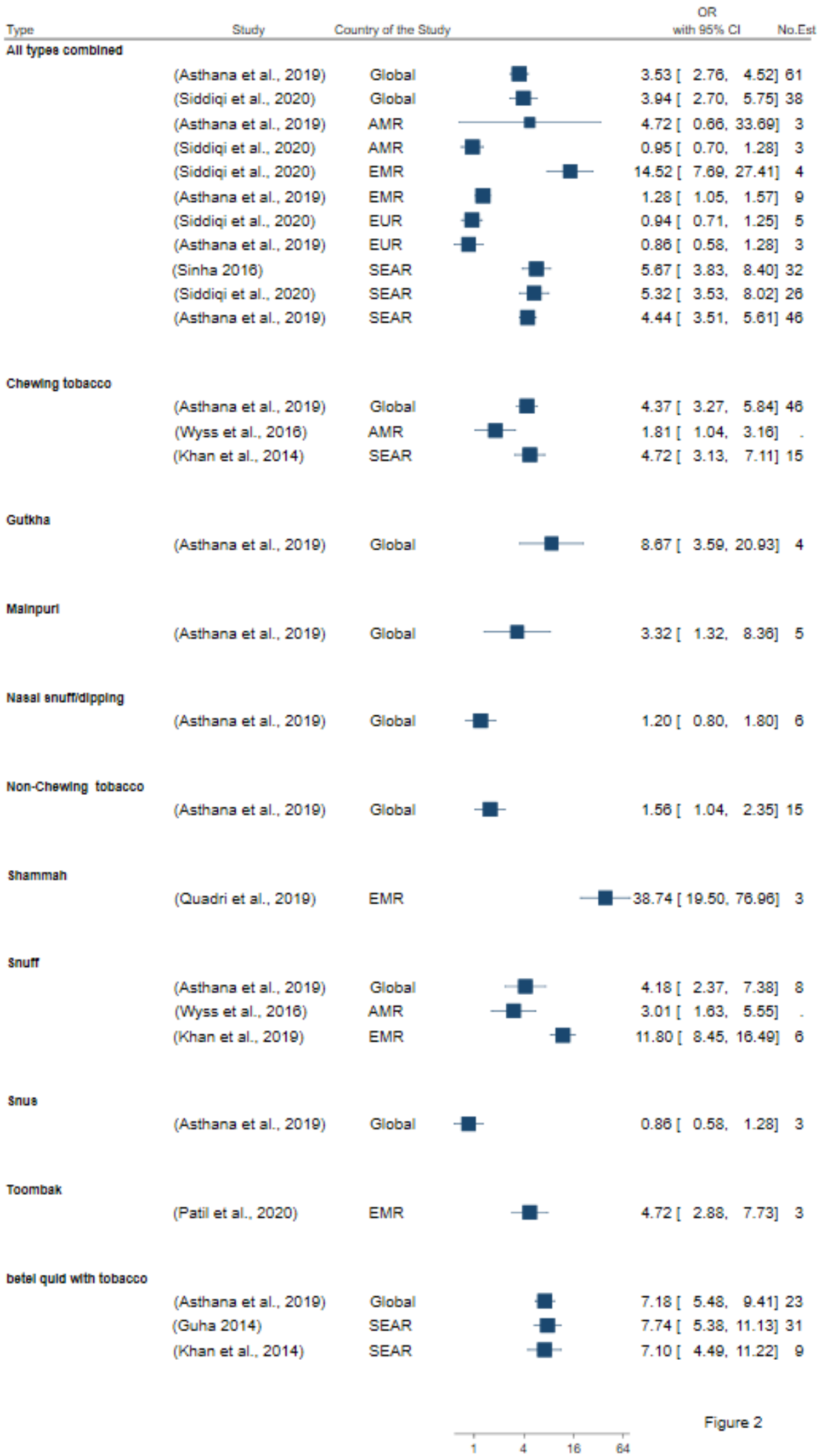
Type
Study
Country of the Study
OR with 95% CI
No.Est
All types combined
(Asthana et al., 2019) Global 3.53 [2.76, 4.52] 61
(Siddiqi et al., 2020) Global 3.94 [2.70, 5.75] 38
(Asthana et al., 2019) AMR 4.72 [0.66, 33.69] 3
(Siddiqi et al., 2020) AMR 0.95 [0.70, 1.28] 3
(Siddiqi et al., 2020) EMR 14.52 [7.69, 27.41] 4
(Asthana et al., 2019) EMR 1.28 [1.05, 1.57] 9
(Siddiqi et al., 2020) EUR 0.94 [0.71, 1.25] 5
(Asthana et al., 2019) EUR 0.86 [0.58, 1.28] 3
(Sinha 2016) SEAR 5.67 [3.83, 8.40] 32
(Siddiqi et al., 2020) SEAR 5.32 [3.53, 8.02] 26
(Asthana et al., 2019) SEAR 4.44 [3.51, 5.61] 46
Chewing tobacco
(Asthana et al., 2019) Global 4.37 [3.27, 5.84] 46
(Wyss et al., 2016) AMR 1.81 [1.04, 3.16] .
(Khan et al., 2014) SEAR 4.72 [3.13, 7.11] 15
Gutkha
(Asthana et al., 2019) Global 8.67 [3.59, 20.93] 4
Mainpuri
(Asthana et al., 2019) Global 3.32 [1.32, 8.36] 5
Nasal snuff/dipping
(Asthana et al., 2019) Global 1.20 [0.80, 1.80] 6
Non-Chewing tobacco
(Asthana et al., 2019) Global 1.56 [1.04, 2.35] 15
Shammah
(Quadri et al., 2019) EMR 38.74 [19.50, 76.96] 3
Snuff
(Asthana et al., 2019) Global 4.18 [2.37, 7.38] 8
(Wyss et al., 2016) AMR 3.01 [1.63, 5.55] .
(Khan et al., 2019) EMR 11.80 [8.45, 16.49] 6
Snus
(Asthana et al., 2019) Global 0.86 [0.58, 1.28] 3
Toombak
(Patil et al., 2020) EMR 4.72 [2.88, 7.73] 3
betel quid with tobacco
(Asthana et al., 2019) Global 7.18 [5.48, 9.41] 23
(Guha 2014) SEAR 7.74 [5.38, 11.13] 31
(Khan et al., 2014) SEAR 7.10 [4.49, 11.22] 9
1
4
16
64

Figure 2

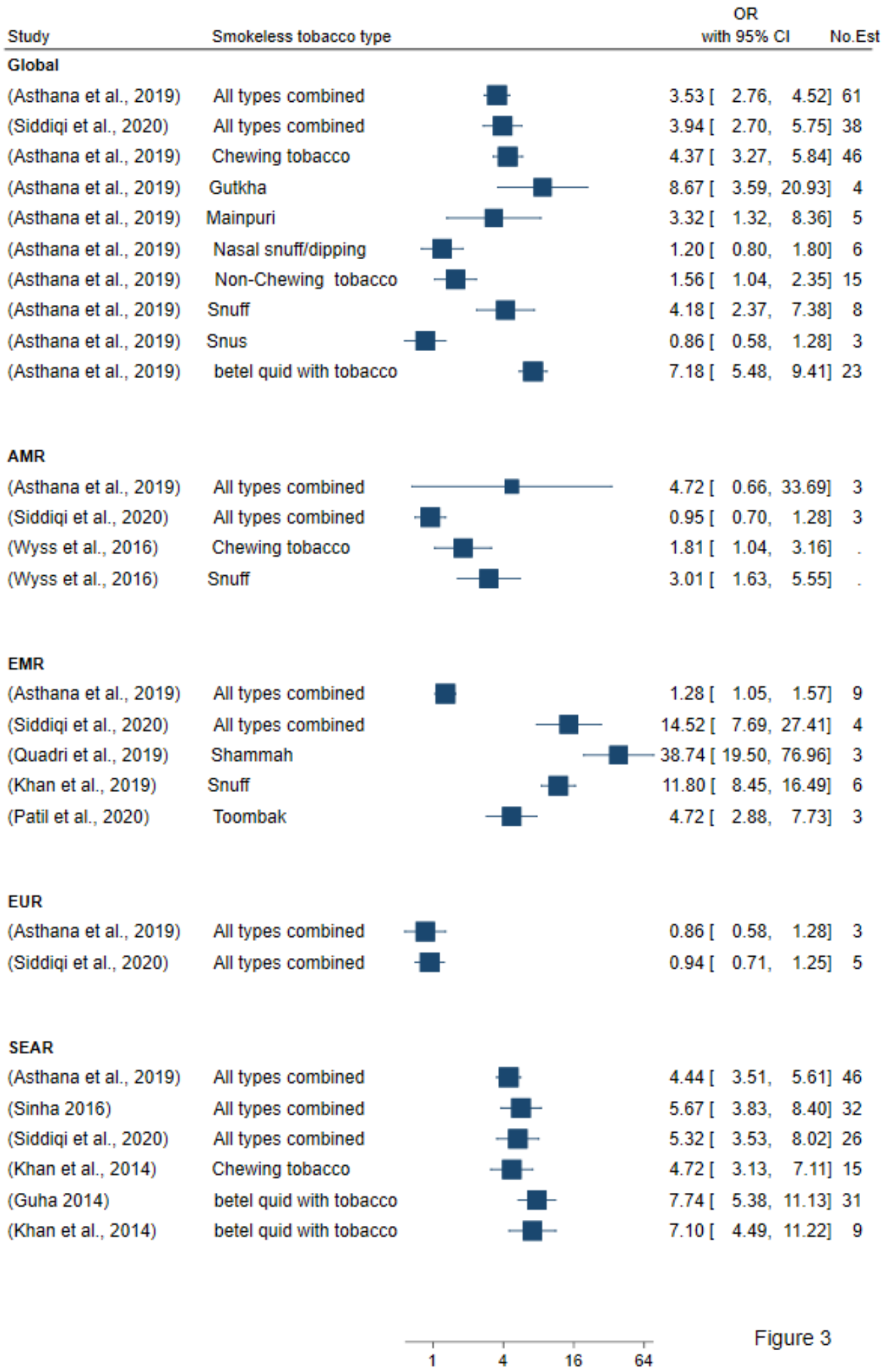
Study
Smokeless tobacco type
OR with 95% CI
No.Est
Global
(Asthana et al., 2019) All types combined 3.53 [2.76, 4.52] 61
(Siddiqi et al., 2020) All types combined 3.94 [2.70, 5.75] 38
(Asthana et al., 2019) Chewing tobacco 4.37 [3.27, 5.84] 46
(Asthana et al., 2019) Gutkha 8.67 [3.59, 20.93] 4
(Asthana et al., 2019) Mainpuri 3.32 [1.32, 8.36] 5
(Asthana et al., 2019) Nasal snuff/dipping 1.20 [0.80, 1.80] 6
(Asthana et al., 2019) Non-Chewing tobacco 1.56 [1.04, 2.35] 15
(Asthana et al., 2019) Snuff 4.18 [2.37, 7.38] 8
(Asthana et al., 2019) Snus 0.86 [0.58, 1.28] 3
(Asthana et al., 2019) betel quid with tobacco 7.18 [5.48, 9.41] 23
AMR
(Asthana et al., 2019) All types combined 4.72 [0.66, 33.69] 3
(Siddiqi et al., 2020) All types combined 0.95 [0.70, 1.28] 3
(Wyss et al., 2016) Chewing tobacco 1.81 [1.04, 3.16] .
(Wyss et al., 2016) Snuff 3.01 [1.63, 5.55] .
EMR
(Asthana et al., 2019) All types combined 1.28 [1.05, 1.57] 9
(Siddiqi et al., 2020) All types combined 14.52 [7.69, 27.41] 4
(Quadri et al., 2019) Shammah 38.74 [19.50, 76.96] 3
(Khan et al., 2019) Snuff 11.80 [8.45, 16.49] 6
(Patil et al., 2020) Toombak 4.72 [2.88, 7.73] 3
EUR
(Asthana et al., 2019) All types combined 0.86 [0.58, 1.28] 3
(Siddiqi et al., 2020) All types combined 0.94 [0.71, 1.25] 5
SEAR
(Asthana et al., 2019) All types combined 4.44 [3.51, 5.61] 46
(Sinha 2016) All types combined 5.67 [3.83, 8.40] 32
(Siddiqi et al., 2020) All types combined 5.32 [3.53, 8.02] 26
(Khan et al., 2014) Chewing tobacco 4.72 [3.13, 7.11] 15
(Guha 2014) betel quid with tobacco 7.74 [5.38, 11.13] 31
(Khan et al., 2014) betel quid with tobacco 7.10 [4.49, 11.22] 9
1
4
16
64

Figure 3

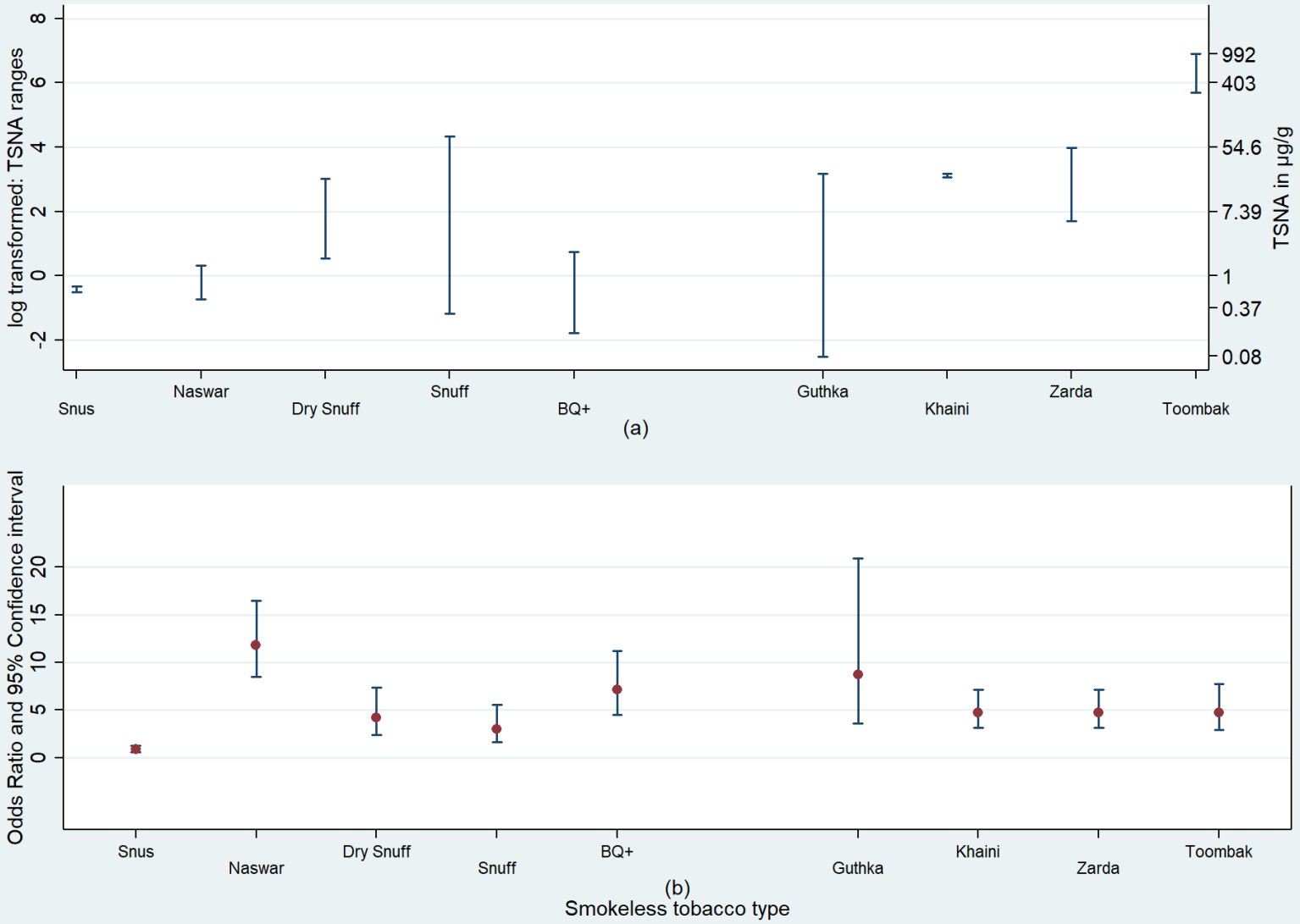
log transformed: TSNA ranges
8
6
4
2
0
-2
992
403
54.6
7.39
1
0.37
0.08
TSNA in µg/g
Snus
Naswar
Dry Snuff
Snuff
BQ+
Guthka
Khaini
Zarda
Toombak
(a)
Odds Ratio and 95% Confidence interval
20
15
10
5
0
Snus
Naswar
Dry Snuff
Snuff
BQ+
Guthka
Khaini
Zarda
Toombak
(b)
Smokeless tobacco type

Figure 4