Systematic Review

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A systematic review on association between smokeless tobacco & cardiovascular diseases

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***Background & objectives*: The association of smokeless tobacco (SLT) with cardiovascular diseases has remained controversial due to conflicting reports from various countries. Earlier meta-analyses have shown significantly higher risk of fatal myocardial infarction and stroke in SLT users. However, the risk of hypertension (HTN) with SLT products has not been reviewed earlier. This systematic review was undertaken to summarize the evidence available from global literature on the association of SLT with cardiovascular outcomes – heart disease, stroke and HTN.**

***Methods*: A systematic literature search was performed in PubMed and Google Scholar since their inception till October 2017 using pre-decided search terms and inclusion/exclusion criteria. Data were extracted from studies included independently by two authors and reviewed.**

***Results*: The review included 50 studies - 23 on heart disease, 14 on stroke and 14 on HTN. Majority of the studies evaluating heart disease or stroke were conducted in the European Region and most of these did not find a significant association between SLT use and either of these outcomes. On the other hand, 70 per cent of the studies on HTN were reported from South-East Asian Region and about half of the studies found a higher risk of HTN in SLT users.**

***Interpretation & conclusions*: Current available evidence is insufficient to conclusively support the association of cardiovascular diseases with SLT use due to variability in results and methodological constraints in most of the studies. Region and product-specific well-designed studies are required to provide this evidence to the policymakers. However, advice on cessation of SLT products should be offered to patients presenting with cardiovascular diseases.**

Key words Cardiovascular - hypertension - myocardial infarction - smokeless tobacco - stroke

Smokeless tobacco (SLT) is a large heterogeneous group of products used either orally or nasally without combustion[1]. Over the years, SLT has assumed global epidemic proportions with users in more than 100 countries[2]. The International Agency for Research on Cancer (IARC) has accepted the causative role of SLT products in oral cancer[3]. However, the linkage of SLT with cardiovascular diseases, *i.e.,* coronary heart disease (CHD)/myocardial infarction (MI)/heart failure, stroke and hypertension (HTN), has not been

accepted widely. This is due to the interregion variation in the results available in existing literature, which in turn has been attributed to the differing chemical composition, manufacturing practices and methods of use of products used in various regions[4]. Various studies have demonstrated deep-rooted community perceptions favouring the use of SLT despite evidence supporting the deleterious health effects of these products. A study from Bangladesh showed that SLT was considered to be a remedy for toothache though almost all participants accepted that these products caused heart disease, cancer and tuberculosis[5]. A recent study from Nigeria revealed that SLT users believed it to aid in sleep, protect against cold and act as a cure for headaches, apart from giving a 'feel of high'[6].

Earlier meta-analyses have demonstrated a higher risk of fatal CHD and stroke in SLT users, though significant positive association with non-fatal outcome was not demonstrated. These analyses have also highlighted the regional variation in these associations[4,7-9]. HTN has been included in a few studies for its association with SLT use[10,11]. However, the same has not been summarized as yet in the available literature.

Hence, the present systematic review was undertaken to summarize the available updated evidence on the association of SLT use with heart disease, stroke and HTN with a focus on the debate regarding the association between SLT and CHD.

Material & Methods

Literature search was undertaken independently by two experts (RG and SG) who reviewed all publications. In the event of disagreement, discussions were held to reach a consensus regarding the suitability of the publication. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were followed[12]. The inclusion criteria included as follows: (*i*) Articles published till October 2017 in English language or other languages with summary providing detailed results in English; (*ii*) Exposure variable: SLT. Studies including both smokers as well as SLT users were considered only if separate results for SLT users were provided; (*iii*) Outcome variable: cardiovascular disease, CHD or MI or heart failure or stroke or HTN or high blood pressure (BP); and (*iv*) Study design: case-control, cohort or cross-sectional studies with at least 150 total participants.

Case reports, case studies, letters or reviews were excluded. Studies reporting on cardiovascular risk factors only and not including outcome were also excluded from the study. PubMed and Google Scholar were used as the primary databases for literature search. An initial search yielded 792 articles. In addition, cross-references of all selected publications as well as earlier reviews on this topic were checked for more articles. The search strategy is outlined in Figure.

Results

A total of 50 studies were included in this review (23 with outcome of heart disease, 14 reports on stroke and 14 on HTN).

Smokeless tobacco and heart disease: Of the 23 studies reporting on the risk of heart disease in SLT users (Table I), 11 were conducted in European Region (EUR)[13-23], three each in American Region (AMR)[24-26] and Eastern Mediterranean Region (EMR)[27-29] and five were reported from South-East Asia Region (SEAR)[30-34]. One study, INTERHEART[35], was multicountry, though the majority of SLT users belonged to SEAR Region.

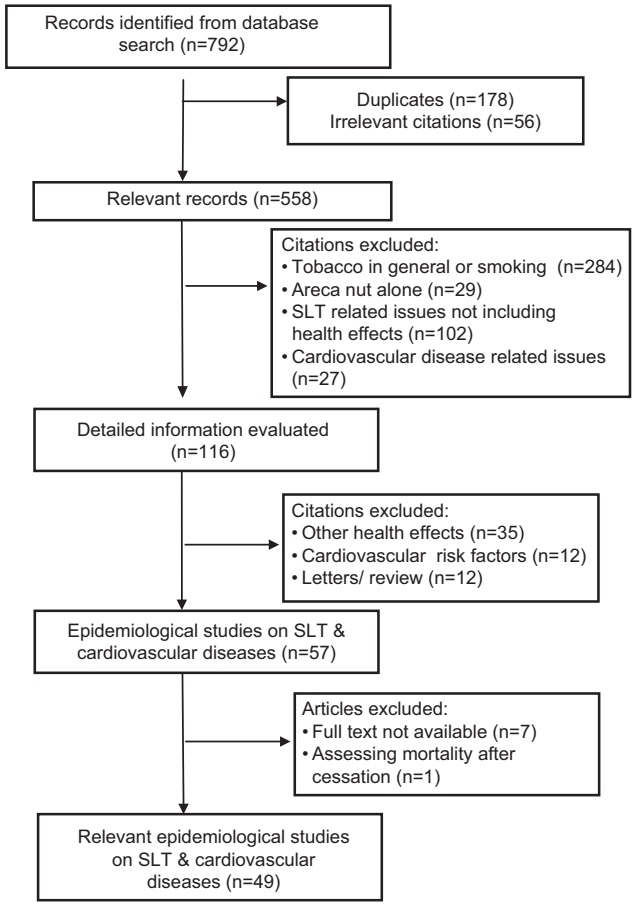

Figure. Search strategy for epidemiological studies on smokeless tobacco (SLT) and cardiovascular diseases included in systematic review.

Table I. Detailed characteristic of studies on smokeless tobacco (SLT) and heart disease included in the systematic review

Author/year	Study design	Sample size	Age of participants (yr)	Gender	Type of SLT	Outcome studied	ORs/RRs (95% CI)	Confounders adjusted
European Region								
Huhtasaari *et al*, 1992[13]	Case control	Cases 585 Controls 589	35-64	Men	Snuff	Fatal and non-fatal	0.89 (0.62-1.29)	Age
Bolinder *et al*, 1994[14]	Cohort	84,781	16-65	Men, never-smokers	SLT not specified	Fatal	2.0 (1.4-2.9) 35-54 yr 1.20 (1.0-1.5) 55-65 yr	Age, smoking, place of residence
Huhtasaari *et al*, 1999[15]	Case control	Cases 687 Controls 687	25-64	Men	Snuff	Fatal and non-fatal	1.50 (0.45-5.03)	Age, BP, diabetes, cholesterol, education
Hergens *et al*, 2005[16]	Case control	Cases 1432 Controls 1810	45-70	Men, never-smokers	Snuff	Fatal and non-fatal	Fatal 1.70 (0.48-5.5) Non-fatal 0.59 (0.25-1.4)	Age, smoking, residence
Johansson *et al*, 2007[17]	Cohort	3120	30-74	Men, never-smokers	Snuff	Fatal and non-fatal	1.41 (0.61-3.28)	Age, BMI, physical activity, diabetes, BP, smoking
Hergens *et al*, 2007[18]	Cohort	118,395	-	Men, never-smokers	Snuff	Fatal and non-fatal	Non-fatal 0.94 (0.83-1.06) Fatal 1.32 (1.08-1.61) Fatal with heavy use 1.96 (1.08-3.58)	Age, smoking, BMI, residence
Wennberg *et al*, 2007[19]	Case control	Cases 525 Controls 1798	30-60	Men, never-smokers	Snuff	Fatal and non-fatal	Non-fatal 0.82 (0.46-1.43) Fatal within 24 h 1.18 (0.38-3.70) Fatal within 28 days 1.12 (0.38-3.29)	Age, smoking, BMI, cholesterol, education, physical activity
Haglund *et al*, 2007[20]	Cohort	5002	16-74	Men	Snuff	Fatal and non-fatal	Fatal 1.15 (0.54-2.41) Non-fatal 0.77 (0.51-2.41)	Age, residence, self-reported health, number of long illness, physical activity
Hansson *et al*, 2009[21]	Cohort	16,642 twins	>40	Men, never-smokers	Snus	Fatal and non-fatal	0.85 (0.51-1.41)	Age, smoking, BP, diabetes, cholesterol
Janzon and Hedblad 2009[22]	Cohort	27,227	45-73	Men and women, never-smokers	Snuff	Fatal and non-fatal	0.75 (0.3-1.8)	Age, smoking, BMI, BP, diabetes, physical activity, occupation, marital status
Arefalk *et al*, 2012[23]	Cohort	119,491	>30	Men	Snus	Non-fatal	ULSAM 2.08 (1.03-4.22) CWC 1.28 (1.00-1.64)	Age, smoking, hypertension

Contd...

Author/year	Study design	Sample size	Age of participants (yr)	Gender	Type of SLT	Outcome studied	ORs/RRs (95% CI)	Confounders adjusted
American Region								
Accortt *et al*, 2002[24]	Cohort	12,451	25-74	Men and women, never-smokers	SLT not specified	Fatal	Men 0.60 (0.3-1.2) Women 1.40 (0.8-2.2)	Age, smoking, BMI, systolic BP, cholesterol, alcohol intake, gender, socioeconomic status
Henley *et al*, 2005[25]	Cohort	77,407 CPS I 113,970 CPS II	>30	Men, never-smokers	Chewing tobacco/ snuff	Fatal	CPS I cohort 1.12 (1.03-1.21) CPS II cohort 1.26 (1.08-1.47)	Age, smoking, BMI, alcohol intake, education, exercise, fruit and vegetable intake, aspirin use
Timberlake *et al*, 2017[26]	Cohort	348,282	>30	Men and women, never-smokers	SLT	Fatal	1.24 (1.05-1.46) current user	Age, gender, race, education, family income, smoking
Eastern Mediterranean Region								
Alexander 2013[27]	Case control	Cases 6051 Controls 6871	Adults	Men and women, never-smokers	Naswar/ chewing tobacco	Non-fatal	Naswar 1.46 (1.2-1.77) Chewing 1.71 (1.46-2.0)	Age, sex, recruitment centre, ethnicity, LDL cholesterol, waist-hip ratio, smoking, BP, diabetes
Islami *et al*, 2013[28]	Cross-sectional	50045	40-75	Men and women	Nass chewing	Non-fatal	0.85 (0.73-1.00)	Age, sex, ethnicity, residence, education, wealth, physical activity, BMI, hypertension, smoking, self-reported diabetes
Etemadi *et al*, 2017[29]	Cohort	50,045	40-75	Men and women	Nass chewing	Fatal	1.16 (0.87-1.55)	Age, SES, Residence, Education, Smoking
South East Asian Region								
Gupta *et al*, 2005[30]	Cohort	97,244	>35	Men and women, exclusive SLT users	Mishri and others	Fatal	Men 0.89 (0.75-1.05) Women 1.25 (1.05-1.49)	Age, smoking, education

Contd...

Author/year	Study design	Sample size	Age of participants (yr)	Gender	Type of SLT	Outcome studied	ORs/RRs (95% CI)	Confounders adjusted
Rahman and Zaman 2008[31]	Case control	Cases 69 Controls 138	20-49	Men and women	Dried tobacco leaves	Non-fatal	Males 1.60 (0.3-7.5) Females 4.50 (1.2-16.7)	Age, smoking, BP
Rahman *et al*, 2012[32]	Case control	Cases 302 Controls 1510	40-75	Men and women, never-smokers	Jarda, sada pata, gul	Non-fatal	0.80 (0.51-1.24)	Age, smoking, BP, diabetes, acute psychosocial stress
Ram and Trivedi 2012[33]	Case control	Cases 135 Controls 135	31-80	Not mentioned	SLT not specified	Non-fatal	1.77 (1.04-3.01)	Age
Gajalakshmi and Kanimozhi 2015[34]	Case control	Cases 22,000 Controls 429,000	35-69	Men and Women, Never smokers	Chewing tobacco	Fatal	Urban men 1.0 (0.9-1.2) Rural men 1.0 (0.9-1.2) Urban women 1.0 (0.9-1.1) Rural women 1.2 (1.1-1.4)	Age, smoking, gender, education, alcohol
Multicountry								
Teo *et al*, 2006[35]	Case control	Cases 12,461 Controls 14,637	44-75	Men and women (chewing tobacco alone)	Chewing	Non-fatal	2.23 (1.41-3.52)	Age, smoking, BP, diabetes, obesity, exercise, diet

BP, blood pressure; BMI, body mass index; SES, socioeconomic status; ULSAM, Uppsala Longitudinal Study of Adult Men; CWC, Construction Workers' Cohort; ORs, odds ratios; RRs, risk ratios; CPS, Cancer Prevention Study

Studies from European region (EUR): Seven of 11 studies from this Region were cohort while four were case control. Except for the study by Janzon and Hedblad[22], all other reports included only male SLT users in the adult age range. The predominant type of SLT consumed was snuff (eight studies) or snus (two studies), while the study by Bolinder *et al*[14] did not specify the SLT product used by study participants. The outcome evaluated in one study was fatal CHD[14] while in four others, separate results were given for fatal as well as non-fatal CHD[16,18-20]. In five studies, both fatal and non-fatal outcomes were included, though separate results were not given[13,15,17,21,22]. One study evaluated the risk of first hospitalization due to heart failure[23].

Of the 11 studies, two reported the significant positive association of fatal CHD with SLT use[14,18]. The other three studies reporting on fatal CHD did not find a similar association. The rest of the studies also did not report a significantly increased risk of CHD in SLT users. The study assessing the association of SLT and heart failure demonstrated a higher risk of failure in current snus users[23].

Smoking was adjusted in eight studies (including three with positive association). However, other confounding risk factors for CHD such as body mass index, BP, diabetes and cholesterol levels were adjusted in fewer studies.

Studies from South-East Asia Region (SEAR): Majority (four of five) of the studies were case-control design and included both males and females though gender-wise results were provided in only three studies[30,31,34]. SLT product included in these studies was predominantly chewable tobacco in the form of *mishri, jarda, sada pata, gul* and others. Three studies evaluated non-fatal outcome[31-33] while two included only fatal CHD[30,34]. Two studies showed an overall significant positive association between SLT use and non-fatal CHD[31,33]. Two studies[30,34] reported significantly increased risk of fatal CHD in female SLT users only. Smoking was adjusted in four out of five studies while other risk factors were adjusted in fewer studies.

Studies from American Region (AMR) and Eastern Mediterranean Region (EMR): All the three reports from AMR were cohort studies evaluating only fatal outcome. Two studies included both males and females[24,26] while the other had only male participants[25]. All the studies adjusted for smoking while two adjusted for body mass index (BMI). In contrast, one study from

EMR was cohort[29], one was case-control[27] and the third was cross-sectional[28]. All studies included males and females using *naswar*/*nass* or chewing tobacco. The outcome evaluated was fatal in one study[29] and non-fatal in other[27,28]. Smoking was adjusted in all studies; however, other factors such as BP, diabetes and cholesterol were adjusted in only one study[27].

Of the studies from AMR, two reported significantly higher risk of fatal CHD in SLT users[25,26] while the third study did not find an association between the two[24]. The results in studies from EMR were also variable (significant in one[27] and not in other two[28,29]).

The landmark INTERHEART case-control study[35] reported a significantly higher risk of non-fatal CHD in tobacco chewers [odds ratio (OR) 2.23, 95% confidence interval (CI) 1.41-3.52]. The study adjusted for factors such as smoking, BP, diabetes and obesity.

Smokeless tobacco (SLT) and stroke: Fourteen studies were retrieved on the topic of risk of stroke in SLT users. Seven were reported from EUR[14,20-22,36-38], three each from SEAR[30,34,39] and AMR[24-26] and one from EMR[29] (Table II). Majority (10) were cohort studies, one nested case-control and two case-control design. Six of seven EUR studies included only males while one included both genders. Only fatal stroke was reported in six studies while non-fatal outcome was reported in three. Four studies included both outcomes, though only two of these provided separate results for fatal stroke.

All the EUR studies failed to report a significant positive association between SLT use and stroke. One study from SEAR and one from AMR demonstrated a significantly higher risk of fatal stroke in SLT users[25,34]. Most of the studies (13 of 14) adjusted for smoking as a confounding factor or included never-smoking participants. Only five studies considered HTN as a confounding variable[14,21,22,24,39] while diabetes was adjusted in four studies[14,21,22,39].

Hypertension in smokeless tobacco users: In contrast to CHD and stroke, a majority of the included studies on the participant of risk of HTN in SLT users were reported from SEAR (eight from India[10,11,40-45] and two from Bangladesh[46,47]). Two studies were retrieved from EUR[48,49] and one each from AFR[50] and EMR[51]. Most of the studies were cross-sectional and all included adult participants (Table III). Ten of the 14 studies included only men while one had only female participants. In five studies, participants used chewing tobacco, three focused on snuff while the rest six studies did not specify the SLT product used.

Six of 14 studies demonstrated a significant positive association between SLT use and HTN. One study reported significant risk of diastolic HTN in SLT users but not for systolic HTN. Another study found a significant risk of diastolic HTN in SLT users of all age groups (16-65 yr) while systolic HTN was higher in the age range of 46-65 yr[49]. The remaining six studies did not find any significant association between HTN and SLT use. Only four studies adjusted smoking as confounding variable while three considered salt intake as a confounder.

Discussion

Although SLT has been causatively linked to adverse health effects including addiction, cancers of oral cavity, oesophagus and pancreas and poor reproductive outcomes, its association with cardiovascular diseases has not been accepted widely[52]. This has mainly been due to the conflicting reports on this topic from various Regions and countries[4,7-9]. Meta-analyses conducted so far on the participant of SLT use and cardiovascular risk have included CHD or MI and stroke[4,7-9]. None of these included the assessment of risk of HTN in SLT users. In the present review all the three cardiovascular outcomes were included in SLT users.

Smokeless tobacco use and heart disease: Heart disease was the most frequently studied cardiovascular outcome with maximum number of studies. Marked regional variation was identified in the results on the association of SLT use with heart disease. Majority of the studies from EUR did not report significantly increased risk of CHD in SLT users while studies from SEAR[30,31,34] showed positive association between the two. This regional difference has been attributed to the variation in chemical composition of the products used in these Regions[4].

Although European studies do not support the association of CHD with SLT, there have been reports of higher mortality rate due to CHD in individuals switching from cigarettes to spit tobacco [hazard ratio (HR) 1.13, 95% CI 1.00-1.29] in multivariate model adjusted for the duration and number of cigarettes smoked per day before switching apart from other confounding factors[53]. In this context, reduction of post-MI mortality risk in snus quitters as opposed to continuing snus users (HR 0.57, 95% CI 0.32-1.02) has also been demonstrated[54]. Such reports support the hypothesis of deleterious effects of SLT products on

Table II. Studies evaluating smokeless tobacco (SLT) and stroke included in the review

Author/year	Type of study	Sample size	Age range	Gender	Type of SLT	Outcome studied	OR/RR (95% CI)	Confounders adjusted
European Region								
Bolinder *et al*, 1994[14]	Cohort	135036	>35 yr	Men	ND	Fatal	35-54 yr 1.9 (0.6-5.7) 55-65 yr 1.2 (0.7-1.8)	Smoking, age, area of domicile, BP, previous cardiac symptoms, DM, BMI
Asplund *et al*, 2003[36]	Nested case control	Cases 276 Controls 551	25-74	Men	Snuff	Both	0.87 (0.41-1.83)	Smoking, BP, education, marital status, DM, cholesterol
Haglund *et al*, 2007[20]	Cohort	5002	16-74	Men	Snuff	Both	IR 1.07 (0.65-1.77) MR 1.01 (0.35-2.92)	Age, SES, residence, self-reported health, longstanding illnesses, physical activity
Hergens *et al*, 2008[37]	Cohort	118465	ND	Men	Snuff	Both	Non-fatal 1.02 (0.91-1.14) Fatal 1.38 (0.99-1.91)	Age, smoking, BMI, residence
Janzon and Hedblad 2009[22]	Cohort	27227	45-73	Men and women	Snuff	Both	0.59 (0.2-1.5)	Age, BMI, smoking, DM, HTN, activity, marital status, occupation
Hansson *et al*, 2009[21]	Cohort	16642	>40 yr	Men	Snus	Both	1.18 (0.67-2.08)	Age, DM, BP, cholesterol, smoking
Hansson *et al*, 2014[38]	Pooled cohort	130485	Mean age 68	Men, never-smokers	Snus	Both	1.04 (0.92-1.17) Overall 1.32 (1.08-1.61) Fatal	Age, BMI, smoking
American Region								
Accortt *et al*, 2002[24]	Cohort	6805	45-75	Men and women	ND	Fatal	Men 0.7 (0.2-2) Women 1 (0.3-2.9)	Age, race, poverty index, alcohol, exercise, fruit/vegetable intake, systolic BP, smoking
Henley *et al*, 2005[25]	Cohort	CPS I 7745 CPS II 3327	>30 yr	Men	Both	Fatal	CPS I 1.46 (1.3-1.64) CPS II 1.4 (1.1-1.79)	Age, race, education, BMI, exercise, alcohol, fruit, aspirin use, employment status, fat consumption
Timberlake *et al*, 2017[26]	Cohort	349282	>30 yr	Men and women, never-smokers	SLT	Fatal	0.92 (0.67-0.27)	Age, gender, race, education, family income, smoking
South East Asian Region								
Gupta *et al*, 2005[30]	Cohort	97,244	>35 yr	Men and women	Chewing	Fatal	Men 1.32 (0.94-1.84) Women 1.15 (0.84-1.59)	Age, education, smoking
Agashe and Gawde 2010[39]	Case control	Cases 80 Controls 80	Mean 61.8 yr	Men	Chewing	Non-fatal	1.5 (0.8-2.79)	HTN, alcohol, DM, smoking
Gajalakshmi and Kanimozhi 2015[34]	Case control	Cases 22000 Controls 429000	35-69 yr	Men and women	Chewing	Fatal	Urban men 1.1 (0.7-1.7) Rural men 2.2 (1.6-3.0) Urban women 1.3 (1.1-1.7) Rural women 1.3 (1.0-1.6)	Age, education, smoking, alcohol
Eastern Mediterranean Region								
Etemadi *et al*, 2016[29]	Cohort	1393	40-75	Men and women	Nass	Fatal	0.98 (0.65-1.47)	Age, SES, residence, education, smoking

BP, blood pressure; DM, diabetes mellitus; BMI, body mass index; HTN, hypertension; IR, incidence ratio; MR, mortality ratio

Table III. Study characteristics of included reports on risk of hypertension in smokeless tobacco (SLT) users

Author/year	Study design	Sample size	Age (yr)	Gender	SLT type	OR/RR (95% CI)	Confounder adjusted
European Region							
Bolinder *et al*, 1992[49]	Cross-sectional	97586	16-65	Men	SLT	Diastolic BP 16-35 yr 1.3 (1.0-1.7) 36-45 yr 1.3 (1.0-1.6) 46-55 yr 1.8 (1.5-2.1) 56-65 yr 1.3 (1.1-1.4) Systolic BP 16-35 yr 1.0 (0.5-1.7) 36-45 yr 1.3 (0.8-2.1) 46-55 yr 1.7 (1.3-2.1) 56-65 yr 1.2 (1.1-1.4)	Not mentioned
Hergens *et al*, 2008[48]	Cohort	120930	Adults	Men	Snuff	1.25 (1.16-1.35)	Age, BMI, residence, smoking
South East Asian Region							
Hazarika *et al*, 2004[40]	Pop based	3180	>30	Men and women	Chewing	1.1 (0.94-1.3)	Not mentioned
Gupta *et al*, 2007[41]	Case control	200 cases, 200 controls	46.8 mean	Men and women	Chewing	Systolic 1.76 (1.14-2.7) Diastolic 2.59 (1.72-3.92)	Not mentioned
Pandey *et al*, 2009[43]	Cross sectional	443	35.4 mean	Men	SLT	Systolic 1.4 (0.8-2.7) Diastolic 2.7 (1.4-4.9)	Not mentioned
Kannan & Satyamoorthy 2009[42]	Cross sectional	750	>30	Men and women	Chewing	1.5 (0.99-2.27)	Not mentioned
Bhadoria *et al*, 2014[10]	Cross sectional	939	>20	Men and women	Chewing	Urban 6.8 (2.8-16.2) Rural 2.1 (1.16-3.53)	Age, family history, salt, smoking, physical, BMI
Sen *et al*, 2015[11]	Survey	916	20-60	Men	SLT	0.48 (0.26-0.89)	Age, SBP, BMI, Family history
Islam *et al*, 2015[46]	Cross sectional	730	>25	Men and women	SLT	3.61 (2.33-4.14)	Age, sex, education, marital, employment, income, extra salt, activity, family history, smoking
Khanam *et al*, 2015[47]	Cross sectional	6094	>25	Men and women	Chewing	0.89 (0.74-1.07)	Age, sex, education, BMI, smoking, physical
Ismail *et al*, 2016[44]	Community based	600	39.8 mean	Men and women	SLT	2.12 (1.4-3.2)	Not mentioned
Choudhury & Ojah 2017[45]	Cross sectional	870	>30	Men and women	SLT	1.13 (0.77-1.65)	Not mentioned
African Region							
Ayo-Yusuf & Omole 2008[50]	Cross sectional	4092	49.2 mean	Women	Snuff	Up to eight times 1.01 (0.75-1.96) >8 times 2.07 (0.89-4.82)	Age, smoking, body weight, salt intake, diabetes, family history
Eastern Mediterranean Region							
Shah *et al*, 2001[51]	Cross sectional	4203	>18	Men and women	Snuff	1.59 (1.31-1.92)	Not mentioned

SBP, systolic blood pressure

cardiac functions independently of concurrent or past smoking status. A recently published meta-analysis on the association of SLT use with CHD from our group[9] showed significantly higher risk of fatal CHD in SLT users (1.10, 95% CI 0.00-1.27). Regional variation was also reported in this analysis with higher risk for European users compared to other Regions[9].

The effect of SLT over cardiovascular risk factors has also been evaluated. *Gutka* chewers were found to have a significant higher resting heart rate and lower delta heart rate (the difference between maximal heart rate and resting rate) immediately after chewing *gutka*[55]. Delta heart rate has been reported to be a risk factor for cardiovascular mortality independent of age, smoking, systolic BP, serum cholesterol and triglyceride level and physical fitness[56]. Others have reported greater prevalence of risk factors such as obesity, tachycardia at rest, HTN, high total and low-density lipoprotein (LDL) cholesterol and changes on electrocardiogram in SLT users[41]. A study from Turkey has found impairment in left atrial mechanical function and prolongation of atrial electromechanical coupling intervals in users of maras powder and suggested these changes to be markers of tendency for atrial fibrillation[57]. Altered lipid profile with lower serum high-density lipoprotein cholesterol and significantly increased total cholesterol, LDL cholesterol and triglycerides have been demonstrated with SLT products such as *naswar* and chewing tobacco[58,59]. However, these results and their implications for cardiovascular disease need to be confirmed in further studies.

Smokeless tobacco use and cerebrovascular disease: Cerebrovascular disease, especially stroke, is a global health problem and a leading cause of disability and death. Smoking has been incriminated as a major risk factor in causation of stroke[60,61]. However, the association with SLT is similar to that for CHD with conflicting results in studies from various Regions and within a particular Region as well. Majority of the European studies did not report any significant positive association between SLT and stroke, though Hergens *et al*[37] found a significant risk of fatal ischaemic stroke in SLT users, but the same was not detected for haemorrhagic stroke. This difference in risk according to subtype of stroke could well be explained on the basis of differing aetiologic mechanisms of haemorrhagic and ischaemic stroke[62].

An earlier meta-analysis demonstrated that 12.8 per cent higher risk of stroke in current users of SLT especially for studies from the United States but not for Swedish users. The risk of fatal stroke was also found to be higher in SLT users in this analysis[7]. Vidyasagaran *et al*[4] found no overall association of SLT use and non-fatal stroke while risk of fatal events was 13.9 per cent higher in SLT users. Similar results were reported in another meta-analysis of cause-specific mortality in SLT users[8]. One study evaluated the risk of subarachnoid haemorrhage (SAH) in smokers and snuff users. The authors found 2.5 times higher risk of SAH in smokers; however, consumption of snuff did not impart a similar risk ratio (relative risk 0.48, 95% CI 0.17-1.30)[63].

In addition to the studies included in this review, two other reports that evaluated risk of cardiovascular disease (including both MI and stroke) in SLT users were found[50,64]. These did not provide separate results for the outcomes and hence, were not included in the present review. One of these studies found an excess risk of cardiovascular disease-related disability pension in the age group of 56-65 yr (OR 1.5, 95% CI 1.1-1.9)[50]. The other study reported a 1.27-fold greater incidence of cardiovascular diseases in current SLT users (95% CI 1.06-1.52) compared to nonusers, and this risk was independent of demographic, socio-economic and other tobacco-related variables[64]. Hence, there appears to be a significant positive association between SLT use and fatal stroke.

Hypertension and smokeless tobacco use: HTN, an important risk factor for death and morbidity globally, is one of the major causes of ischaemic heart disease, stroke and heart failure[65-67]. For developing countries like India, rule of halves[68], *i.e.*, half of the hypertensives are undetected, half of those detected are untreated and half of treated are not well controlled is still valid and poses a significant challenge for control of HTN and incident cardiovascular diseases[68,69].

Cigarette smoking has been shown to cause an acute elevation of BP and heart rate due to effect of nicotine on sympathetic nervous system[70]. However, chronic effect of smoking on BP has not been effectively established due to conflicting reports. Thuy *et al*[71] reported a dose-response relationship between smoking and HTN while others have found a lower BP in smokers compared to non-smokers[72]. The causal association of SLT with HTN is also similarly debated with approximately half of the studies reporting a significant positive association between the two parameters and the rest not corroborating

the same. Some authors have demonstrated an acute increase in heart rate and BP along with elevation of plasma epinephrine after administration of SLT products[73]. Studies reporting a positive association of SLT use with HTN postulate that frequent use of these products leads to continuous moderate levels of nicotine in blood causing sympathetic nervous system activation and rise in BP[48]. Additives such as sodium and licorice used in some SLT products are also thought to have hypertensive effects[74]. A study from SEAR compared BP between smokers and SLT users and found a significantly higher mean diastolic BP in SLT users compared to smokers[75]. However, this study was limited by the small sample size. A study of ambulatory 24 h BP monitoring in healthy SLT users demonstrated a significantly higher mean systolic BP during daytime as well as in 24 h recordings[76]. In participants ≥45 yr old, all daytime diastolic and most of systolic BP recordings were significantly elevated in SLT users. BP in SLT users was found to have a strong positive association with serum cotinine values (r=0.48, $P<0.001$), indicating predominant effect of nicotine on these circulatory parameters[76].

Strengths and limitations: The main strengths of this review were the global perspective, comprehensive nature of cardiovascular diseases considered and thoroughness of the literature search on this topic. An earlier policy statement from the American Heart Association summarized the potential cardiovascular effects of SLT use, including all three diseases, but included only Swedish and American studies[74]. Other reviews and meta-analyses have evaluated MI and/ or stroke only[4,7-9]. This review provides an updated global evidence on all three major cardiovascular outcomes – heart disease, stroke and HTN.

The major limitation of this review was the lack of adequate confounder adjustment in many studies. Although smoking was adjusted as a confounder or study participants included only never-smokers in majority of the reports, other disease-specific risk factors were not adjusted universally in all studies. For instance, risk factors such as HTN, BMI, serum cholesterol levels and physical activity were considered in only a few studies evaluating CHD or MI. Similarly, most of the studies on the risk of HTN in SLT users did not adjust for excess salt intake, obesity, level of physical activity, alcohol intake and stress. In particular, studies from SEAR were found to be poor in confounder adjustment. There is also paucity of studies from African and Western Pacific Regions in the current literature in spite of high prevalence of SLT use in some areas of these Regions. Since the present review was not aimed for a quantitative analysis of risk estimate, it was not possible to comment conclusively on the risk association of cardiovascular diseases with SLT use. However, the available literature does indicate a significantly higher risk of fatal cardiac and cerebrovascular events in SLT users.

Conclusion & way forward

To elucidate a clear view of the cardiovascular risk associated with SLT use, future well-designed studies, preferably multicountry with uniformity in case definition, study methods and relevant confounder adjustments, are imperative. Since regional variability in cardiovascular effects has been demonstrated due to differences in product composition, studies from all regions are required for definitive opinion on the participant. Clarity on the issue of association of cardiovascular disease with SLT would assist the policymakers to include mandatory SLT cessation advice for patients presenting with one of these diseases or their risk factors.

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