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Full Length Research Paper

A systematic review of epidemiological studies on the association between smokeless tobacco use and coronary heart disease

Muhammad Aziz Rahman[1]*, Mohammad Afzal Mahmood[1], Nicola Spurrier[1], Mahmudur Rahman[2] and Stephen Leeder[3]

[1]Discipline of Public Health, University of Adelaide, Adelaide, Australia.
[2]Institute of Epidemiology, Disease Control and Research (IEDCR), Dhaka, Bangladesh.
[3]The Menzies Centre for Health Policy, University of Sydney, Sydney, Australia.

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A systematic review was conducted of epidemiological studies focusing on the association between smokeless tobacco (SLT) use and coronary heart disease (CHD) in order to summarize the evidence and to identify scope for further study in South Asian countries. PubMed and ISI Web of Science databases were searched to find epidemiological studies (cohort, case-control and cross-sectional) published until 27 October, 2011. The search revealed 592 relevant references, from which 18 epidemiological studies were selected. Among the 18 studies, 11 studies were conducted in Sweden, 4 in the USA, 1 in India, 1 in Bangladesh, and 1 study was multi-centric involving 52 countries. Twelve studies included only men and six studies included both sexes. Three studies used South Asian SLT products. Nine studies found no statistically significant positive association between SLT use and CHD, while nine studies did find a positive association. Results of these studies differed according to age, gender, and SLT constituents. Currently published research does not provide conclusive evidence regarding the association between SLT use and CHD. SLT products and usage pattern in South Asia differ from those in Western settings, and cannot be extrapolated immediately to South Asian settings.

Key words: Smokeless tobacco, chewing tobacco, oral tobacco, coronary heart disease, cardiovascular diseases.

INTRODUCTION

Smokeless tobacco (SLT) includes “a large variety of commercially or non-commercially available products and mixtures that contain tobacco as the principal constituent and are used either orally or nasally without combustion” (International Agency for Research on Cancer, 2007). The oral forms of SLT are chewed or kept between cheek and gum, whereas nasal forms are inhaled. SLT products are used alone or as ingredients in other products, some in the raw form and others as commercial products. SLT, the use of which has spread to many countries in recent years, has been used by the South American and South Asian people for thousands of years (US National Cancer Institute, 2002). SLT is commonly used in many countries of Europe, America, Africa, and in Asian countries such as India, Pakistan and Bangladesh (International Agency for Research on Cancer, 2007). The use of SLT varies by age, sex, ethnicity and socioeconomic status, both within and among countries (Boffetta et al., 2008).

Coronary heart disease (CHD), which accounted for more than seven million deaths in 2004, is the leading cause of mortality worldwide (World Health Organization, 2008). Among the risk factors of CHD, tobacco use is the second most important following hypertension (World Health Organization, 2009). According to the World

*Corresponding author. E-mail: aziz.rahman@adelaide.edu.au. Tel: +61 423640496.

Abbreviations: CHD, coronary heart disease; **CVD,** cardiovascular diseases; **SLT,** smokeless tobacco.

Health Organization (WHO), tobacco is the most important preventable cause of death (World Health Organization, 2008). It is projected that the number of tobacco-attributable deaths will increase from 5.4 million in 2004 to 8.3 million in 2030 (World Health Organization, 2008). Of these 5.4 million deaths, 0.9 million deaths were due to CHD caused by tobacco use in 2004 (World Health Organization, 2008).

The association between smoking and CHD is well established, but the association between SLT use and CHD is in dispute (Piano et al., 2010; Lee, 2011). Most reviews of the epidemiological studies on SLT use and CHD have included Swedish studies only (Asplund, 2003; Critchley et al., 2003; Critchley et al., 2004; Gupta et al., 2004), or both Swedish and US studies (Lee, 2007; Boffetta et al., 2009). Meta-analysis of these Western studies (Lee, 2007; Boffetta and Straif, 2009) did not find a significant positive association between current SLT use and CHD. The result was similar when Swedish and US studies were analyzed separately, although there was a significant positive association when only fatal CHD was considered (RR 1.17, 95% CI 1.09 to 1.25) (Boffetta and Straif, 2009). On the other hand, a review published in 2010 (Zhang et al., 2010), which included eight Asian studies but excluded Western studies, found a significant association between use of chewed products and CHD (RR 1.27, 95CI 1.02 to 1.52); chewed products included betel chewing with or without tobacco. However, when analyses were confined to three South Asian studies, the association was not significant statistically (RR 1.64, 95% CI 0.60 to 2.68) (Zhang et al., 2010).

In South Asian countries, betel-quid chewing is one of the long standing cultural traditions of the people. Betel-quid includes betel leaf, areca nut and slaked lime; SLT products are commonly used as an ingredient with betel-quid chewing (Gupta et al., 2003, 2004). Over 250 million people, constituting 17% of the total population of the WHO South-East Asia region, use SLT products (International Agency for Research on Cancer, 2007). In south Asian countries, while smoking by women is not supported by traditional values, SLT use does not have any such stigma (Gupta and Ray, 2003). Therefore, prevalence of SLT use is high among women in this region (Centers for Disease Control and Prevention) unlike the Western settings. On the other hand, prevalence of CHD is the highest among South Asian people compared to other parts of the world, not only due to behavioural factors but also for the genetic predisposition (Nishtar, 2002). Although studies from Taiwan (Guh et al., 2007; Lin et al., 2008; Yen et al., 2008) reported a significant positive association between betel-quid chewing and CHD, studies exploring the association between SLT use and CHD within South Asian context are very limited. We only considered CHD for our review, as CHD is the most important preventable cardiovascular diseases (CVD) (Nishtar, 2002). Furthermore, South Asian people have an early onset of CHD and die prematurely due to CHD compared to other Caucasians (Silbiger et al., 2011).

Our aim was to review the existing epidemiological studies regarding the association between SLT use and CHD in order to summarise the currently available evidence, consider strengths and limitations of previous studies and through this process explore the rational for conducting further studies, particularly in South Asia.

METHODS

Muhammad Aziz Rahman, Nicola Spurrier and Mohammad Afzal Mahmood discussed and agreed on the search terms required and the approach to the literature search. Muhammad Aziz Rahman undertook the literature search and reviewed all publications systematically using set criteria. Muhammad Aziz Rahman reviewed the search results three times before confirming the results. We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Moher et al., 2009). We searched the literature in the manner recommended by The Cochrane Collaboration (Higgins and Green, 2011) and Bown et al. (2010). We selected SLT use as the main exposure variable and CHD as the main outcome variable for this review. Our focus was to identify the studies reporting CHD as the outcome, not the risk factors for CHD (blood pressure, body mass index, and lipid profile). PubMed and ISI Web of Science were selected as the primary databases for this review, as others have done (Lee, 2007; Boffetta and Straif, 2009; Zhang et al., 2010). Inclusion criteria were English language and data published until 27 October, 2011. Searching PubMed for literature on SLT only, 4500 references were obtained. Searching PubMed on CHD only, 1295852 references were obtained. Combining SLT and CHD, 231 references were obtained.

The search terms used to obtain references for SLT and CHD were: “Tobacco, smokeless [mh], Smokeless tobacco*[tiab], chewing tobacco*[tiab], Chewable tobacco*[tiab], Oral tobacco*[tiab], tobacco chewing*[tiab], Tobacco chewer*[tiab], Spit tobacco*[tiab], Snuff*[tiab], Snus*[tiab], Betel quid*[tiab], Betel chewing*[tiab], Betel nut*[tiab], or Betel leaf*[tiab] and Ischemic heart disease*[tiab], Ischaemic heart disease*[tiab], cardiovascular diseases*[mh], cardiovascular disease*[tiab], Cardiovascular risk*[tiab], Myocardial ischemia*[tiab], or Myocardial ischaemia*[tiab], or Acute Coronary Syndrome*[tiab], Angina Pectoris*[tiab], Unstable angina*[tiab], Microvascular Angina*[tiab], Coronary Disease*[tiab], Coronary heart disease*[tiab], Coronary Aneurysm*[tiab], Coronary Artery Disease*[tiab], Coronary Occlusion*[tiab], Coronary Stenosis*[tiab], Coronary Thrombos*[tiab], Coronary Vasospasm*[tiab], Myocardial Infarct*[tiab], Myocardial Stunning*[tiab], cardiogenic shock*[tiab], Myocardial Reperfusion Injur*[tiab] or Heart disease*[tiab]”.

The same search strategy and terms were then used for ISI Web of Knowledge. The initial search yielded 6869 references on SLT and 523337 references on CHD. When search terms were combined for SLT and CHD, 334 references were obtained.

Figures 1 and 2 summarises the search strategy used and the number of articles obtained at each step. Among the 565 references retrieved from both PubMed and ISI Web of Science, 105 duplicates were excluded. Titles and abstracts were reviewed, and references which did not clearly relate to tobacco and/or heart disease were excluded (n=118), resulting in 342 references.

Then, searches were extended to EMBASE and The Cochrane Library, which are considered the richest databases along with PubMed (The Cochrane Collaboration, 2006; Bown and Sutton, 2010). Additional searches were conducted using Scopus, Google Scholar and WHO publications. To ensure all studies from Asian countries were included, further search was conducted using the following terms: Asia*[mh], India*[tiab], Pakistan*[tiab], Bangladesh*[tiab], or South Asia*[tiab]. In addition, local databases

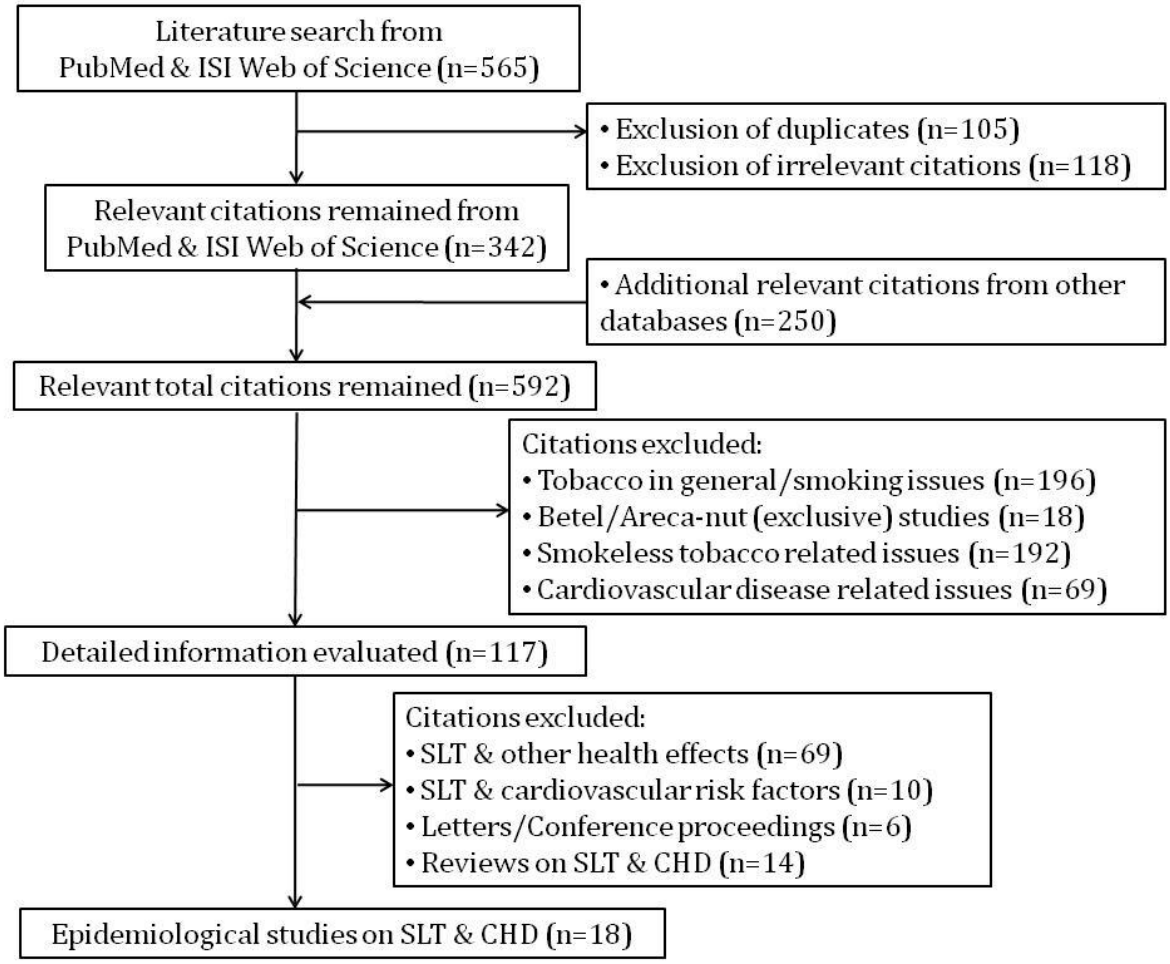

Figure 1. Search strategy for selection of epidemiological studies exploring the association between coronary heart disease and smokeless tobacco use.

of Bangladesh, India and Pakistan were also reviewed. These included the WHO Bangladesh publications, Bangladesh Journals Online, ICDDRB publications, Indian Journal of Public Health, Journal of the Associations of Physicians of India (JAPI) and PakMediNet. Finally, the reference lists of all SLT-related articles were hand searched. All of these additional searches identified 250 more references. A total of 592 relevant references were obtained.

References concerned with tobacco-related issues in general or different smoking-related issues such as harmful effects of smoking, smoking cessation interventions and nicotine replacement therapies were excluded (n=196). Although 'betel-quid', 'betel-nut' or 'areca-nut' chewing does not contain tobacco (Wen et al., 2005; Guh et al., 2007; Lan et al., 2007; Lin et al., 2008; Yen et al., 2008), we included them initially as SLT products in the search terms to allow the widest coverage of the available literature. When it was clear that the study did not include other SLT products, the study was excluded from the review (n=18). Then, SLT-related issues in general such as prevalence estimation, molecular/genetic change analyses, constituent analyses, impact of SLT use on smoking, comparing health effects of smoking and SLT use, SLT cessation strategies, perception analyses, harm reduction potential and policy were also excluded (n=192). In addition, cardiovascular disease-related issues such as prevalence estimation, risk factor analysis and prevention strategies were also excluded (n=69).

The remaining references (n=117) were reviewed and references relating to SLT and health effects other than CHD (n=69), SLT and risk factors for cardiovascular diseases (CVD) such as hypertension, body mass index, and lipid profile (n=10), letters and conference proceedings related to SLT and CHD (n=6), and reviews on SLT and CHD (n=14) were excluded. Eighteen studies remained, which explored the association between SLT use and CHD. For our reviews, we searched the results specific for CHD, but if any study reported only CVD in general we also included that result. For the association between SLT use and CHD, we tried to find out the association among never-smoker population in that study.

RESULTS

Characteristics of the included studies

Among the 18 studies, 10 were cohort studies (Bolinder et al., 1994; Accortt et al., 2002; Gupta et al., 2005; Henley et al., 2005; Johansson et al., 2005; Haglund et al., 2007; Hergens et al., 2007; Hansson et al., 2009;

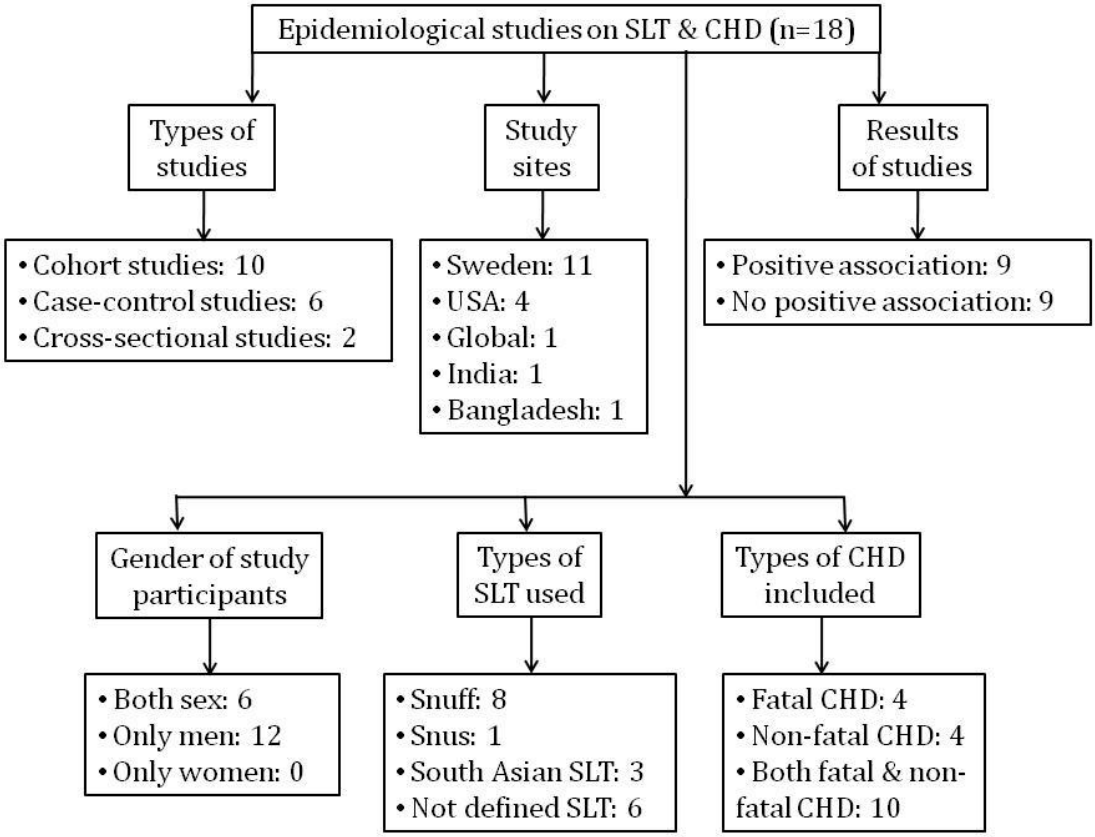

Figure 2. Characteristics of the selected epidemiological studies exploring the association between coronary heart disease and smokeless tobacco use.

Janzon et al., 2009; Yatsuya et al., 2010), six were case-control studies (Huhtasaari et al., 1992, 1999; Hergens et al., 2005; Teo et al., 2006; Wennberg et al., 2007; Rahman and Zaman, 2008) and two were cross-sectional studies (Bolinder et al., 1992; Nasir et al., 2010). Studies were conducted mainly in Sweden (n=11) and the Swedish studies concentrated on the use of snuff (n=8). Three studies used South Asian SLT products, but only two studies (Gupta et al., 2005; Rahman and Zaman, 2008) were conducted in South Asian regions (India and Bangladesh). The third study was global, INTERHEART study (Teo et al., 2006), which included SLT products from 52 countries including few South Asian countries. Men only were included in the majority of the studies (n=12), either during recruitment of the study participants or during analyses of the findings; as report of SLT use was much lower among women. The Swedish studies concentrated on the use of snuff (n=8), and only two studies were concerned with South Asian SLT products exclusively. Four studies reported outcome as fatal CHD, three reported outcome as non-fatal CHD, and ten studies reported outcome as both fatal and non-fatal CHD.

Nine studies reported a statistically significant positive association between SLT use and CHD (Bolinder et al., 1992, 1994; Gupta et al., 2005; Henley et al., 2005; Teo et al., 2006; Hergens et al., 2007; Rahman and Zaman, 2008; Nasir et al., 2010; Yatsuya and Folsom, 2010), and nine studies failed to find a significant association (Huhtasaari et al., 1992, 1999; Accortt et al., 2002; Hergens et al., 2005; Johansson et al., 2005; Haglund et al., 2007; Wennberg et al., 2007; Hansson et al., 2009; Janzon and Hedblad, 2009). Among those nine studies showing positive association, four studies reported a significant association among a subset of study participants (Bolinder et al., 1992; Gupta et al., 2005; Hergens et al., 2007; Nasir et al., 2010). One Swedish study (Hergens et al., 2007) reported a significant positive association between SLT use and fatal CHD, but did not find an association for non-fatal CHD. The Indian study (Gupta et al., 2005) reported a significant positive association between SLT use and fatal CHD among women (OR 1.25, 95% CI 1.05 to 1.49), but did not find an association among men (OR 0.94, 95% CI 0.83 to 1.06). Similarly, the US study reported a significant positive association between SLT use and fatal CHD among women (OR 1.25, 95% CI 1.05 to 1.49), but did not find an association among men (Nasir et al., 2010). The remaining study reported a significant association between SLT use and non-fatal CHD among older men

(56 to 65 years), but did not find a significant association among younger men (46 to 55 years) (Bolinder et al., 1992). Three studies used SLT products from South Asia and reported a significant positive association between SLT use and CHD (Gupta et al., 2005; Teo et al., 2006; Rahman and Zaman, 2008).

Analysis of the Western studies

Table 1 shows the analysis of the studies conducted in Western settings. Three out of eleven studies conducted in Sweden reported a significant positive association between SLT use and CHD (Bolinder et al., 1992, 1994; Hergens et al., 2007). One cross-sectional study based on the Swedish construction worker study (Bolinder et al., 1992) reported a significant positive association between SLT use and non-fatal CVD in general. However, the study reporting the cohort analyses of that research (Bolinder et al., 1994) showed a significant positive association between SLT use and fatal CHD. The result did not change when further follow-up was reported by Hergens et al. (2007) with that cohort.

Four Swedish cohort studies failed to find a statistically significant association between SLT use and CHD (Johansson et al., 2005; Haglund et al., 2007; Hansson et al., 2009; Janzon and Hedblad, 2009). One study did not also find any association with frequency and duration of SLT use and CHD (Hansson et al., 2009). Another four Swedish case-control studies did not find any statistically significant association between SLT use and CHD (Huhtasaari et al., 1992, 1999; Hergens et al., 2005; Wennberg et al., 2007). Subgroup analyses based on age in one study (Huhtasaari et al., 1992) were not contributory, although this study did not consider the known risk factors for CHD as potential confounders during analyses. One study (Huhtasaari et al., 1992) also examined whether there was a dose-response relationship between SLT use and CHD, but none was detected. All of these Swedish studies included both fatal and non-fatal CHD cases (Table 1)

Among the four US studies, three studies reported a significant positive association between SLT use and CHD (Henley et al., 2005; Nasir et al., 2010; Yatsuya and Folsom, 2010). Although the US Cancer Prevention Study (Henley et al., 2005) found a significant association between SLT use and fatal CHD, frequency and duration of SLT use were not associated with CHD. In addition, the study population included only men. The other two studies did not report results for CHD or stroke separately (Nasir et al., 2010; Yatsuya and Folsom, 2010). One of them (Nasir et al., 2010) reported a significant association among women only. The only US study (Accortt et al., 2002) that did not find any significant association between SLT use and fatal CHD, reported similar results when data were analysed according to gender (Table 1).

In summary, the majority of the Swedish studies did not find any significant positive association between SLT use and CHD. Results from all of these Swedish studies represent men only and were based on SLT products used in Sweden. On the other hand, the majority of the US studies showed a significant positive association between SLT use and CHD. Results from all of these US studies were based on SLT products used in the USA.

Analysis of the South Asian studies

Table 2 shows the analysis of the studies conducted in South Asian settings. The Indian cohort study (Gupta et al., 2005) reported a significant association for fatal CHD among women only, not among men. Although the study reported the association between use of different Indian SLT products and CHD mortality along with other tobacco-related mortality, the authors acknowledged limitations in ascertaining the accurate causes of deaths for all participants (Gupta et al., 2005). In addition, there was no separate report for the association between fatal CHD and specific SLT product, which is particularly important as SLT products included betel-quid in that study (Gupta et al., 2005).

On the other hand, although the Bangladeshi study (Rahman and Zaman, 2008) included betel-quid within SLT products, the study reported each type of SLT product separately. Dried tobacco leaf chewing was significantly associated with CHD (OR 2.2, 95% CI 1.1 to 4.5). Similar to the Indian study, the study reported a statistically significant association between SLT use and CHD among women only (OR 4.5, 95% CI 1.2 to 16.7); the confidence interval was wide due to small number of participants (n=83) (Rahman and Zaman, 2008). In addition, that study was limited by having a small sample size (n=207) posing the risk of reduced power of the study, and recruiting controls from within a hospital setting (Rahman and Zaman, 2008). However, unlike other studies, this study included younger population (20 to 49 years) as the study participants.

Analysis of the global study

The global INTERHEART study (Teo et al., 2006) reported a significant positive association between chewing tobacco and CHD. However, the study did not report different SLT products separately for each participant country. Furthermore, betel was included in addition to chewing tobacco within South Asian SLT products (Teo et al., 2006). It was not clear from the study whether the significant positive association obtained was due to chewing tobacco alone or betel chewing alone or both in South Asia (Table 2).

This is particularly important for clarification in future studies because some studies have reported a significant

Table 1. Summary of the Western studies exploring the association between coronary heart disease (CHD) and smokeless tobacco (SLT) use.

Source	Study location (country)	Types of study	Recruitment and Follow-up year	Sample size	Gender	Age(yrs) at baseline	Types of SLT use as exposure	Types of CHD as outcome (only CHD data were considered)	Results presented in this table, based on the comparison groups	Key findings regarding association between SLT use and CHD	Comments
Positive association between SLT use and CHD											
Bolinder et al. (1992)	Sweden	Cross-sectional	1971-74	97586	Men	16-65	SLT (types of SLT not defined)	Non-fatal CVD	Current SLT users vs. never tobacco users, (a)	Age 46-55yrs: OR = 1.6 (95%CI 0.7-3.5); Age 56-65yrs: OR = 1.5 (95%CI 1.1-1.9)	Results for men only, no separate reports for CHD or stroke, possibility of healthy worker effects on the association
Bolinder et al. (1994)	Sweden	Cohort	1971-74, 1974-85	84781	Men	16-65	SLT (types of SLT not defined)	Fatal CHD	Current SLT users vs. never tobacco users, (b)	Age 35-54yrs: RR = 2.0 (95%CI 1.4-2.9); Age 55-65yrs: RR = 1.2 (95%CI 1.0-1.5)	Results for men only, SLT use data old
Hergens et al. (2007)	Sweden	Cohort	1978-93, 1978-2004	118395	Men	16-65	Snuff	Fatal and non-fatal CHD	Current snuff users (never smoked) vs. never tobacco users, (c)	Non-fatal CHD: RR = 0.94 (95%CI 0.83-1.06); Fatal CHD: RR = 1.32 (95%CI 1.08-1.61); Heavy snuff use (≥50gm/day) and fatal CHD among 55-65 years: RR = 2.46 (95% CI 1.09-5.55)	Results for men only
Henley et al. (2005)	USA	Cohort	1959, 1959-72	77407 (CPS-I study)	Men	≥30	SLT (Chewing tobacco, snuff)	Fatal CHD	Current SLT users vs. never tobacco users, (d)	HR = 1.12 (95%CI 1.03-1.21)	Results for men only, SLT use data collected at baseline only
			1982, 1982-2000	113970 (CPS-II study)						HR = 1.26 (95%CI 1.08-1.47); Frequency and duration of SLT use were not associated with CHD	
Yatsuya et al. (2010)	USA	Cohort	1987-89, 1987-2008	14498	Both	45-64	SLT (types of SLT not defined)	Fatal and non-fatal CVD	Current SLT users (never smoked) vs. never tobacco users, (e)	HR = 1.31 (95% CI 1.06-1.61)	No separate reports for CHD or stroke
Nasir et al. (2010)	USA	Cross-sectional (Surveillance data analyses)	1999-2001	10332	Both	18-70+	SLT (types of SLT not defined)	Non-fatal CVD	Current SLT users vs. never tobacco users, (f)	Overall: OR = 1.14 (95% CI 0.55-2.39), Men: OR = 1.11 (95% CI 0.87-1.40), Women: OR = 1.72 (95% CI 1.12-2.65)	No separate reports for CHD or stroke

Table 1. Contd.

No positive association between SLT use and CHD											
Johansson et al. (2005)	Sweden	Cohort	1988-89, 1988-2000	3120	Men	30-74	Snuff	Fatal and non-fatal CHD	Current snuff users (never smoked) vs. non-current snuff users, (g)	HR = 1.41 (0.61-3.28)	Results for men only, SLT use data collected at baseline only
Haglund et al. (2007)	Sweden	Cohort	1988-89, 1988-2003	5002	Men	16-74	Snuff	Fatal and non-fatal CHD	Current snuff users vs. never tobacco users, (h)	Non-fatal CHD: IRR = 0.77 (95%CI 0.51-1.15); Fatal CHD: MRR = 1.15 (95%CI 0.54-2.41)	Results for men only
Hansson et al. (2009)	Sweden	Cohort	1998-2002, 1998-2005	16642	Men	40-72	Snus	Fatal and non-fatal CHD	Current snus users (never smoked) vs. never tobacco users, (i)	RR = 0.85 (95%CI 0.51-1.41); Frequency and duration of snus use were not associated with CHD	Results for twin men only
Janzon et al. (2009)	Sweden	Cohort	1991-96, 1991-2004	27227	Men	45-73	Snuff	Fatal and non-fatal CHD	Current snuff users (never smoked) vs. never tobacco users, (j)	RR = 0.75 (95%CI 0.3-1.8)	Results for men only
Huhtasaari et al. (1992)	Sweden	Case-control	1989-91	1174 (585 cases & 589 controls)	Men35-64		Snuff	Fatal & non-fatal CHD. Cases were selected from hospital records and death registers; controls were selected from population registers	Current snuff users vs. never tobacco users, (k)	All age: OR = 0.89 (95%CI 0.62-1.29); Age 35-54yrs: OR = 0.96 (95%CI 0.56-1.67); Age 55-64yrs: OR = 1.24 (95%CI 0.67-2.30); No dose response relationship	Results for men only, known potential confounders for CHD were not considered, never tobacco users included former smoker/snuffers as well as occasional smokers/snuffers during analysis
Huhtasaari et al. (1999)	Sweden	Case-control	1991-93	1374 (687 cases & 687 matched controls)	Men25-64		Snuff	Fatal & non-fatal CHD. Cases were selected from hospital records and death registers; controls were selected from population registers	Current snuff users vs. never tobacco users, (l)	Fatal CHD: OR = 1.50 (95%CI 0.45-5.03); Both fatal and non-fatal CHD: OR = 0.58 (95%CI 0.35-0.94)	Results for men only
Hergens et al. (2005)	Sweden	Case-control	1992-94	3242 (1432 cases & 1810 matched controls)	Men45-70		Snuff	Fatal and non-fatal CHD. Cases were selected from hospitals and mortality register, controls were selected from communities	Current snuff users (never smoked) vs. never tobacco users, (m)	Fatal CHD: OR = 1.7 (95%CI 0.48-5.5); Non-fatal CHD: OR = 0.59 (95%CI 0.25-1.4); Both fatal and non-fatal CHD: OR = 0.73 (95%CI 0.35-1.5)	Results for men only

Table 1. Contd.

Wennberg et al. (2007)	Sweden	Case-control	1985-89	2323 (525 cases & 1798 matched controls)	Men	30-60	Snuff	Fatal and non-fatal CHD, Cases & controls selected both from hospitals and communities	Current snuff users (Never smoked) vs. never tobacco users, (n)	Fatal CHD: OR = 1.12 (95% CI 0.38-3.29); Non-fatal CHD: Both fatal and non-fatal CHD: OR = 0.82 (95%CI 0.46-1.43)	Results for men only, controls selected from hospital settings having the possibility of under-estimation of results using hospital controls, no separate reports for hospital controls or community controls
Accortt et al. (2002)	USA	Cohort	1971-75, 1971-92	12451	Both	45-75	SLT (types of SLT not defined)	Fatal CHD	Ever SLT users (never smoked) vs. never tobacco users, (o)	Men: HR = 0.6 (95%CI 0.3-1.2); Women: HR = 1.4 (95%CI 0.8-2.2)	Never tobacco users included other smokers (pipe/cigar)

CVD = cardiovascular diseases, RR = risk ratio, HR = hazard ratio, IRR = incidence rate ratio, MRR = mortality risk ratio, 95%CI = 95% confidence intervals. a) Matching not relevant. Adjusted for: Age, gender, race, body mass index, smoking; b) Adjusted for: Age, residential areas, body mass index, blood pressure, diabetes, history of heart symptoms or blood pressure medication, smoking; c) Adjusted for: Age, body mass index, residence; d) Adjusted for: Age, race, education, alcohol use, exercise, aspirin use, body mass index, vegetables and fruits intake, dietary fat consumption, occupation; e) Adjusted for: Age, gender, race, education, total annual household income, usual alcohol consumption, sports index score, cigarette smoking status, cigarette-years of smoking, pipe use, cigar use, second-hand smoke exposure, systolic blood pressure, use of antihypertensive medication, diabetes, waist circumference, total and high-density lipoprotein, cholesterol, triglycerides; f) Adjusted for: Age, gender, race, body mass index, smoking; g) Adjusted for: Age, blood pressure, body mass index, diabetes, physical activities; h) Adjusted for: Age, socioeconomic status, residence, self-reported health, number of longstanding illness, physical activity; i) Adjusted for: Age, smoking, diabetes, hypertension, serum cholesterol level; j) Adjusted for: Age, body mass index, smoking, diabetes, hypertension, physical activity, marital status, occupation; k) Not matched. Adjusted for: Age, education; l) Matched for: Age, residential areas. Adjusted for: Age, residence, smoking, hypertension, diabetes, high cholesterol, education, marriage, family history of cardiac death; m) Matched for: Age, hospital catchment areas. Adjusted for: Age, hospital catchment areas, diabetes, hyperlipidemia, hypertension, overweight, physical activity, job strain; n) Matched for: Age, gender, date of health survey and geographical region. Adjusted for: Serum cholesterol level, body mass index, physical activity, education; o) Adjusted for: Age, race, poverty index ratio, alcohol use, physical activities, fruits and vegetables intake, systolic blood pressure, serum cholesterol level, body mass index.

Table 2. Summary of the studies using South Asian smokeless tobacco (SLT) products to explore the association between coronary heart disease (CHD) and smokeless tobacco (SLT) use.

Source	Study location (country)	Types of study	Recruitment and Follow-up year	Sample size	Gender	Age (yrs) at baseline	Types of SLT use as exposure	Types of CHD as outcome (only CHD data were considered)	Results presented in this table, based on the comparison groups	Key findings regarding association between SLT use and CHD	Comments
Gupta et al. (2005)	India	Cohort	1992-94, 1992-99	99570	Both	≥35	Mishri, other SLT products (tobacco plus lime)	Fatal CHD	Current SLT users vs. never tobacco users, (a)	Men: RR = 0.89 (95%CI 0.75-1.05); Women: RR = 1.25 (95%CI 1.05-1.49)	Causes of deaths had limitations in classifying, did not report the association separately for each SLT
Rahman and Zaman, (2008)	Bangladesh	Case-control	2006-07	207 (69 cases & 138 controls)	Both	20-49	Dried tobacco leaf	Non-fatal CHD. Cases & controls both were selected from hospitals, (b)	Ever dried tobacco leaf users vs. never tobacco users	OR = 2.2 (95%CI 1.1-4.5).	Small sample size, hospital-based study
Teo et al. (2006)	Global	Case-control	1999-2003	26568 (12133 cases & 14435 matched controls)	Both	44-75	SLT (from different 52 countries)	Non-fatal CHD, Cases were selected from hospitals; controls were selected both from hospitals and communities, (c)	Ever use of SLT (never smoked) vs. never tobacco users	OR = 2.23 (95% CI 1.41-3.52)	No reports for specific SLT product of any country, no separate reports for hospital controls or community controls

OR = odds ratio, 95%CI = 95% confidence intervals; a) Not matched. Adjusted for: Age, education; b) Not matched. Adjusted for: Age, gender, hypertension; c) Matched for: Age, gender (but 14% cases and 5% controls were not matched perfectly, therefore, unmatched analysis was done). Adjusted for: Age, gender, geographic region, obesity, hypertension, diabetes, apolipoprotein B/apolipoprotein A ratio, diet, physical activity, alcohol use.

positive association between betel chewing alone and CHD (Guh et al., 2007; Lin et al., 2008). Although betel-quid does not contain tobacco, the association was thought to be due to the presence of substances in betel-quid which have both sympathetic and parasympathetic activities (Guh et al., 2007; Lin et al., 2008).

Quality level of the selected studies

We used the Cochrane GRADE approach to rate the quality of the included studies (Higgins and Green, 2011). Grading was undertaken by "Muhammad Aziz Rahman". The GRADE approach has perhaps more relevance for systematic reviews of clinical studies and because of this all observational studies have a default rating of 'low'. However, upgrading and downgrading can occur by considering the following: design and implementation, consistency of results, directness of evidence, precision or results, probability of publication bias, magnitude of effect, presence of confounders, and dose response gradient (Higgins and Green, 2011). Three of the studies in this review (Teo et al., 2006; Hergens et al., 2007; Hansson et al., 2009) could be upgraded to 'moderate', whilst no other studies in the review required downgrading.

DISCUSSION

The systematic review showed that in general,there was no association between SLT use and CHD in Swedish studies, but the US and South Asian studies have shown an association. It is plausible that these differences reflect differences in the content of SLT products across countries. Alternatively it could be due to differences in the pattern of SLT usage between countries, with more pervasive and regular use common in South Asian countries. In addition, SLT products are commonly consumed with betel-quid in South Asian countries and the positive association in South Asian studies could be due to the fact that betel chewing is independently associated with CHD (Guh et al., 2007; Lin et al., 2008). The results also differed according to age and gender in some studies as detailed in the foregoing.

Results regarding the association between SLT use and CHD differed by age groups of the study participants. While the Swedish cross-sectional study did not find a significant association between SLT use and CHD among young construction workers of 46 to 55 years (Bolinder et al., 1992), the Swedish cohort study reported a significant association among young as well as older people (Bolinder et al., 1994). However, as the participants of those studies were recruited from a volunteer health check-up group, the possibility of healthy worker effects (Shah, 2009) on the non-association in the cross-sectional study (Bolinder et al., 1992) cannot be ruled out. In addition, another Swedish case-control study did not report any significant association across different age groups (Huhtasaari et al., 1992). Although age was considered for adjustment during calculation in those studies, there remains uncertainty regarding the effects of age on the association of SLT use and CHD. On the other hand, the cohort study with Swedish construction workers collected SLT use data at baseline (Bolinder et al., 1994). SLT usage patterns as well as SLT constituents might have been changed within the 12-years follow-up period, which was not considered in that study. The subsequent cohort study (Hergens et al., 2007) utilizing data from the Swedish construction worker cohort considered this issue and reported comprehensive data on SLT use.

SLT usage pattern differs by gender and by country. While results of all Swedish studies represent men only, both genders were considered in three US studies (Accortt et al., 2002; Nasir et al., 2010; Yatsuya and Folsom, 2010). Two of them (Accortt et al., 2002; Nasir et al., 2010) reported an increased risk of CHD with SLT use among women compared to men. Similarly, the Indian cohort study (Gupta et al., 2005) and the Bangladeshi case-control study (Rahman and Zaman, 2008) reported a significant positive association among women only. Although prevalence of SLT use is similar among women and men in South Asia (Gupta and Ray, 2003; World Health Organization-Bangladesh, 2009), frequency, amount and duration of SLT use may be different between men and women, which were not considered in either study. Therefore, it is important to explore this gender variation in future studies of SLT use and CHD.

The forms of SLT products used in South Asia differ from the Western SLT products in constituents, nicotine concentration, manufacturing and storage (US National Cancer Institute, 2002; McKee et al., 2007). Therefore, it is presumed that those Western studies would not be generalizable to the South Asian settings. Studies using South Asian SLT products exclusively are very limited and showed a significant association between SLT use and CHD thus far (Gupta et al., 2005; Teo et al., 2006; Rahman and Zaman, 2008). But SLT products are also not same across all South Asian countries (Stanfill et al., 2011), results of the studies might be different due to this chemical diversity of SLT products. Therefore, it would be interesting to have further studies in South Asia to explore whether the association between SLT use and CHD vary by different types of SLT products.

Inconsistent results can also be explained by some methodological constraints. As for example, some cohort studies (Bolinder et al., 1994; Henley et al., 2005; Johansson et al., 2005) did not report any information whether users switched from SLT use to smoking or not during the follow-up period, which is not an uncommon practice (Tomar, 2003; Boffetta and Straif, 2009). If the

SLT users switched and/or used both tobacco products, the positive association in those cohort studies might not be true. In a similar way, if the SLT users stopped using SLT products during the follow-up period, the non-association findings of the cohort studies could be due to this behavior change. On the other hand, one case-control study (Wennberg et al., 2007), which did not find a significant positive association between SLT use and CHD, included partial controls from hospital settings. Whilst hospital controls and community controls differ in a number of ways such as distribution of exposure variables and confounders, recall history, non-response, the ORs reported in that study is likely to be under-estimated due to these issues although there was no separate report for hospital controls or community controls (Wennberg et al., 2007). Another case-control study did not consider the potential confounders for CHD during reporting the non-association between SLT use and CHD (Huhtasaari et al., 1992). The Indian cohort study may have been affected by the difficulty in a developing country of having an incomplete death register; the outcome in this study was fatal-CHD and there may have been inconsistencies in the classification of the cause of death (Gupta et al., 2005). Finally, presence of unmeasured confounding effects on either cohort or case-control studies to explore the association between SLT use and CHD cannot be ruled out, such as socioeconomic status (SES). Although there is an inverse relationship between SES and risk of CHD across different ethnic groups (Kraus et al., 1980); SLT users are generally from lower SES in South Asian countries (Gupta et al., 2003), the opposite may be true for some Western countries. SES is an independent risk factor for CHD and may be difficult to adequately adjust for even with multivariable analyses.

Conclusion

This systematic literature review summarized the existing evidence regarding the association between SLT use and CHD, both in Western and South Asian settings. Considering the variable constituents of SLT products and different patterns of SLT use between Western and South Asian settings, results from Western countries cannot be easily applied to South Asian countries.

Further evidence is required from South Asia regarding the association between SLT use and CHD, specifically focusing on gender variation and different types of SLT products. Studies also need to focus on methodological rigour and on populations who have been using SLT products as a socio-cultural tradition for hundreds of years.

LIMITATIONS

Limitations of this review include the possibility of excluding relevant studies in this review, as could happen to any systematic review (Critchley and Unal, 2004). But it is unlikely that we missed any important study as the search strategy was comprehensive and was conducted by an expert in this field. We did not undertake a meta-analysis, because different methodologies were employed by studies and different types of SLT products were measured. Meta-analyses have been performed earlier with Western studies only (Boffetta and Straif, 2009) and Asian studies only (Zhang et al., 2010). Our objective was to summarise the currently available evidence, consider plausible reasons for the different findings and through this process, explore the rationale for conducting further studies particularly in South Asia. We did not seek to make a definitive conclusion at this stage about the association between SLT use and CHD.

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