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Abstract

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**Background**

Most epidemiological studies exploring the association between smokeless tobacco (SLT) use and coronary heart disease (CHD) have been in Western populations and have focused on the SLT products used in those countries. Studies from South Asia are limited and the results have been inconsistent. There is widespread use of SLT products in Bangladesh particularly associated with betel chewing, with a prevalence of 27% among the Bangladeshi adult population including urban and rural.

**Objectives**

- To determine whether there is an association between SLT use and CHD among non-smoking adults in Bangladesh.
- To explore the perceptions of Bangladeshi adults regarding health effects of SLT use.
- To assess whether hospital controls can be used in case-control studies with minimal bias, where resource constraints limit recruitment of community controls.
- To determine the utility of the Rose Angina Questionnaire (RAQ) for detecting CHD among Bangladeshi adults.

**Methods**

A case-control study of non-smoking adults aged 40-75 years, residing within Dhaka City Corporation areas, was conducted in 2010. Cases of CHD were selected from two cardiac hospitals. Controls were selected from both hospital and community settings. Cases were classified as incident cases (diagnosed within last one-year) of CHD if diagnosed as such by the hospital cardiologists.
Neighbourhood residents of the CHD cases, not known to have any cardiac disease, were selected as community controls. Hospital controls were those patients who attended cardiac outpatient departments, but on clinical examination were considered not to have CHD by attending cardiologists. Four community controls were matched to each case on age (±5 years), gender, residential area and socioeconomic status. One hospital control was matched to each case on age and gender. A structured questionnaire was used for the case-control study and a semi-structured questionnaire was used to explore perceptions of SLT use. The RAQ was also used to re-classify cases and controls, and to validate its utility in Bangladesh.

Results

The study enrolled 302 cases, 1208 community controls, and 302 hospital controls (male: female 50:50; mean age 53±8.5 years). Current (during the last one year) use of SLT was higher among community controls (38%) compared to cases (33%) and hospital controls (32%). Current use of SLT was not associated with an increased risk of CHD when community controls were used (adjusted OR 0.87, 95% CI 0.63-1.19, p>0.05), when hospital controls were used (adjusted OR 1.00, 95% CI 0.63-1.60, p>0.05), or when both controls were combined (adjusted OR 1.00, 95% CI 0.74-1.34, p>0.05). All analyses were adjusted for potential confounders. Risk of CHD did not increase with use of individual types except gul, frequency, duration, past use of SLT products, or using the RAQ re-classification of cases and controls. There was a significant association between gul use and CHD when both controls were combined (adjusted OR 2.93, 95% CI 1.28-6.70). Study participants believed that Bangladesh people used SLT products primarily due to addiction (52%) and habituation to SLT products (23%). The influence of...
family members was the main reason given for initiating SLT use. Almost all respondents (97%) considered SLT products to be harmful, and cited heart disease, cancer and tuberculosis as the major SLT-related diseases. There were significant differences found between hospital controls and community controls in terms of confounding variables, but not for SLT use. The RAQ had a sensitivity of 53%, specificity of 89% and a positive likelihood ratio of 4.8 in detecting CHD among Bangladeshi adults compared with diagnoses done by cardiologists.

Conclusions

In this study, there was no statistically significant association between SLT use in general and CHD. Public health campaigns should focus on other detrimental health effects of SLT use. Tobacco control activities should consider addressing the role of the family in SLT initiation and use. The study also suggests that in resource constrained settings, carefully selected hospital controls may be an alternative to community controls if confounders are measured and are adjusted for. Finally, the RAQ may be a useful tool in large scale epidemiological research in Bangladesh.
I, Muhammad Aziz Rahman, certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Signed: ................................................................................................

(Dr. Muhammad Aziz Rahman)

Date: .....................................................................................................
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>BCSIR</td>
<td>Bangladesh Council of Scientific and Industrial Research</td>
</tr>
<tr>
<td>BDT</td>
<td>Bangladesh Taka</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CAG</td>
<td>Coronary Artery Angiogram</td>
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<tr>
<td>CCU</td>
<td>Coronary Care Unit</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Intervals</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular diseases</td>
</tr>
<tr>
<td>DCC</td>
<td>Dhaka City Corporation</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ETT</td>
<td>Exercise Tolerance Test</td>
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<tr>
<td>FCTC</td>
<td>Framework Convention on Tobacco Control</td>
</tr>
<tr>
<td>IEDCR</td>
<td>Institute of Epidemiology, Disease Control &amp; Research</td>
</tr>
<tr>
<td>IFST</td>
<td>Institute of Food Science and Technology</td>
</tr>
<tr>
<td>IPDs</td>
<td>Inpatient departments</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>NICVD</td>
<td>National Institute of Cardiovascular Diseases</td>
</tr>
<tr>
<td>NHF&amp;RI</td>
<td>National Heart Foundation Hospital &amp; Research Institute</td>
</tr>
<tr>
<td>OPDs</td>
<td>Outpatient departments</td>
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<tr>
<td>ORs</td>
<td>Odds Ratios</td>
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<tr>
<td>PCCU</td>
<td>Post Coronary Care Unit</td>
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<tr>
<td>RAQ</td>
<td>Rose Angina Questionnaire</td>
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<tr>
<td>SES</td>
<td>Socio-economic status</td>
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<td>SLT</td>
<td>Smokeless tobacco</td>
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<td>WHO</td>
<td>World Health Organization</td>
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CHAPTER 1

Background
Chapter outline
This chapter provides an overview of the use of smokeless tobacco (SLT) products and coronary heart disease (CHD), at first from a global perspective followed by the Bangladesh context. The overview includes the health effects of SLT use with a particular focus on CHD. Research questions and objectives for this study are then described. The rationale for conducting this study is then discussed. Finally, chapters of the entire thesis are outlined.

1.1. Introduction

1.1.1. Smokeless tobacco
Smokeless tobacco (SLT), which is also known as chewing tobacco or oral tobacco, 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” ¹. SLT is the term generally used in literature; however, it must be carefully noted that there is a wide variation in the amount of nicotine in different SLT products. Commercial manufacturers from different countries prepare their own SLT products by altering the constituents in ways intended to maximize appeal to consumers. Snus and snuff are the most popular names of such SLT products globally.

SLT, the use of which has spread to many countries in recent years, has been used by South American and South Asian people for thousands of years ². SLT is commonly used in many countries of Europe, America, Africa, and in countries of South Asia ¹. South Asia includes Afghanistan, Bangladesh, Bhutan, India, Iran, Maldives, Nepal, Pakistan, and Sri Lanka ¹. Over 250 million people, constituting 17% of the total population of the WHO South-East Asia region, use SLT products
Eighty-two percent of users are from India and 13% are from Bangladesh. The use of SLT also varies by age, sex, ethnicity and socioeconomic status, both within and between countries. Use of SLT products is associated with various health effects although most of the available studies have focused on cancers. Further details will be provided in chapter two and three.

1.1.2. Coronary heart disease

Coronary heart disease (CHD), which caused more than seven million deaths in 2004, is the leading cause of mortality worldwide. Tobacco use is the second most important risk factor for CHD, followed by hypertension. According to the World Health Organization (WHO), tobacco is the most important preventable cause of death. It is projected that the number of tobacco-attributable deaths will increase from 5.4 million in 2004 to 8.3 million in 2030. Of these 5.4 million deaths, 0.9 million deaths were due to CHD caused by tobacco use in 2004. It is also projected that more than 80% of these deaths will take place in low- and middle-income countries.

1.1.3. Smokeless tobacco and coronary heart disease

The association between smoking and CHD is well established, but the association between SLT use and CHD is in dispute. A number of studies have been conducted to ascertain the association between SLT use and CHD. However, the majority of these studies which were carried out in Sweden and USA, had inconsistent results. Further details will be provided in chapter two. Studies also indicated that the deleterious effects of SLT on CHD were much less than those associated with tobacco smoking.
1.1.4. Bangladesh context

Bangladesh, where aggregate tobacco consumption exceeds production\textsuperscript{15}, is an example of the low- and middle-income countries in the South-East Asia region\textsuperscript{5}. Both smoking and use of SLT are widespread in the country. The recent Global Adult Tobacco Survey (GATS) revealed that 43.3\% (41.3 million) of Bangladeshi adults use tobacco in some form\textsuperscript{16}. The prevalence of SLT use is 27\%, with similar rates in men (26\%) and women (28\%), and is more prevalent in rural areas (29\%) compared with urban areas (23\%)\textsuperscript{16}. Only oral forms of SLT products are used by the Bangladeshi population\textsuperscript{17, 18}. These products are used usually with paan (betel leaf), with or without lime. ‘Paan with jarda’ (tobacco leaf commercially processed for chewing) is the most common form of SLT used\textsuperscript{18-20}.

There is no study on the incidence of CHD in Bangladesh. Moreover, data on the prevalence of CHD among the Bangladeshi population are limited. Some of the available studies were conducted in Bangladesh and in other studies among the Bangladeshi expatriates in UK. Studies on the native Bangladeshi population reported CHD prevalence of 6.1\%, with a slightly higher prevalence among men than women\textsuperscript{21-24}. The studies among Bangladeshi residents of the UK have shown an overall increased prevalence (10.1\%) of CHD compared with the native studies\textsuperscript{25}. According to the WHO, cardiovascular diseases accounted for 23\% of all deaths (1,107,000 total deaths) in Bangladesh in 2002\textsuperscript{26}. In addition, the standardised mortality rate was the highest among Bangladeshi men compared with other South Asians and Europeans in a UK study during 2001-2003\textsuperscript{27}.

Studies exploring the association between SLT use and CHD in Bangladesh are very limited. Whilst a number of studies in Bangladesh have examined tobacco
use[^22, 28, 29], the only study focusing on the SLT-CHD association had a small sample (n=207), which had included smokers, and recruited cases and controls from a hospital setting[^19].

### 1.1.5. Scope of further study

The majority of the studies exploring the association between SLT use and CHD involved Western populations. The results of these studies focused on the use of SLT products used in those communities. The forms of SLT products used in South Asia differ from the snuff or snus by their constituents, nicotine concentration, manufacture and storage[^2, 30]. Therefore, it is presumed that those Western studies would not be generalisable to the South Asian settings. Therefore, there is scope for further research on this association from South Asian countries.

This study also provided an opportunity to investigate the issue of control selection for a case-control study and to determine the utility of the Rose Angina Questionnaire to detect CHD among Bangladeshi adults. Selection of an appropriate control is crucial in a case-control study to avoid selection bias. Hospital controls and community controls can potentially differ in a number of ways. Whilst there is a theoretical possibility of bias using hospital controls in a case-control study, there are limited studies to support this hypothesis. Considering the financial implications to recruit community controls, this issue is of particular importance for a resource-poor developing country where funding for research is scarce. On the other hand, the questionnaire-based tool, RAQ, has been used in many countries as a standard tool to detect coronary heart disease (CHD) in epidemiological research. While sensitivity and specificity of the
questionnaire may vary between countries, studies validating the RAQ to detect CHD among South Asian populations are very limited. Within the context of potential influence of socio-cultural factors, and as there are reports about varying RAQ performance amongst different population groups, further studies are recommended to establish cross-cultural validity of the RAQ.

1.2. Research questions and objectives

1.2.1. Research questions

In order to determine the association between SLT use and CHD, this study addressed the following research questions:

- Is there any association between SLT use and CHD among non-smoking adults in Bangladesh?
- What are the perceptions of Bangladeshi adults about the health effects of SLT use?
- Does using hospital controls or community controls in a case-control study in Bangladesh give different results?
- What is the utility of the Rose Angina Questionnaire (RAQ) for detecting CHD among Bangladeshi adults?

1.2.2. Research Objectives

The objectives of this study were:

- To determine the association between SLT use and CHD among non-smoking adults in Bangladesh using a case-control study.
- To explore the perceptions of Bangladeshi adults regarding the health effects of SLT use.
To assess whether hospital controls can be used in case-control studies with minimal bias, where resource constraints limit recruitment of community controls.

To determine the utility of the Rose Angina Questionnaire (RAQ) for detecting CHD among Bangladeshi adults, by comparing RAQ categorization with diagnosis by a cardiologist.

1.3. Justification for the study

1.3.1. Rationale for studying SLT

There is ongoing debate regarding the use of SLT products as possibly being a relatively less harmful alternative to active smoking. The tobacco control community is divided on this issue; one group suggests use of SLT products and the other opposes the promotion of any form of tobacco. One group considers Sweden as a successful example of decreasing smoking-related morbidity and mortality through SLT promotion, whereas opponents of this approach do not believe in the replicability to other cultural settings. Tobacco companies are also promoting alternate forms of tobacco for smokers, since this promotion might increase the chance of dual use of tobacco and attract new consumers. Therefore, the debate continues as to whether SLT products are potentially harm reducing products or whether they act as a gateway to smoking.

Background of SLT promotion

The deleterious effects of smoking on health are well known and public health efforts to contain this health hazard are continuing. Some tobacco control laws have already been instituted in many countries to protect people from the effects of tobacco consumption and second-hand tobacco smoke. This includes
advocating a warning message regarding the adverse effects of smoking on each cigarette pack, bans on selling cigarettes to minors, restrictions on advertisements, restrictions on smoking in open public spaces, and increased taxes on cigarettes. One of the most recent and extreme advances for global tobacco control is the legislation for plain packaging recently introduced in Australia, which has the potential to significantly reduce smoking prevalence in the future. The World Health Organization (WHO) adopted the Framework Convention on Tobacco Control (FCTC) in 2003 in response to the globalization of the tobacco epidemic, and to protect present and future generations around the world from tobacco-related deaths and diseases. Tobacco companies have tried to explore the potential of other tobacco products instead of cigarette marketing in response to these tobacco related laws, the downturn in cigarette popularity, smoking related health concerns and reduced social acceptability.

Potential harm reduction due to shifting from smoking to SLT

Many public health advocates argue that the health hazards of tobacco could be reduced by shifting the smokers to less hazardous SLT products. Nicotine replacement therapy (NRT) has included nicotine chewing gum, transdermal patches, nasal sprays, lozenges etc. In Sweden, snus has been reported as an alternate and preferred approach to quit smoking. As some of the studies showed that the deleterious effects of snus or snuff were much less than those of smoking, using these SLT products could potentially reduce the burden of smokers on the health system due to smoking. In Sweden, tobacco companies were successful in shifting smokers to SLT products, as evidenced by a decline in smoking prevalence. Researchers suggested that the reduction in tobacco-related mortality and the burden of cardiovascular diseases in Sweden might be
due to that shift from smoking to SLT products\textsuperscript{44, 48}. Success in Sweden is frequently used by tobacco companies to support their marketing of SLT products\textsuperscript{49}.

\textit{Potential risks of shifting from smoking to SLT}

There is an important concern that promotion of SLT products might initiate smoking specifically among adolescents\textsuperscript{50, 51}, which could also attract new consumers in a previous non-smoking community\textsuperscript{47}. Therefore, promotion of switching may not be an effective strategy to reduce the tobacco-burden in a society. In addition, shifting from smoking to SLT products has the potential risks of dual use of smoking and SLT. Internal research by the multinational cigarette company, Philip Morris, showed that most smokers do not intend to switch completely; rather, they like to use SLT products when they are not able to smoke\textsuperscript{52}. Cigarette manufacturing companies have produced SLT for smokers who would have otherwise quit; and following this, they have focused on promoting SLT products to augment cigarette use advertising “when smoking is not possible”\textsuperscript{32}. They have also commenced manufacture of spitless SLT products with different flavours, which are more acceptable and convenient forms for consumers, and may be attractive to a younger market\textsuperscript{53}. Thus, marketing strategies of tobacco companies have the potential to encourage the dual use of smoking and SLT products, and to recruit new users. The concomitant users of SLT and cigarette smoking are less likely to achieve complete cessation compared with individuals who only smoke or use only SLT products\textsuperscript{54}. One large prospective cohort study among US adults showed that those who switch from smoking to smokeless tobacco products had higher risks of dying from major tobacco-related diseases compared with the absolute quitters\textsuperscript{55}. 
Shifting pattern and benefits are country-specific

The counter argument is that the success of Swedish snus is culture-specific and may not be transferrable to other countries\textsuperscript{31,44,56}. Switching between smoking and SLT products varies by country. For example, tobacco consumers shifted from smoking to SLT in Sweden\textsuperscript{48}, but the opposite transition pattern has been observed among the tobacco users in USA\textsuperscript{57}. Moreover, SLT use has not been associated with a reduction in smoking prevalence, either in USA or in Norway, where SLT products are also largely used\textsuperscript{56,58}. Tomar pointed out that the trends of SLT use in USA, Sweden and Norway do not support the effectiveness of SLT as an aid to complete cessation, rather SLT served as a partial substitute for smoking cessation\textsuperscript{58}.

These polarized views have been based mainly on research conducted in developed countries. It is crucial to explore the effects of SLT use on health in developing countries. SLT products have been widely used in many developing countries for many years and are also associated with significant morbidities and mortalities\textsuperscript{59}. These products differ in terms of constituents and manufacturing from those used in western countries\textsuperscript{30}. As tobacco control policies vary strikingly between countries\textsuperscript{47}, there is a potential for introducing Western SLT products as a harm-reduction agent into the developing countries of South Asia\textsuperscript{44}. The risk of this, however, is that tobacco companies may see this as a way of increasing their profits. For example, Philip Morris Company explicitly believes that the marketing of SLT products in developing countries would present less competition and fewer restrictions compared to the US markets\textsuperscript{60,61}. The negative health effects of SLT in a developing country context are important for local policy makers.
1.3.2. Rationale for studying SLT and CHD

A number of studies have been carried out to explore the effects of SLT use on health. However, most of these studies focused on cancers \(^4,62\). A few studies assessed the association with CHD and the results regarding the association between SLT use and CHD are inconsistent in these studies \(^12,63\). In addition, studies from developing countries are also limited.

*Health effects of SLT use*

The association between SLT use and cancers of different organs has been explored in both developed and developing countries. Studies have shown a consistent association between SLT use and oral cancer \(^64,65\), laryngeal and pharyngeal cancer \(^66\), oesophageal cancer \(^67\), lung cancer \(^68\), pancreatic cancer \(^69\), breast cancer \(^70\), and penile cancer \(^71\). Oral precancerous lesions \(^72\), dental diseases \(^73\), diabetes \(^74\), and poor reproductive outcomes \(^75\) were also associated with use of SLT products. Some studies have reported a positive association between SLT use and addiction, and also showed that addiction was lower than with cigarette smoking \(^76,77\). A few studies also showed an increased risk of tobacco-related mortality among the SLT users \(^55,68\).

*Debate on the association between SLT use and CHD*

SLT use is associated with risk factors for cardiovascular disease (CVD) such as raised blood pressure and a less healthy lipid profile \(^78,79\). However, results of the epidemiological studies assessing the association between SLT use and CHD, stroke or CVD in general are inconsistent \(^12\). Detailed analysis of epidemiological studies regarding this inconsistent association is described in Chapter 2.
SLT use alone vs. dual tobacco use

Harmful effects of SLT alone on CHD appear to be lower than those for smoking, but the effects are greater when an individual uses both forms of tobacco. In the INTERHEART study, SLT users had a lower risk of developing CHD than smokers, and the risk was much greater among the users of both forms of tobacco. An increased risk of CHD was also evident in a population-based prospective cohort study in Sweden, when both smoking and SLT were used. A prior small scale study in Bangladesh conducted by the author of this thesis also showed that the users of both smoking and SLT had more risk of CHD compared to either smokers or SLT users alone.

Reviews of the available epidemiological studies indicate the need to conduct further studies on SLT use and CHD, specifically from developing countries. This is explored further in chapter two, which presents a systematic review of literature addressing this association.

1.3.3. Rationale for a study in Bangladesh

As a developing country in South-East Asia, Bangladesh has been experiencing an epidemiological transition from communicable diseases to non-communicable diseases. Among all of the non-communicable diseases, CHD is responsible for a quarter of all deaths. Studies exploring the association between CHD and SLT use, which is widely used in Bangladesh, are very limited. In addition, as South Asian SLT products vary considerably from Western products, findings from Western countries are not necessarily applicable to Bangladesh. In addition, opportunities for future interventions will differ depending on the SLT products and patterns of use.
Available studies from India

Among the studies conducted in India, only one study explored the association between SLT use and CHD, and other studies investigated the association between SLT use and different risk factors for CHD. The only study exploring the association between SLT use and CHD found a significant positive association between SLT use and fatal CHD among women only. In a population-based case-control study in India, multiple risk factors for CHD such as obesity, tachycardia, hypertension, blood cholesterol and electrocardiographic changes were more prevalent among SLT users than among non-users of tobacco. Another Indian study showed an abnormal serum lipid profile enhancing the risk of CHD among SLT users. A large prospective cohort study at Mumbai in India showed that users of SLT had an increased risk of all-cause mortality, and women had a greater risk than men.

Limited studies from Bangladesh

Bhopal et al. explored the prevalence of CHD and related risk factors (both biochemical and behavioural) among Bangladeshi expatriates living in UK, but did not consider SLT products. In another study from the UK, Bangladeshis were found to have the highest prevalence of risk factors for CHD compared with Indian, Pakistani, Nepalese and Sri Lankan immigrants. Studies conducted in Bangladesh have focused on documenting conventional risk factors for CVD, prevalence of CVD, prevalence of tobacco use, and other tobacco-related issues such as socio-demographic characteristics of tobacco users or socio-economic determinants of tobacco use. Although SLT products are widely used in the country, there is a lack of studies exploring the association between SLT use and CHD. Thus far, there is only one small scale study reporting this
association in Bangladesh, which was conducted in 2007 by the author of this thesis 19.

Evidence from the precursor study in Bangladesh

The precursor study for this project was a small hospital-based case-control study among Bangladeshi adults, which showed a significant positive association between SLT use and CHD (adjusted odds ratio 2.8, 95% confidence intervals 1.1-7.3) 19. This association was similar to the association between smoking and CHD 19. The study was limited by a small sample size (n=207), confining the age limit to 20-49 years, and recruiting cases and controls from within a hospital setting. However, the main limitation was including smokers in that study, which could have confounded on the association.

Low level of awareness regarding the health effects of SLT use

For centuries, betel leaf (paan) and/or other SLT products have been used by the Bangladeshi people as a common cultural tradition. These items are often offered to visitors in rural areas 90. Many rural people in India believe that some of the SLT products are beneficial to health such as relieving toothache, headache and stomach-ache, and this belief influences the use of SLT products 59. Similar beliefs regarding medicinal benefits were found in a Pakistani study 91. There has been no study thus far focusing on the perceptions of Bangladeshi people about tobacco or SLT use. An exploration of the perceptions of SLT use would enable identification of the initiating factors, reasons for continuation, benefits of using such products, and knowledge about potential harmful effects of SLT use. This information would assist in formulating future tobacco control strategies in Bangladesh.
Therefore, the current study provided scope to explore the perceptions of SLT use, as well as determining the association between SLT use and CHD in Bangladesh.

1.3.4. Methodological constraints of earlier studies

Most observational studies exploring the association between CHD and risk factors have potential methodological constraints. For case-control studies, choosing controls is a crucial issue. Community controls are preferred to hospital controls because of the theoretical risk of underestimating or overestimating odds ratios (ORs) by using hospital controls. However, logistic constraints (particularly lack of funding) to recruit community controls also need to be considered within a developing country context. Thus far, there is no study from Bangladesh or South Asia comparing the use of different control groups in a case-control study. Secondly, most of the studies on CHD involve substantial financial resources to include physicians or sophisticated diagnostic tools in ascertaining outcomes. However, such approaches are not always feasible in a resource-poor research setting. Finally, many studies of CHD use prevalent cases instead of incident cases, entailing a risk of bias because recent behavior patterns may have been influenced by the experience of illness.

Choice of controls for a case-control study

As noted above, a significant issue in case-control studies is the choice of controls. Controls need to be identified from the same source population of the selected cases, need to be free from the disease of interest, and need to be independent of the exposure variable in a study. Controls are most often selected from either hospital settings or from community settings. Selection of an appropriate control is fundamental to avoid selection bias and to allow valid
inferences to be made from a case-control study. These issues are described more fully in chapter five.

Selecting a diagnostic tool for resource-poor settings

In a resource-poor setting, a diagnostic tool for CHD needs to be standardized, sensitive, specific and affordable. Electrocardiography (ECG) has limitations as a diagnostic tool because 40% patients with CHD may have normal tracings at rest. Rose developed and validated a standardized questionnaire based on clinical symptoms only, to detect CHD for epidemiological surveys. The Rose Angina Questionnaire (RAQ) can be a potentially useful tool for detecting CHD for Bangladesh settings. The case-control study conducted for this dissertation provided an opportunity to explore the use of the RAQ in Bangladesh, and analyses accompanying this are described in chapter six.

Use of incident cases vs. use of prevalent cases

Selecting prevalent cases of CHD instead of incident cases to explore the relationship with SLT use has some potential risks, because the behavior of an individual may change after an episode of coronary symptoms. If prevalent cases of CHD are selected for research, there is a possibility of missing the true exposure history of SLT use from the CHD cases. In addition, if prevalent cases are used, there is a risk that exposure may have preceded the outcome. Ideally, risk factor status should be determined for a period that precedes the onset of CHD. In practice, however, it may be difficult to identify incident cases in a developing country such as Bangladesh, as there are no systematic registries of disease morbidity or mortality. Diagnostic technologies for CHD like ECG and cardiac enzymes are also not available to primary levels of health care in
Bangladesh. Even if available, Bangladeshi people particularly those from rural areas have limited ability to pay for such tests. A physician usually depends upon clinical features and experience to diagnose CHD in such a situation. In addition, it is presumed that most Bangladeshi people with CHD will have the first symptoms long before the diagnosis is made, as many will not seek medical care until symptoms become intolerable. This adds to the challenge of identifying incident cases of CHD in Bangladesh as in other developing countries. To address that issue in the current study, we have defined an incident case of CHD as follows, “The incident case is a patient diagnosed as CHD by any cardiologist for the first time within the preceding twelve months.”

In summary, the study design of this project attempted to address the limitations of earlier studies to explore the association between SLT use and CHD. In addition, the study design allowed exploration of the issue of choice of controls and assessment of the utility of the RAQ for detecting CHD. These are particularly important for a resource-constrained setting such as Bangladesh.

1.4. Thesis outline

Five manuscripts have been prepared in a style suitable for publication in peer-reviewed journals; these constitute five chapters for this thesis:

i. Rahman MA, Mahmood MA, Spurrier N, Rahman M, Leeder S. A systematic review of epidemiological studies on the association between smokeless tobacco use and coronary heart disease. This paper is accepted by Journal of Public Health and Epidemiology on 15\textsuperscript{th} November 2011.

ii. Rahman MA, Spurrier N, Mahmood MA, Rahman M, Choudhury SR, Leeder S. Is there any association between use of smokeless tobacco
products and coronary heart disease in Bangladesh? This paper has been submitted to *PLoS One* and the editor has suggested addressing the comments from the reviewers. The revised version was sent on 28\textsuperscript{th} November 2011.

iii. Rahman MA, Mahmood MA, Spurrier N, Rahman M, Choudhury SR, Leeder S. Why do Bangladeshi people use smokeless tobacco products? This paper has been submitted to *Asia Pacific Journal of Public Health* on July 2011.

iv. Rahman MA, Spurrier N, Mahmood MA, Rahman M, Choudhury SR, Leeder S. Hospital controls vs. community controls: choice for a case-control study in Bangladesh. This paper has been submitted to *Epidemiologic Perspectives and Innovations* on October 2011.

v. Rahman MA, Spurrier N, Mahmood MA, Rahman M, Choudhury SR, Leeder S. Rose Angina Questionnaire: validation with cardiologists’ diagnoses to detect coronary heart disease in Bangladesh. This paper has been submitted to *The Southeast Asian Journal of Tropical Medicine and Public Health* on November 2011.

Chapter 2 presents the manuscript of the systematic review of literature regarding the association between SLT use and CHD. The objective of this manuscript is to highlight the limitations of prior epidemiological studies and to indicate the scope for improvement in the present study.

Chapter 3 presents the manuscript that describes the case-control study exploring the association between SLT use and CHD among non-smoking Bangladeshi adults. It addresses the first research question:
• Is there any association between SLT use and CHD among non-smoking Bangladeshi adult population?

It describes the descriptive as well as analytic results of the study. Cases are compared with community controls, hospital controls, and both control groups during analyses. Analyses are conducted for current users, quitters or ever users of SLT products as well as using never-smokers, ex-smokers, and both groups separately. In addition, further analyses are conducted using the re-classification of cases and controls by the RAQ to explore the association between SLT use and CHD.

Chapter 4 presents the manuscript that describes the perceptions of SLT use among non-smoking Bangladeshi adults. It addresses the second research question:
• What are the perceptions of Bangladeshi adults about the health effects of SLT use?

It describes the perceptions of Bangladeshi adults in general as well as compares the perceptions between SLT users and non-users of SLT products.

Chapter 5 presents the manuscript that addresses the control selection issue which is inferred from the case-control study. It addresses the third research question:
• Does using hospital controls or community controls in a case-control study in Bangladesh give different results?

It compares hospital controls with community controls in terms of socio-demographic variables, risk factors for CHD, and SLT use. Based on the findings, the manuscript indicates an inference regarding the selection of controls for a case-control study.
Chapter 6 presents the manuscript that addresses the utility of the RAQ to detect CHD among Bangladeshi population. It addresses the forth research question:

- What is the utility of the Rose Angina Questionnaire (RAQ) for detecting CHD among Bangladeshi adults?

It describes the accuracy of the RAQ for detecting CHD by comparing with the diagnoses made by the cardiologists.

Chapter 7 and 8 are additional chapters, which describe the methods and results of this research in a more detailed way, which are not included in the manuscripts.

Chapter 9 summarizes the entire study findings according to the study objectives. It also addresses the strengths and limitations of this study. Finally, recommendations are proposed based on the findings of this PhD research.

Appendices include the study questionnaire both in English and Bengali, and ethics approvals.
CHAPTER 2

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

This chapter presents the manuscript of the systematic review of literature regarding the association between SLT use and CHD. This manuscript is accepted by *Journal of Public Health and Epidemiology* on 15th November 2011:

Rahman MA, Mahmood MA, Spurrier N, Rahman M, Leeder S. A systematic review of epidemiological studies on the association between smokeless tobacco use and coronary heart disease.

Although the original manuscript was formatted according to the specific journal instruction, I have followed a consistent reference style throughout the entire thesis and the reference numbers are also chronologically arranged from the beginning to the end of this thesis. In addition, the table and figure numbers are also not based on each manuscript separately; rather they are sequenced chronologically in this thesis.

Rationale for developing this manuscript

There are inconsistent results regarding the association between SLT use and CHD in the published studies. The constituents and usage patterns of SLT products are different between Western and South Asian settings. Therefore, results from Western countries cannot be easily applied to South Asian countries. In addition, studies from South Asia which explore this association are also very limited. The earlier systematic reviews on the association between SLT use and CHD included either Western studies or Asian studies only. There is no comprehensive summary to include both Western and Asian studies. Therefore, this manuscript summarizes the currently available evidence both from Western and Asian countries; identifies strengths and limitations of previous studies and through this process will explore the scope for conducting further studies, particularly in South Asia.
Rationale for choosing *Journal of Public Health and Epidemiology*

Journal of Public Health and Epidemiology (JPHE) is an open access peer-reviewed journal that provides a rapid publication (monthly) of public health articles\(^9^9\). It includes articles from all areas of public health research and the articles are published freely online to attract a wide range of audience. Considering the benefit of rapid and widely accessible publication option, JPHE was selected for this particular manuscript.

**Authors’ contributions**

MAR, NS and MAM discussed and agreed on the search terms required and the approach to the literature search. MAR undertook the literature search and reviewed all publications systematically using the set criteria. MAR reviewed the search results three times before confirming the results. MAR also graded the quality of each selected studies using the Cochrane guideline. MAR prepared the draft manuscript. NS, MAM, MR, SL reviewed drafts of the manuscript, provided feedback and incorporated their inputs. All of the authors read and approved the final version of the manuscript.
Statement of authorship

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

Journal of Public Health and Epidemiology (Accepted on November 15, 2011)

Muhammad Aziz Rahman (candidate)
Discussed with Nicola Spurrier and Mohammad Afzal Mahmood about the search terms required and agreed with the approach to the literature search. Undertook the literature search and reviewed all publications systematically using the set criteria. Reviewed the search results three times before confirming the results and graded the quality of each selected studies using the Cochrane guideline. Prepared the draft manuscript, reviewed based on co-authors’ inputs, submitted to the journal, and acted as a corresponding author.

Signed……………………………………………………………………… Date…………………………

Mohammad Afzal Mahmood
My contribution to this paper involved: Discussed and agreed with the search terms required and the approach to the literature search. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed……………………………………………………………………… Date…………………………
Nicola Spurrier
My contribution to this paper involved: Discussed and agreed with the search terms required and the approach to the literature search. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed............................................................................. Date....................................

Mahmudur Rahman
My contribution to this paper involved: Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

(Signature is included in the appendix VI)

Stephen Leeder
My contribution to this paper involved: Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

(Signature is included in the appendix VI)
A systematic review of epidemiological studies on the association between smokeless tobacco use and coronary heart disease

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Abstract

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 27th 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, four in the USA, one in India, one in Bangladesh, and one study was multi-centric involving 52 countries. Twelve studies included men only 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. The types of SLT products and their usage pattern in South Asia are different from that of Western settings. Therefore, the evidence from Western countries cannot be extrapolated to South Asian settings.

Keywords
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” \(^1\). 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 raw form and others as commercial products. While SLT use has spread to many countries in recent years, SLT has been used by the South American and South Asian people for thousands of years \(^2\). SLT is commonly used in many countries of Europe, America, Africa, and in Asian countries such as India, Pakistan and Bangladesh \(^1\). The use of SLT varies by age, sex, ethnicity and socioeconomic status, both within and among countries \(^4\).

Coronary heart disease (CHD), which accounted for more than seven million deaths in 2004, is the leading cause of mortality worldwide \(^5\). Among the risk factors of CHD, tobacco use is the second most important following hypertension \(^6\). According to the World Health Organization (WHO), tobacco is the most important preventable cause of death \(^7\). It is projected that the number of tobacco-attributable deaths will increase from 5.4 million in 2004 to 8.3 million in 2030 \(^5\). Of these 5.4 million deaths, 0.9 million deaths were due to CHD caused by tobacco use in 2004 \(^7\).

The association between smoking and CHD is well established, but the association between SLT use and CHD is in dispute \(^100, 101\). Most reviews of the epidemiological studies on SLT use and CHD have included Swedish studies only \(^9, 10, 102, 103\), or both Swedish and US studies \(^11, 12\). Meta-analysis of these Western studies did not find a
significant positive association between current SLT use and CHD \(^{11, 12}\). The result was similar when Swedish and US studies were analyzed separately. However, there was a significant positive association when only fatal CHD was considered (RR 1.17, 95% CI 1.09-1.25) \(^{12}\). On the other hand, a review published in 2010, which included eight Asian studies but excluded Western studies, found a significant association between use of chewed products and CHD (RR 1.27, 95 CI 1.02-1.52); chewed products included betel chewing with or without tobacco \(^{63}\). However, when analyses were confined to three South Asian studies, the association was not significant statistically (RR 1.64, 95% CI 0.60-2.68) \(^{63}\).

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 \(^{59, 104}\). Over 250 million people, constituting 17% of the total population of the WHO South-East Asia region, use SLT products \(^1\). In South Asian countries, while smoking by women is not supported by traditional values, SLT use does not have any such stigma \(^{59}\). Therefore, prevalence of SLT use is high among women in this region \(^{105}\) unlike the Western countries. In contrast, prevalence of CHD is the highest among South Asian people compared to other parts of the world, due to behavioural factors and genetic predisposition \(^{106}\). While studies from Taiwan reported a significant positive association between betel-quid chewing and CHD \(^{107-109}\), studies exploring the association between SLT use and CHD within the South Asian context are very limited. We considered only CHD for our review, as CHD is the most important preventable cardiovascular diseases (CVD) \(^{106}\). Furthermore, South Asian people have an early onset of CHD and die prematurely due to CHD compared to other
Caucasians\textsuperscript{110}. 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**

MAR, NS and MAM discussed and agreed on the search terms required and the approach to the literature search. MAR undertook the literature search and reviewed all publications systematically using set criteria. MAR reviewed the search results three times before confirming the results. We followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines\textsuperscript{111}. We conducted a literature search in the manner recommended by The Cochrane Collaboration\textsuperscript{112} and Bown et al.\textsuperscript{113}. We selected SLT use as the main exposure variable and CHD as the main outcome variable for this review. Our focus was to identify those studies reporting CHD as the outcome, not the risk factors for CHD (blood pressure, body mass index, and lipid profile). In accordance with other studies, PubMed and ISI Web of Science were selected as the primary databases for this review\textsuperscript{11, 12, 63}. Inclusion criteria were English language and data published until 27th 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] OR Smokeless tobacco*[tiab] OR chewing tobacco*[tiab] OR

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. Figure 1 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.
Figure 1: Search strategy for selection of epidemiological studies exploring the association between coronary heart disease and smokeless tobacco use.
Then searches were extended to EMBASE and The Cochrane Library, which are considered the richest databases along with PubMed\textsuperscript{112,113}. 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\textsuperscript{[mh]} OR India\textsuperscript{[tiab]} OR Pakistan\textsuperscript{[tiab]} OR Bangladesh\textsuperscript{[tiab]} OR South Asia\textsuperscript{[tiab]}. In addition, local databases of Bangladesh, India and Pakistan were also reviewed. These included the WHO Bangladesh publications, Bangladesh Journals Online, ICDDR\textsuperscript{B} 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\textsuperscript{107-109,114,115}, 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). 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 (Figure 1). 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 \(^{68, 81, 83, 92, 116-121}\), six were case-control studies \(^{13, 14, 19, 80, 122, 123}\) and two were cross-sectional studies \(^{124, 125}\). Studies were conducted mainly in Sweden (n=11). Swedish studies concentrated on the use of snuff (n=8). Three studies used South Asian SLT products, while only two studies were conducted in South Asian regions (India and Bangladesh) \(^{19, 83}\). The third study was global, INTERHEART study, which included SLT products from 52 countries including few South Asian countries \(^{80}\). 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 reporting of SLT use was much lower among women. The Swedish studies focused on snuff use (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 (Figure 2).

Nine studies reported a statistically significant positive association between SLT use and CHD 19, 68, 80, 83, 116, 118, 121, 124, 125, and nine studies failed to find a significant association 13, 14, 81, 92, 117, 119, 120, 122, 123. Among those nine studies showing positive association, four studies reported a significant association among a subset of study participants 83, 118, 124, 125. One Swedish study reported a significant positive association between SLT use and fatal CHD, but did not find an association for non-fatal CHD 118. The Indian study reported a significant positive association between SLT use and fatal CHD among women (OR 1.25, 95% CI 1.05-1.49), but did not find an association among men (OR 0.94, 95% CI 0.83-1.06) 83. Similarly, the US study reported a significant positive association between SLT use and fatal CHD among women (OR 1.25, 95% CI 1.05-1.49), but did not find an association among men 125. The remaining study reported a significant association between SLT use and non-fatal CHD among older men (56-65 years), but did not find a significant association among younger men (46-55 years) 124. Three studies used SLT products from South Asia and reported a significant positive association between SLT use and CHD 19, 80, 83.
Figure 2: Characteristics of the selected epidemiological studies exploring the association between coronary heart disease and smokeless tobacco use
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 \(^{116, 118, 124}\). One cross-sectional study based on the Swedish construction worker study reported a significant positive association between SLT use and non-fatal CVD in general \(^{124}\). However, the study reporting the cohort analyses of that research showed a significant positive association between SLT use and fatal CHD \(^{116}\). The result did not change when further follow-up was reported by Hergens et al. with that cohort \(^{118}\).

Four Swedish cohort studies failed to find a statistically significant association between SLT use and CHD \(^{81, 117, 119, 120}\). One study also did not find any association with frequency and duration of SLT use and CHD \(^{119}\). Another four Swedish case-control studies did not find any statistically significant association between SLT use and CHD \(^{13, 14, 122, 123}\). Subgroup analyses based on age in one study were not contributory, although this study did not consider the known risk factors for CHD as potential confounders during analyses \(^{122}\). One study also examined whether there was a dose-response relationship between SLT use and CHD, but none was detected \(^{122}\). 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 \(^{68, 121, 125}\). Although the US Cancer Prevention Study found a significant association between SLT use and fatal CHD, frequency and duration of SLT use were not associated with CHD \(^{68}\). In addition, the study
population included men only. The other two studies did not report results for CHD or stroke separately. One of them reported a significant association among women only. The only US study 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 reported a significant association for fatal CHD among women only, not among men. Although the study reported the association between different Indian SLT use and CHD mortality along with other tobacco-related mortality, the authors acknowledged limitations in ascertaining the accurate causes of deaths for all participants. 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.

On the other hand, although the Bangladeshi study 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 1.1-4.5). 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 1.2-16.7); the confidence interval was wide due to small number of participants (n=83) \(^{19}\). 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 \(^{19}\). However, unlike other studies, this study included younger population (20-49 years) as the study participants (Table 2).

**Analysis of the Global study**

The global INTERHEART study reported a significant positive association between chewing tobacco and CHD \(^{80}\). 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 \(^{80}\). 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 to clarify in future studies because some studies have reported a significant positive association between betel chewing alone and CHD \(^{107-109, 114, 115}\). 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 \(^{107-109, 114, 115}\).

**Quality level of the selected studies**

We used the Cochrane GRADE approach to rate the quality of the included studies \(^{126}\). Grading was undertaken by MAR. 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 126. Three of the studies in this review could be upgraded to ‘moderate’, whilst no other studies in the review required downgrading 80, 118, 119.
Table 1: Summary of the Western studies exploring the association between coronary heart disease (CHD) and smokeless tobacco (SLT) use

<table>
<thead>
<tr>
<th>Source</th>
<th>Study location (country)</th>
<th>Types of study</th>
<th>Recruitment &amp; Follow-up year</th>
<th>Sample size</th>
<th>Gender</th>
<th>Age (yrs) at baseline</th>
<th>Types of SLT use as exposure</th>
<th>Types of CHD as outcome (only CHD data were considered)</th>
<th>Results presented in this table, based on the comparison groups</th>
<th>Key findings regarding association between SLT use and CHD</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolinder et al. (1992)</td>
<td>Sweden</td>
<td>Cross-sectional</td>
<td>1971-74</td>
<td>97586</td>
<td>Men</td>
<td>16-65</td>
<td>SLT (types of SLT not defined)</td>
<td>Non-fatal CVD</td>
<td>Current SLT users vs. never tobacco users, (a)</td>
<td>Age 46-55yrs: OR = 1.6 (95%CI 0.7-3.5); Age 56-65yrs: OR = 1.5 (95%CI 1.1-1.9)</td>
<td>Results for men only, no separate reports for CHD or stroke, possibility of healthy worker effects on the association</td>
</tr>
<tr>
<td>Bolinder et al. (1994)</td>
<td>Sweden</td>
<td>Cohort</td>
<td>1971-74, 1974-85</td>
<td>84781</td>
<td>Men</td>
<td>16-65</td>
<td>SLT (types of SLT not defined)</td>
<td>Fatal CHD</td>
<td>Current SLT users vs. never tobacco users, (b)</td>
<td>Age 35-54yrs: RR = 2.0 (95%CI 1.4-2.9); Age 55-65yrs: RR = 1.2 (95%CI 1.0-1.5)</td>
<td>Results for men only, SLT use data old</td>
</tr>
<tr>
<td>Hergens et al. (2007)</td>
<td>Sweden</td>
<td>Cohort</td>
<td>1978-93, 1978-2004</td>
<td>118395</td>
<td>Men</td>
<td>16-65</td>
<td>Snuff</td>
<td>Fatal and non-fatal CHD</td>
<td>Current snuff users (never smoked) vs. never tobacco users, (c)</td>
<td>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)</td>
<td>Results for men only</td>
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</tbody>
</table>

Positive association between SLT use and CHD
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Type</th>
<th>Year Range</th>
<th>Sample Size</th>
<th>Gender</th>
<th>Age</th>
<th>SLT Form</th>
<th>Outcome</th>
<th>Comparison</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Results Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henley et al. (2005)</td>
<td>USA</td>
<td>Cohort</td>
<td>1959, 1959-72</td>
<td>77407</td>
<td>Men</td>
<td>≥30</td>
<td>SLT (Chewing tobacco, snuff)</td>
<td>Fatal CHD</td>
<td>Current SLT users vs. never tobacco users, (d)</td>
<td>HR = 1.12 (95%CI 1.03-1.21)</td>
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<td></td>
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<td>1982, 1982-2000</td>
<td>113970</td>
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<td>HR = 1.26 (95%CI 1.08-1.47); Frequency and duration of SLT use were not associated with CHD</td>
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<tr>
<td>Yatsuya et al. (2010)</td>
<td>USA</td>
<td>Cohort</td>
<td>1987-89, 1987-2008</td>
<td>14498</td>
<td>Both</td>
<td>45-64</td>
<td>SLT (types of SLT not defined)</td>
<td>Fatal and non-fatal CVD</td>
<td>Current SLT users (never smoked) vs. never tobacco users, (e)</td>
<td>HR = 1.31 (95% CI 1.06-1.61)</td>
<td></td>
<td>No separate reports for CHD or stroke</td>
</tr>
<tr>
<td>Nasir et al. (2010)</td>
<td>USA</td>
<td>Cross-sectional (Surveillance data analyses)</td>
<td>1999-2001</td>
<td>10332</td>
<td>Both</td>
<td>18-70+</td>
<td>SLT (types of SLT not defined)</td>
<td>Non-fatal CVD</td>
<td>Current SLT users vs. never tobacco users, (f)</td>
<td>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)</td>
<td></td>
<td>No separate reports for CHD or stroke</td>
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</table>

**No positive association between SLT use and CHD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Type</th>
<th>Year Range</th>
<th>Sample Size</th>
<th>Gender</th>
<th>Age</th>
<th>SLT Form</th>
<th>Outcome</th>
<th>Comparison</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Results Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johansson et al. (2005)</td>
<td>Sweden</td>
<td>Cohort</td>
<td>1988-89, 1988-2000</td>
<td>3120</td>
<td>Men</td>
<td>30-74</td>
<td>Snuff</td>
<td>Fatal and non-fatal CHD</td>
<td>Current snuff users (never smoked) vs. non-current snuff users, (g)</td>
<td>HR = 1.41 (0.61-3.28)</td>
<td>Results for men only, SLT use data collected at baseline only</td>
<td></td>
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<tr>
<td>Haglund et al. (2007)</td>
<td>Sweden</td>
<td>Cohort</td>
<td>1988-89, 1988-2003</td>
<td>5002</td>
<td>Men</td>
<td>16-74</td>
<td>Snuff</td>
<td>Fatal and non-fatal CHD</td>
<td>Current snuff users vs. never tobacco users, (h)</td>
<td>Non-fatal CHD: IRR = 0.77 (95%CI 0.51-1.15); Fatal CHD: MRR = 1.15 (95%CI 0.54-2.41)</td>
<td>Results for men only</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>Time Period</td>
<td>Sample Size</td>
<td>Gender</td>
<td>Age Range</td>
<td>Product</td>
<td>Status</td>
<td>Etiology</td>
<td>Comparison</td>
<td>Results</td>
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<tr>
<td>Hansson et al. (2009)</td>
<td>Sweden</td>
<td>Cohort</td>
<td>1998-2002, 1998-2005</td>
<td>16642</td>
<td>Men</td>
<td>40-72</td>
<td>Snus</td>
<td>Fatal and non-fatal CHD</td>
<td>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</td>
<td>Results for twin men only</td>
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<tr>
<td>Janzon et al. (2009)</td>
<td>Sweden</td>
<td>Cohort</td>
<td>1991-96, 1991-2004</td>
<td>27227</td>
<td>Men</td>
<td>45-73</td>
<td>Snuff</td>
<td>Fatal and non-fatal CHD</td>
<td>Current snuff users (never smoked) vs. never tobacco users, (j) RR = 0.75 (95%CI 0.3-1.8)</td>
<td>Results for men only</td>
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<tr>
<td>Huhtasaari et al. (1992)</td>
<td>Sweden</td>
<td>Case-control</td>
<td>1989-91</td>
<td>1174</td>
<td>Men</td>
<td>35-64</td>
<td>Snuff</td>
<td>Fatal &amp; non-fatal CHD. Cases were selected from hospital records and death registers; controls were selected from population registers</td>
<td>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</td>
<td>Results for men only, known potential confounders for CHD were not considered, never tobacco users included former smokers/snuffers as well as occasional smokers/snuffers during analysis</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>Time Period</td>
<td>ID</td>
<td>Age</td>
<td>Gender</td>
<td>Tobacco Use</td>
<td>Comparisons</td>
<td>Results for men only</td>
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<tr>
<td>Huhtasaari et al. (1999)</td>
<td>Sweden</td>
<td>Case-control</td>
<td>1991-93</td>
<td>1374 (687 cases &amp; matched controls)</td>
<td>Men</td>
<td>25-64</td>
<td>Snuff</td>
<td>Fatal &amp; non-fatal CHD. Cases were selected from hospital records and death registers; controls were selected from population registers</td>
<td>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)</td>
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<tr>
<td>Hergens et al. (2005)</td>
<td>Sweden</td>
<td>Case-control</td>
<td>1992-94</td>
<td>3242 (1432 cases &amp; matched controls)</td>
<td>Men</td>
<td>45-70</td>
<td>Snuff</td>
<td>Fatal and non-fatal CHD. Cases were selected from hospitals and mortality register, controls were selected from communities</td>
<td>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)</td>
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</table>

Results for men only
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Years</th>
<th>Study Population</th>
<th>Age Range</th>
<th>Substances Used</th>
<th>Analysis</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wennberg et al. (2007)</td>
<td>Sweden</td>
<td>Case-control</td>
<td>1985-89</td>
<td>2323 (525 cases &amp; 1798 matched controls)</td>
<td>Men 30-60 Snuff</td>
<td>Fatal and non-fatal CHD, Cases &amp; controls selected both from hospitals and communities</td>
<td>Current snuff users (Never smoked) vs. never tobacco users, (n)</td>
<td>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)</td>
</tr>
<tr>
<td>Accortt et al. (2002)</td>
<td>USA</td>
<td>Cohort</td>
<td>1971-75, 1971-92</td>
<td>12451</td>
<td>Both 45-75 SLT (types of SLT not defined)</td>
<td></td>
<td>Fatal CHD</td>
<td>Ever SLT users (never smoked) vs. never tobacco users, (n)</td>
</tr>
</tbody>
</table>

**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.
| Source                  | Study location (country) | Types of study | Recruitment & 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 et al. (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

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.
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. The results also differed according to age and gender in some studies as detailed below.

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 46-55 years, the Swedish cohort study reported a significant association among young as well as older people. However, as the participants of those studies were recruited from a volunteer health check-up group, the possibility of healthy worker effects on the non-association in the cross-sectional study cannot be ruled out. In addition, another Swedish case-control study did not report any significant association across different age groups. 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. 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 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. Two of them reported an increased risk of CHD with SLT use among women compared to men. Similarly, the Indian cohort study and the Bangladeshi case-control study reported a significant positive association among women only. Although prevalence of SLT use is similar among women and men in South Asia, 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. Therefore, it is presumed that those Western studies would not be generalisable 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. However, SLT products are also not same across all South Asian countries, 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\textsuperscript{68,81,116} 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\textsuperscript{12,129}. If the SLT users switched and/or used both tobacco products, the positive association in those cohort studies might not be true. In the 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, which did not find a significant positive association between SLT use and CHD, included partial controls from hospital settings\textsuperscript{14}. 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. There was no separate report for hospital controls or community controls\textsuperscript{14}. Another case-control study did not consider the potential confounders for CHD during reporting the non-association between SLT use and CHD\textsuperscript{122}. 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\textsuperscript{83}. 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\textsuperscript{130}, SLT users are generally from lower SES in South Asian countries\textsuperscript{59}, 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 multivariate analyses.
Limitations of this review include the possibility of excluding relevant studies in this review, as could happen to any systematic review. 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 and Asian studies only. Our objective was to summarise the currently available evidence, consider plausible reasons for the different findings and through this process explore the rational 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.

**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.
CHAPTER 3

Is there any association between use of smokeless tobacco products and coronary heart disease in Bangladesh?
Chapter outline

This chapter presents the manuscript that describes the case-control study exploring the association between SLT use and CHD among non-smoking Bangladeshi adults. It addresses the first research question:

- Is there any association between SLT use and CHD among non-smoking Bangladeshi adult population?

It describes the descriptive as well as analytic results of the study. Cases are compared with community controls, hospital controls, and both control groups during analyses. Analyses are conducted for current users, quitters or ever users of SLT products as well as using never-smokers, ex-smokers, and both groups separately. In addition, further analyses are conducted using the re-classification of cases and controls by the RAQ to explore the association between SLT use and CHD. This manuscript was submitted to *PLoS One* journal and based on reviewers’ comments, the revised version has been submitted on 28th November 2011:

Rahman MA, Spurrier N, Mahmood MA, Rahman M, Choudhury SR, Leeder S. Is there any association between use of smokeless tobacco products and coronary heart disease in Bangladesh?

Although the original manuscript was formatted according to the specific journal instruction, I have followed a consistent reference style throughout the entire thesis and the reference numbers are also chronologically arranged from the beginning to the end of this thesis. In addition, the table and figure numbers are also not based on each manuscript separately; rather they are sequenced chronologically in this thesis.
Rationale for developing this manuscript

There are inconsistent results regarding the association between SLT use and CHD in the published studies. The constituents and usage patterns of SLT products are different between Western and South Asian settings. Therefore, results from Western countries cannot be easily applied to South Asian countries. In addition, studies from South Asia in exploring this association are also very limited. Therefore, this manuscript explores the association between SLT use and CHD among non-smoking Bangladeshi adults.

Rationale for choosing *PLoS One*

*PLoS One* is an open access peer-reviewed journal that publishes a wide range of quality research on different public health issues \(^{131}\). It is also unique in providing post-publication tools to indicate quality and impact of each published article. Considering all of these benefits, *PLoS One* was selected for this particular manuscript.

Authors’ contributions

MAR, NS and MAM discussed the need for and the overall constructs and concepts of the study design. MR, SRC and SL also contributed in the design of the study. MR provided support for the field activities in Bangladesh. MAR collected data from field sites, analysed and interpreted data, and finally, prepared the draft manuscript. NS, MAM, MR, SRC and SL reviewed drafts of the manuscript, provided feedback and incorporated their inputs. All of the authors read and approved the final version of the manuscript.
Statement of authorship

Is there any association between use of smokeless tobacco products and coronary heart disease in Bangladesh?

*PLoS One* (Revision submitted on November 28, 2011)

**Muhammad Aziz Rahman (candidate)**
Discussed the need for and the overall constructs and concepts of the study design with Nicola Spurrier and Mohammad Afzal Mahmood. Collected data from field sites, analysed and interpreted data. Prepared the draft manuscript, reviewed based on co-authors’ inputs, submitted to the journal, and acted as a corresponding author.

Signed……………………………………………………………….. Date………………………………

**Nicola Spurrier**
My contribution to this paper involved: Discussed the need for and the overall constructs and concepts of the study design. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed……………………………………………………………….. Date………………………………

**Mohammad Afzal Mahmood**
My contribution to this paper involved: Discussed the need for and the overall constructs and concepts of the study design. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed……………………………………………………………….. Date………………………………
Mahmudur Rahman
My contribution to this paper involved: Contributed in the design and provided support for the field activities in Bangladesh. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

(Signature is included in the appendix VI)

Sohel Reza Choudhury
My contribution to this paper involved: Contributed in the design and provided support for the field activities in Bangladesh. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

(Signature is included in the appendix VI)

Stephen Leeder
My contribution to this paper involved: Contributed in the design of the study. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

(Signature is included in the appendix VI)
Is there any association between use of different smokeless tobacco products and coronary heart disease in Bangladesh?

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Abstract

Background
Most epidemiological studies exploring the association between smokeless tobacco (SLT) use and coronary heart disease (CHD) have been in Western populations, and have focused on SLT products used in those countries. Few studies come from South Asian countries.

Objective
To determine the association between SLT use and CHD among non-smoking adults in Bangladesh.

Methods
A matched case-control study of non-smoking Bangladeshi adults aged 40-75 years was conducted in 2010. Incident cases of CHD were selected from two cardiac hospitals. Community controls, matched to CHD cases, were selected from neighbourhoods, and hospital controls were selected from outpatient departments of the same hospitals. The Rose Angina Questionnaire (RAQ) was also used to re-classify cases and controls.

Results
The study enrolled 302 cases, 1208 community controls and 302 hospital controls. Current use was higher among community controls (38%) compared to cases (33%) and hospital controls (32%). Current use of SLT was not significantly associated with an increased risk of CHD when community controls were used (adjusted OR 0.87, 95% CI 0.63-1.19), or when hospital controls were used (adjusted OR 1.00, 95% CI 0.63-1.60), or when both control groups were combined (adjusted OR 1.00, 95% CI 0.74-1.34). Risk of CHD did not increase with use of individual types except gul, frequency, duration, past use of SLT products, or using the RAQ to re-classify cases
and controls. There was a significant association between gul use and CHD when both controls were combined (adjusted OR 2.93, 95% CI 1.28-6.70).

**Conclusions**

There was no statistically significant association between SLT use in general and CHD among non-smoking adults in Bangladesh. Further research on the association between gul use and CHD in Bangladesh along with SLT use and CHD in other parts of the subcontinent where SLT products may differ will guide public health policy and interventions which focus on SLT-related diseases.

**Keywords**

Smokeless tobacco, chewing tobacco, oral tobacco, coronary heart disease, cardiovascular disease, Bangladesh
Introduction

Smokeless tobacco (SLT), commonly used in many countries ¹, is associated with various health effects. Epidemiological studies have consistently reported a significant positive association between SLT use and cancers of various organs such as oropharynx, oesophagus, stomach, pancreas, and lungs amongst others ¹⁰⁰. Studies also report a positive association between SLT use and oral diseases, dental diseases, hypertension, diabetes, poor reproductive outcomes, addiction, and all-cause mortality ¹⁰⁰.

A number of studies have also reported a significant positive association between SLT use and risk factors for cardiovascular diseases (CVD) such as raised blood pressure and a less healthy lipid profile ⁷⁸, ⁷⁹. However, the results of epidemiological studies assessing the association between SLT use and CHD, stroke or CVD in general are inconsistent ¹². While several cohort ⁶⁸, ¹¹⁶, ¹²¹ and case-control studies ¹⁹, ⁸⁰ have reported a significant positive association, other sufficiently powered cohort ⁹², ¹¹⁹, ¹²⁰ and case-control studies ¹³, ¹²², ¹²³ have not reported such an association. Some studies undertaken in Western countries (Sweden and USA) have found an association ⁶⁸, ¹¹⁶, ¹²¹ whereas others have not ⁹², ¹¹⁹, ¹²⁰. South Asian SLT products differ from Western products in terms of constituents, nicotine concentration, manufacturing, and storage methods ³⁰. Usage patterns are also likely to be different and may explain the different results from studies conducted across various settings ⁹.

There are a limited number of studies from South Asian countries focusing on the association between SLT use and CHD. One Indian cohort study ⁸³ and another
multinational case-control study (INTERHEART) involving 52 countries \(^{80}\) reported a significant positive association and did include South Asian SLT products. However, betel-quid and areca-nut were included as SLT products although these products do not contain tobacco. In addition, the INTERHEART study did not report results separately for any South Asian country \(^{80}\). A small number of Taiwanese studies \(^{107-109}\) found a significant positive association between betel-quid chewing and CHD, but not with SLT use. The only study which has included SLT products available in Bangladesh \(^{19}\), all of which contain tobacco, showed a significant positive association between SLT use and CHD (adjusted odds ratio 2.2, 95% confidence interval 1.1-4.5) and was conducted by the first author.

As a developing country in South-East Asia, Bangladesh has high rates of smoking and SLT usage. Half of those aged \(\geq 15\) years (43\%≈41 million) use tobacco in some form \(^{16}\). The prevalence of SLT use has been estimated as 27\% with similar rates in men (26\%) and women (28\%), but more prevalent in rural areas (29\%) compared to urban areas (23\%) \(^{16}\). Whilst a number of studies in Bangladesh have examined tobacco use \(^{22,28,29}\), the only study focusing on the SLT-CHD association \(^{19}\) had a small sample size (n=207), included smokers, and recruited cases and controls from a hospital setting.

Betel-leaf (paan) chewing is a cultural tradition of Bangladeshi people extending back many centuries \(^{90}\). In Bangladesh, as in other countries of the subcontinent, people chew betel-leaf with/without SLT products routinely at various cultural and social events \(^{59}\). As there has been no large systematic study conducted in the Subcontinent, and the results of studies conducted in Western settings are
inconsistent, we conducted the current study to determine whether there was any association between SLT use and CHD among non-smoking adults in Bangladesh.

**Methods**

**Ethics statement**

Informed written consent was requested from each participant in the prescribed consent form. Privacy and confidentiality were maintained regarding the collected data. The protocol including the information sheet and consent forms for this project was approved by The University of Adelaide Human Research Ethics Committee, Australia (H-117-2009) and the local ethics committee of Bangladesh Medical Research Council, Bangladesh (BMRC/NREC/2007-2010/125).

**Study design and study sites**

A matched case-control study was conducted in 2010. Data were collected through structured interviews. CHD cases were recruited from inpatient facilities of the National Institute of Cardiovascular Diseases (NICVD) and the National Heart Foundation Hospital and Research Institute (NHFH&RI), Dhaka, Bangladesh. Both hospitals are accessible to people from all socio-economic groups as minimal costs are associated with cardiac care. During the recruitment period, approximately 550 patients per day were admitted to the six cardiovascular units of the NICVD and 110 patients per day were admitted to the seven cardiovascular units of NHFH&RI. Four hundred patients per day and 75 patients per day attended the outpatient facilities of the NICVD and the NHFH&RI respectively. Both hospital controls and community controls were selected in this study in order to assess whether results differed according to the use of different control groups. Hospital controls were recruited
amongst individuals attending cardiac outpatient facilities of the NICVD and the
NHFH&RI, while community controls were recruited from the neighbourhood
households of CHD cases within Dhaka City Corporation (DCC) areas.

Study population
Inclusion criteria were: age 40-75 years, non-smoker, residence within DCC areas,
and well enough to undertake a 20 minute interview. Non-smokers were defined as
either (i) never smokers or (ii) ex-smokers who had not smoked a single puff in the
past 10 years. This was because most studies suggest that the maximum reduction
in CHD risk occurs within 4-14 years following smoking cessation\textsuperscript{132-134}, and from a
practical perspective, only including never smokers would have been difficult.

CHD cases
CHD patients admitted to the two hospitals and diagnosed as incident cases of CHD
(diagnosis for the first time within the preceding twelve months) by hospital
cardiologists, were selected as cases. Cardiologists diagnosed CHD cases based on
clinical judgment (a combination of classical symptoms with positive results from
electrocardiogram, cardiac enzymes, exercise tolerance test, or coronary artery
angiogram). Either angina and/or myocardial infarction were included in the definition
of CHD for the purpose of this study.

Community controls
Neighbourhood residents of the CHD cases who had no self-reported cardiac
disease, were selected as community controls. Control subjects were matched by
age (±5 years), sex and socio-economic status (SES) to the corresponding case. If a
suitable control subject could not be located in a suburb of the CHD case, the next adjacent suburb was used (this happened in 28% of cases).

**Hospital controls**

Hospital controls were also used in this study. This was to determine whether any systematic bias existed in the use of hospital controls as is often postulated in the literature\(^ {135, 136} \). These additional analyses are not the focus of this particular article and will be presented elsewhere. Patients, who attended cardiac outpatient facilities of the same hospitals and were diagnosed as not suffering from CHD by hospital cardiologists, were selected as hospital controls. It is to be noted that unlike a developed country, many individuals with symptoms of chest pain or breathlessness attend outpatient facilities of cardiac hospitals for screening of cardiac disease; either self-referred or referred by a general practitioner in Bangladesh. About two-thirds (64%) of the hospital controls were selected from the hypertension clinic of NHFH&RI, which was the only available source of recruiting controls from that hospital. This poses a risk of potential bias because SLT use is known to be associated with hypertension\(^ 78 \). Diagnoses for these patients included hypertension (62%), non-specific chest pain (48%), and gastric hyper-acidity (13%). Some patients were not assigned a diagnosis, and symptoms of palpitation (10%) or breathlessness (8%) were given in the case-notes. Each hospital control was matched with a corresponding case by age (±5 years) and sex.
Cases and controls re-classified by the Rose Angina Questionnaire (RAQ)

In addition to our study definition of cases and controls, we also used the RAQ\textsuperscript{97} to re-classify study participants into RAQ cases and RAQ controls. Individuals responding affirmatively to the RAQ were re-classified as RAQ cases and the negative responders were re-classified as RAQ controls as shown in Figure 3. It is to be noted that the RAQ cases and the RAQ controls were not matched.

Sample size

Sample size was calculated using Epi-info version 3.5.1. With 95% confidence intervals, 80% power, a control: case ratio of 4:1, a correlation for matched design of 0.1, an expected frequency of SLT use among controls of 25%\textsuperscript{22}, and a clinically significant odds ratio considered to be 1.5\textsuperscript{19,83}, 302 cases and 1,208 controls were required for this study. Additionally, one hospital control was selected for each case (302 additional controls).

Study tool

A structured interview was conducted to measure exposure and confounding variables. Initially, a screening questionnaire was used to select eligible cases and controls. This included information on age, residence, smoking and heart disease status. Once informed consent was obtained, participants were asked a range of questions covering socio-demographic information, a detailed history of SLT use, and other known risk factors for CHD. Socio-demographic information included age, gender, marital status, highest level of education achieved, primary occupation and monthly house-rent as a proxy to socio-economic status.
Betel-leaf or areca-nut alone was not included as a SLT product, as they do not contain tobacco. If a respondent used any SLT product with/without betel-leaf or areca-nut in the last twelve months, he/she was categorized as a current SLT user. If a respondent ceased using SLT products for at least last twelve months, he/she was categorized as a past SLT user. If a respondent was not using any SLT product currently or in the past, he/she was categorized as never a tobacco user (as they were also non-smokers according to the participant selection criteria). Using frequency and duration of SLT use, we categorized frequency into light use (less than once a day) and heavy use (at least once a day), duration into short duration (<10 years) and long duration (>10 years), and quit duration into short-term quit (2-10 years) and long-term quit (>10 years).

Information on known risk factors for CHD included self-reported history of hypertension, diabetes, family history of heart disease, level of physical activity, use of hormonal contraceptives for women, exposure to indoor passive smoking, and occurrence of acute psycho-social events within last one year.

**Data collection**

Reasons for non-participation were documented. If participants asked whether SLT could cause any health effect, interviewers only provided this information at the completion of the interview. Categorization of CHD cases according to the case definition and the RAQ was undertaken by the first author and selection of the majority of controls was undertaken in his presence. The first author trained the interviewers and undertook regular supervision of all data collection activities. In
addition, the first author re-interviewed 4 cases (1%), 24 community controls (2%) and 6 hospital controls (2%) as a means of quality control of data collection.

Figure 3: Re-classification and analyses of cases and controls using the Rose Angina Questionnaire (RAQ)
Laboratory analysis

To enhance interpretation of the study results, samples of SLT products most commonly used within the DCC areas, were tested for nicotine. Purchased samples of paan-masala (3 samples), jarda (1 sample), and gul (1 sample) were analysed following extraction, steam distillation and silicotungstic acid gravimetric method at the Institute of Food Science and Technology (IFST), Bangladesh Council of Scientific and Industrial Research (BCSIR). Nicotine concentration was reported in percentage by weight (% by wt.). Sada-pata, which is the natural tobacco leaf in dried form, was also used by study participants but was not tested for nicotine because of the natural variation of this product. A recent surveillance study reported nicotine concentrations in Bangladeshi sada-pata as 1.97%.

Data analysis

Analyses were performed using STATA version 10 statistical software. Initially, categorical variables were described as proportions for socio-demographic variables, SLT use, and risk factors for CHD. To determine the association between SLT use and CHD, cases and controls were compared using cross-tabulations at first. To statistically compare cases and controls, we used McNemar’s chi-squared (χ²) tests when the frequency in all of the cells of the cross-tabulation was ≥5 and Fisher’s exact test otherwise. Univariate conditional logistic regression models were fitted to determine the strength of the association between SLT use and CHD, with the effect of SLT use expressed as a matched odds ratios (ORs) with 95% confidence intervals (CIs). Then multivariate conditional logistic regression models were fitted to adjust for potential confounding variables. The most important confounder is the presence of hypertension; this is particular so with analysis using only hospital
controls. Confounding variables were identified initially using a χ2 test relating the variables to CHD. If the p-value from the χ2 test was less than 0.20 and there was no missing data for the confounder, that variable was included into the final multivariate analysis. The adjusted ORs with 95% CIs finally determined the association between SLT use and CHD in this study. To determine whether the inclusion of ex-smokers could have biased the results, analyses were conducted separately for never-smokers, ex-smokers, and combining both groups. Data were analysed separately using community controls, hospital controls, and combining both control groups. We also analysed data with all groups of re-classified cases and controls done by the RAQ to further explore the association between SLT use and CHD (Figure 3). As the RAQ cases and the RAQ controls were not matched, we used univariate and multivariate logistic regression models for these analyses.

Results

Study participants

Eligible participants included 311 hospital cases, 1293 community controls and 316 hospital controls. Nine potential hospital cases (3%), 85 potential community controls (7%), and 14 potential hospital controls (4%) did not consent to participate. Thus, the overall response rate was 94%. Results for the remaining 302 CHD cases from two cardiac hospitals, 1208 community controls and 302 hospital controls are presented in this paper.

Mean age of participants was 53 years (standard deviation ±8.5 years), 49.7% were men. Table 3 shows the distribution of different socio-demographic variables among cases and controls, and there were no significant differences in socio-demographic
variables comparing cases and controls. Amongst the 1812 participants, 1292 (71%) were never-smokers. Never-smoking status was similar between cases (203 out of 302, 67%) and either community controls (864 out of 1208, 72%) or hospital controls (225 out of 302, 75%).

**Risk factors for CHD**

Table 3 shows the distribution of risk factors for CHD among cases and controls. More than two-thirds of hospital controls (67%) were hypertensive compared to half of cases (60%) and one-third of community controls (34%). The majority of these hospital controls were selected from the hypertension clinic of one study hospital which explains this difference.

**Nicotine content of the SLT products**

Nicotine was absent in all three commercial samples of paan-masala products tested. The selected samples of *jarda* and *gul* contained 0.96% and 5.48% nicotine respectively. Therefore, our data analysis included only three types of SLT products containing nicotine: *jarda*, *sada-pata* (1.97% nicotine) and *gul*. 
Table 3: Socio-demographic and risk factor variables for coronary heart disease (CHD) among the study participants

<table>
<thead>
<tr>
<th>Socio-demographic variables</th>
<th>Total, N (%)</th>
<th>Cases, n(%)</th>
<th>Community Controls, n(%)</th>
<th>Hospital controls, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total study participants</td>
<td>1812</td>
<td>302</td>
<td>1208</td>
<td>302</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>53.0 (±8.5)</td>
<td>53.5 (±8.5)</td>
<td>53.1 (±8.5)</td>
<td>51.9 (±8.4)</td>
</tr>
<tr>
<td>Male participants</td>
<td>900 (49.7)</td>
<td>150 (49.7)</td>
<td>600 (49.7)</td>
<td>150 (49.7)</td>
</tr>
<tr>
<td>Married (and living with spouse)</td>
<td>1414 (78.0)</td>
<td>232 (76.8)</td>
<td>939 (77.8)</td>
<td>243 (80.5)</td>
</tr>
<tr>
<td>Highest level of education achieved</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>204 (11.3)</td>
<td>34 (11.3)</td>
<td>151 (12.5)</td>
<td>19 (6.3)</td>
</tr>
<tr>
<td>Can sign names</td>
<td>212 (11.7)</td>
<td>27 (8.9)</td>
<td>150 (12.4)</td>
<td>35 (11.6)</td>
</tr>
<tr>
<td>Primary</td>
<td>527 (29.1)</td>
<td>95 (31.5)</td>
<td>338 (28.0)</td>
<td>94 (31.2)</td>
</tr>
<tr>
<td>Secondary</td>
<td>239 (13.2)</td>
<td>44 (14.6)</td>
<td>153 (12.7)</td>
<td>42 (14.0)</td>
</tr>
<tr>
<td>Higher-secondary</td>
<td>197 (10.9)</td>
<td>33 (10.9)</td>
<td>116 (9.6)</td>
<td>48 (15.9)</td>
</tr>
<tr>
<td>Above higher-secondary</td>
<td>418 (23.1)</td>
<td>66 (21.9)</td>
<td>290 (24.0)</td>
<td>62 (20.6)</td>
</tr>
<tr>
<td>Primary occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Service holder</td>
<td>558 (30.8)</td>
<td>87 (28.8)</td>
<td>369 (30.6)</td>
<td>102 (33.8)</td>
</tr>
<tr>
<td>Businessmen</td>
<td>262 (14.5)</td>
<td>42 (13.9)</td>
<td>180 (14.9)</td>
<td>40 (13.2)</td>
</tr>
<tr>
<td>Housewife</td>
<td>741 (40.9)</td>
<td>126 (41.7)</td>
<td>495 (41.0)</td>
<td>120 (39.7)</td>
</tr>
<tr>
<td>Retired</td>
<td>235 (13.0)</td>
<td>47 (15.6)</td>
<td>149 (12.3)</td>
<td>39 (12.9)</td>
</tr>
<tr>
<td>Socio-economic status (SES) by monthly house-rent (HR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower SES (HR &lt;5000 BDT)</td>
<td>656 (36.2)</td>
<td>109 (36.1)</td>
<td>433 (35.8)</td>
<td>114 (37.7)</td>
</tr>
<tr>
<td>Middle SES (HR 5000-10000 BDT)</td>
<td>930 (51.3)</td>
<td>152 (50.3)</td>
<td>620 (51.3)</td>
<td>158 (52.3)</td>
</tr>
<tr>
<td>Higher SES (HR &gt;10000 BDT)</td>
<td>226 (12.5)</td>
<td>41 (13.6)</td>
<td>155 (12.8)</td>
<td>30 (9.9)</td>
</tr>
<tr>
<td>Presence of other risk factors for CHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>796 (43.9)</td>
<td>180 (59.6)</td>
<td>413 (34.2)</td>
<td>203 (67.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>446 (24.6)</td>
<td>129 (42.7)</td>
<td>244 (20.2)</td>
<td>73 (24.2)</td>
</tr>
<tr>
<td>Family history of heart disease</td>
<td>421 (23.2)</td>
<td>94 (31.5)</td>
<td>248 (21.5)</td>
<td>79 (27.2)</td>
</tr>
<tr>
<td>Undertook physical activity</td>
<td>1116 (61.6)</td>
<td>179 (59.5)</td>
<td>788 (65.3)</td>
<td>149 (50.2)</td>
</tr>
<tr>
<td>Use of hormonal contraceptives</td>
<td>60 (3.3)</td>
<td>9 (3.0)</td>
<td>41 (3.4)</td>
<td>10 (3.3)</td>
</tr>
<tr>
<td>Exposure to indoor passive smoking</td>
<td>321 (17.7)</td>
<td>58 (19.2)</td>
<td>218 (18.0)</td>
<td>45 (14.9)</td>
</tr>
<tr>
<td>Acute psycho-social stress</td>
<td>434 (24.0)</td>
<td>94 (31.1)</td>
<td>265 (21.9)</td>
<td>75 (24.8)</td>
</tr>
</tbody>
</table>

Superscripts indicate which categories show a statistically significant (p<0.05) difference using chi-squared tests between cases and controls: same letter indicates no difference, different letter indicates a difference.

a "Have you ever been told by a doctor or a health-worker that you have raised blood-pressure or hypertension?"
b "Have you ever been told by a doctor or a health-worker that you have raised blood-glucose or diabetes?"
c Physical activity included moderate to vigorous physical activity for at least 30 minutes per week which made them huff and puff (where they can still talk but can’t sing). There were three levels of physical activity: mild (1-2 times/week), moderate (3-4 times/week) and vigorous (≥5 times/week). All these three levels were combined together in this table.
d "Does anyone smoke inside the same room, where you live?"
e Such an incident that caused mental agony, sorrow, unhappiness or anxiety within last one year, like death of family members, divorce, separation, sudden job loss, unemployment, financial loss etc. Financial loss was the mostly reported event (33.6%), followed by various types of family conflict (12.4%), death of siblings (12.0%), and death of parents (10.6%).
Use of SLT products

Amongst the 1812 participants, 648 (36%) were current SLT users. Current use was higher among community controls (38%) compared to that of cases (33%) and hospital controls (32%). Quitting was more common among cases compared to either group of controls. Amongst the never-smoker participants, current use of SLT was more common among community controls (35%) than that of cases (25%) and hospital controls (30%). Amongst the ex-smoker participants, ever use, current use and quitting of SLT products were more common among cases compared to either group of controls. Table 4 shows the status of SLT use among the study participants.

Amongst the individual types of SLT products, use of jarda was more common compared to sada-pata and gul. Current use of jarda was slightly higher among community controls (26%) compared to either cases (21%) or hospital controls (24%). There was no difference between cases and controls for current use of sada-pata. Current use of gul was slightly more common among cases (5%) compared to either group of controls (2%). The majority of exclusive jarda, sada-pata or gul consumers were heavy users and long duration users. Mean duration of jarda use was 16 years (0.1-55 years), sada-pata 28 years (3-60 years), and gul 17 years (0.5-45 years). There was no difference between cases and controls for heavy use or long duration use of each SLT product.

Association between SLT use and CHD

Table 4, 5, 6 show the results of univariate and multivariate analyses. Among the socio-demographic variables and risk factor variables for CHD, age, hypertension, diabetes, and acute psycho-social stress were significantly associated with CHD.
when data were analysed using community controls, hospital controls or both controls. In addition, marital status and indoor passive smoking were significantly associated with CHD when data were analysed with hospital controls. There was no statistically significant association between current SLT use and CHD when community controls were used (adjusted OR 0.87, 95% CI 0.63-1.19), or hospital controls were used (adjusted OR 1.00, 95% CI 0.63-1.60), or when both controls were combined (adjusted OR 1.00, 95% CI 0.74-1.34). There was no association between ever use or cessation of SLT usage and CHD. Similar results were found when data were analysed separately for never-smokers and ex-smokers. Similarly, Table 5 shows that there was no statistically significant association between SLT use and CHD, when data were analysed using the RAQ classified cases and RAQ classified controls.

When we stratified our analyses according to younger (40-57 years) and older (58-75 years) age groups, there was no statistically significant association between current SLT use and CHD among younger and older participants, when community controls were used (younger: adjusted OR 1.08, 95% CI 0.73-1.60, older: adjusted OR 0.54, 95% CI 0.27-1.07), or hospital controls were used (younger: adjusted OR 1.14, 95% CI 0.59-2.19, older: adjusted OR 0.89, 95% CI 0.32-2.47), or when both controls were combined (younger: adjusted OR 1.19, 95% CI 0.82-1.72, older: adjusted OR 0.75, 95% CI 0.42-1.32). Results did not change when data were analysed separately for never-smokers and ex-smokers.

When we stratified our analyses further according to gender, there was no statistically significant association between current SLT use and CHD among men...
and women, when community controls were used (men: adjusted OR 1.30, 95% CI 0.81-2.10, women: adjusted OR 0.62, 95% CI 0.38-0.99), or hospital controls were used (men: adjusted OR 1.08, 95% CI 0.46-2.55, women: adjusted OR 0.84, 95% CI 0.42-1.68), or when both controls were combined (men: adjusted OR 1.36, 95% CI 0.88-2.09, women: adjusted OR 0.73, 95% CI 0.47-1.14). Results did not change when data were analysed separately for never-smokers and ex-smokers.

Table 6 shows that there was no statistically significant association between use of jarda or sada-pata and CHD for current use, quitting or ever use during analyses by different control groups or by different smoking status. However, the product containing highest amount of nicotine (5.48%) in this study, gul, showed a significant positive association with CHD (adjusted OR 2.93, 95% CI 1.28-6.70), when data were analysed using both groups of controls.

There was no statistically significant association between frequency or duration of each SLT product use and CHD, except use of gul. There was a significant positive association between heavy use of gul and CHD (adjusted OR 2.78, 95% CI 1.17-6.57), and long duration use of gul and CHD (adjusted OR 3.57, 95% CI 1.26-10.1) when both controls were used. There may have been a problem with lack of power to make stratified analyses with each SLT product to identify the association with CHD, as there were very few users of each SLT product in this study (Table 6).

Discussion

In this study, there was no statistically significant association between SLT use in general and CHD among non-smoking adults in Bangladesh. However, there was a
significant association between use of gul and CHD. No significant association was found for frequency or duration of each SLT product except gul. Heavy use and long duration of gul use was significantly associated with CHD. Results did not change when community controls, hospital controls, or both control groups were used during analyses, and when never-smoker, ex-smoker, or both groups were used. The results were the same for current users, quitters or ever users of SLT products. In addition, re-classification of cases and controls utilizing the RAQ did not change the findings of association between SLT use and CHD. Separate analyses with different age groups and gender did not change the results as well.

Findings of this study are supported by earlier case-control, cross-sectional as well as cohort studies. None of these case-control studies conducted in Sweden reported a statistically significant positive association between use of snuff and CHD, although the findings were for men only. Similar to case-control studies, none of these cohort studies have reported a significant association between SLT use and CHD. All of these cohort studies except the US study included men only. The US study, which considered only fatal CHD, showed the same results when analysed separately for men (adjusted hazard ratio 0.6, 95% CI 0.3-1.2) and women (adjusted OR 1.4, 95% CI 0.8-2.2).

On the other hand, findings of this study are not supported by other cohort and case-control studies. The Swedish Construction Worker study and the US Cancer Prevention Study involving a larger cohort reported a significant positive association between SLT use and CHD. However, it is to be noted that both of these studies included men and fatal CHD only. Another US cohort study,
which included both sexes as well as fatal and non-fatal CHD, reported a significant positive association between SLT use and CVD, but no separate results were reported for fatal and non-fatal CVD, or for CHD and stroke. All of these cohort studies included Western SLT products and populations. The only South Asian cohort study, conducted in India \(^83\), showed a significant positive association between use of Indian SLT products and CHD among women (adjusted risk ratio 1.25, 95% CI 1.05-1.49), but not among men (adjusted risk ratio 0.89, 95% CI 0.75-1.05). This is also in contrast to what we have found in this study. The constituents of Indian SLT products are likely to be different from Bangladeshi SLT products, which could have resulted in the significant positive association in the Indian study. The INTERHEART \(^80\) and the Bangladeshi case-control study \(^19\) showed a significant positive association between SLT use and non-fatal CHD. All of these studies were limited by various methodological issues as described in the introduction to this paper.

Literature suggests inconsistent evidence regarding the association between SLT use and CHD among different age-groups. We did not find any difference in results by different age group, which is supported by another study that did not find any significant association among younger (35-54 years) and older (55-64 years) population \(^122\). On the other hand, a cross-sectional study with the Swedish construction workers did not find a significant association among younger workers (46-55 years) \(^124\), the subsequent cohort study reported a significant association among young (35-54 years) as well as older workers (55-65 years) \(^116\).
Table 4: Univariate and multivariate matched analysis showing the association between coronary heart disease and use of smokeless tobacco (by smoking status of the participants)

<table>
<thead>
<tr>
<th></th>
<th>Hospital cases vs. community controls</th>
<th>Hospital cases vs. hospital controls</th>
<th>Hospital cases vs. both controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR  95% CI</td>
<td>OR  95% CI</td>
<td>OR  95% CI</td>
</tr>
<tr>
<td>Non-smokers (total study participants)</td>
<td>1.00  1.00</td>
<td>1.00  1.00</td>
<td>1.00  1.00</td>
</tr>
<tr>
<td>Ever users of SLT products</td>
<td>118 (39.1)  0.98  0.74-1.30</td>
<td>118 (39.1)  0.94-1.87  1.11  0.71-1.71</td>
<td>118 (39.1)  0.60-1.37  1.08  0.81-1.44</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>99 (32.8)  0.87  0.65-1.17</td>
<td>99 (32.8)  0.83-1.69  1.00  0.63-1.60</td>
<td>99 (32.8)  0.54-1.04  1.00  0.74-1.34</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>19 (6.3)  2.38  1.16-4.91</td>
<td>19 (6.3)  4.00  1.13-14.2  2.19  0.51-9.44</td>
<td>19 (6.3)  2.38  1.30-5.11  2.08  0.99-4.35</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>203  864</td>
<td>203  225</td>
<td>203  1089</td>
</tr>
<tr>
<td>Ever users of SLT products</td>
<td>60 (29.6)  0.71  0.49-1.02</td>
<td>60 (29.6)  0.59-1.45  1.11  0.59-2.10</td>
<td>60 (29.6)  0.46-1.01  0.77  0.52-1.13</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>51 (25.1)  0.65  0.44-0.95</td>
<td>51 (25.1)  0.54-1.39  1.19  0.62-2.31</td>
<td>51 (25.1)  0.48-1.01  0.76  0.51-1.13</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>9 (4.4)  1.49  0.53-4.24</td>
<td>9 (4.4)  2.00  0.37-10.9  0.37  0.02-5.48</td>
<td>9 (4.4)  1.46  0.54-3.94  0.97  0.33-2.85</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>99  344</td>
<td>99  77</td>
<td>99  421</td>
</tr>
<tr>
<td>Ever users of SLT products</td>
<td>58 (58.6)  1.48  0.84-2.59</td>
<td>58 (58.6)  2.80  1.01-7.78  2.12  0.63-7.18</td>
<td>58 (58.6)  1.58  0.92-2.72  1.44  0.82-2.53</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>48 (48.5)  1.54  0.84-2.83</td>
<td>48 (48.5)  2.20  0.76-6.33  0.85  0.20-3.55</td>
<td>48 (48.5)  1.61  0.89-2.90  1.42  0.77-2.63</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>10 (10.1)  1.03  0.30-3.60</td>
<td>10 (10.1)  3.00  0.30-3.60  0.91  0.15-5.49</td>
<td>10 (10.1)  1.51  0.46-4.99  1.57  0.34-7.17</td>
</tr>
</tbody>
</table>

The variables those were significant (p<0.20) during initial univariate analysis, were selected as confounders and adjusted during multivariate analysis.

|                                    | Adjusted for: age, hypertension, diabetes and acute psycho-social stress; matched for: age, sex, residential areas and monthly house rent. |
|                                    | §Adjusted for: age, hypertension, diabetes and acute psycho-social stress; matched for: age, sex, residential areas and monthly house rent. |
|                                    | ¶ Adjusted for: age, marital status, hypertension, diabetes, indoor smoking exposure and acute psycho-social stress; matched for: age and sex. |
|                                    | Adjusted for: age, hypertension, diabetes and acute psycho-social stress; matched for: age, sex, residential areas and monthly house rent. |

<table>
<thead>
<tr>
<th></th>
<th>Adj.  95% CI</th>
<th>Adj.  95% CI</th>
<th>Adj.  95% CI</th>
<th>Adj.  95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smokers (total study participants)</td>
<td>0.15  0.78  0.83-1.37</td>
<td>0.15  0.78  0.83-1.37</td>
<td>0.15  0.78  0.83-1.37</td>
<td>0.15  0.78  0.83-1.37</td>
</tr>
<tr>
<td>Ever users of SLT products</td>
<td>0.35  0.51  0.48-0.60</td>
<td>0.35  0.51  0.48-0.60</td>
<td>0.35  0.51  0.48-0.60</td>
<td>0.35  0.51  0.48-0.60</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>0.97  0.76  0.76-1.00</td>
<td>0.97  0.76  0.76-1.00</td>
<td>0.97  0.76  0.76-1.00</td>
<td>0.97  0.76  0.76-1.00</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>0.76  0.77  0.77-0.80</td>
<td>0.76  0.77  0.77-0.80</td>
<td>0.76  0.77  0.77-0.80</td>
<td>0.76  0.77  0.77-0.80</td>
</tr>
</tbody>
</table>
Table 5: Univariate and multivariate unmatched analysis showing the association between coronary heart disease and use of smokeless tobacco among the re-classified cases and controls by the Rose Angina Questionnaire (RAQ)

<table>
<thead>
<tr>
<th>RAQ hospital cases vs. RAQ community controls</th>
<th>RAQ hospital cases vs. RAQ hospital controls</th>
<th>RAQ hospital cases vs. RAQ both controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAQ Hospital Cases, n(%)</td>
<td>RAQ Hospital Controls, n(%)</td>
<td>RAQ Hospital Cases, n(%)</td>
</tr>
<tr>
<td>OR</td>
<td>95% CI</td>
<td>Adj. OR</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Never users of any tobacco (Reference)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-smokers (total study participants)</td>
<td>194</td>
<td>1153</td>
</tr>
<tr>
<td>Ever users of SLT products</td>
<td>78 (40.2)</td>
<td>458 (39.7)</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>69 (35.6)</td>
<td>431 (37.4)</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>9 (4.6)</td>
<td>27 (2.3)</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>132</td>
<td>823</td>
</tr>
<tr>
<td>Ever users of SLT products</td>
<td>42 (31.8)</td>
<td>296 (36.0)</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>37 (28.0)</td>
<td>282 (34.3)</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>5 (3.8)</td>
<td>14 (1.7)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>62</td>
<td>330</td>
</tr>
<tr>
<td>Ever users of SLT products</td>
<td>36 (58.1)</td>
<td>162 (49.1)</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>32 (51.6)</td>
<td>149 (45.2)</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>4 (6.5)</td>
<td>13 (3.9)</td>
</tr>
</tbody>
</table>

The variables those were significant (p<0.20) during initial univariate analysis, were selected as confounders and adjusted during multivariate analysis.

* Adjusted for: marriage, level of education, socioeconomic status, hypertension, diabetes, indoor smoking and acute psycho-social stress.

† Adjusted for: age, socioeconomic status, hypertension, diabetes, family history of heart disease, physical activities, indoor smoking and acute psycho-social stress.

‡ Adjusted for: age, socioeconomic status, hypertension, diabetes, family history of heart disease, indoor smoking and acute psycho-social stress.
Table 6: Univariate and multivariate matched analysis showing the association between coronary heart disease and current use of different types of Bangladeshi smokeless tobacco (SLT) products (by smoking status of the participants)

<table>
<thead>
<tr>
<th></th>
<th>Hospital cases vs. community controls</th>
<th>Hospital cases vs. hospital controls</th>
<th>Hospital cases vs. both controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hospital Cases, n(%)</td>
<td>Community Controls, n(%)</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Never users of any tobacco (Reference)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Non-smokers (total study participants)</td>
<td>302</td>
<td>1208</td>
<td></td>
</tr>
<tr>
<td>Current users of any one SLT product</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jarda (0.96% nicotine)</td>
<td>63 (20.9)</td>
<td>314 (26.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>Sada-pata (1.97% nicotine)</td>
<td>8 (2.6)</td>
<td>28 (2.3)</td>
<td>1.17</td>
</tr>
<tr>
<td>Gul (5.48% nicotine)</td>
<td>15 (5.0)</td>
<td>28 (2.3)</td>
<td>2.70</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>203</td>
<td>864</td>
<td></td>
</tr>
<tr>
<td>Current users of any one SLT product</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jarda (0.96% nicotine)</td>
<td>34 (16.7)</td>
<td>205 (23.7)</td>
<td>0.60</td>
</tr>
<tr>
<td>Sada-pata (1.97% nicotine)</td>
<td>5 (2.5)</td>
<td>21 (2.4)</td>
<td>0.95</td>
</tr>
<tr>
<td>Gul (5.48% nicotine)</td>
<td>7 (3.4)</td>
<td>18 (2.1)</td>
<td>1.44</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>99</td>
<td>344</td>
<td></td>
</tr>
<tr>
<td>Current users of any one SLT product</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jarda (0.96% nicotine)</td>
<td>29 (29.3)</td>
<td>109 (31.7)</td>
<td>1.44</td>
</tr>
</tbody>
</table>

The variables those were significant (p<0.20) during initial univariate analysis, were selected as confounders and adjusted during multivariate analysis.

*Adjusted for: age, hypertension, diabetes and acute psycho-social stress; matched for: age, sex, residential areas and monthly house rent.

* Adjusted for: age, marital status, hypertension, diabetes, indoor smoking exposure and acute psycho-social stress; matched for: age and sex.

¶ Adjusted for: age, hypertension, diabetes and acute psycho-social stress; matched for: age, sex, residential areas and monthly house rent.
There was a significant association between use of *gul* and CHD in this study, although the numbers were not large enough to confirm this association from this study as mentioned before. *Gul* is the mixture of tobacco powder, molasses, alkaline modifiers and other ingredients prepared commercially, and used in other parts of South Asia including Bangladesh \(^1,^{128}\). This product is kept between cheek and gum, used alone unlike other SLT products which are usually used with betel leaf in Bangladesh. This product was reported as highest nicotine concentration in this study. A recent surveillance on SLT products from different countries also reported higher nicotine concentration in Bangladeshi *gul* compared to other SLT products \(^{128}\). Frequency and duration of *gul* use was also significantly associated with CHD in the present study. Further well-powered studies need to explore this association between this specific SLT product and CHD in a more detailed way.

Results from existing research in Western countries are inconclusive; studies from South Asia are very limited and have some methodological constraints. The current study addressed some of these methodological issues. Strengths of this study comprise including only non-smoking participants, a wider age range, both men and women, both community controls and hospital controls, and including exclusive SLT products from Bangladesh. Inclusion of non-smokers controlled for the potential strong confounding effects of smoking on CHD at the design stage. In addition, potential confounders were measured and adjusted for. This was particularly important for hypertension, which had the potential of introducing bias when data were analysed using hospital controls. Increasing the age limit of the participants in contrast to the earlier Bangladeshi case-control study helped assess the association between SLT use and CHD among a broader and more representative sample of Bangladeshi population. The consistent findings
regardless of using either hospital controls or community controls support the accuracy of the study results. For the exposure variable, betel-quid or areca-nut was not included as a SLT product unlike other prior studies; rather selection of SLT products was supported by direct analysis of nicotine content. Selecting subjects from the two tertiary care cardiac hospitals and the catchment areas within the DCC, which include people from all socio-economic strata, suggest our results are representative for urban dwellers in Bangladesh. However, the issue of different health care seeking behaviours should be kept in mind. Re-interviewing a percentage of both cases and controls ensured the quality of the collected data. Re-analysing data using the RAQ classification strengthened the study findings because milder or as yet undiagnosed CHD were identified from both hospitals and communities in this study.

The lack of an association between SLT use in general and CHD in this study can be explained in several ways. Nicotine concentration of some Bangladeshi SLT products, specifically gul is higher compared to commercial cigarettes (1.63%) or bidi smoking (2.12%) \textsuperscript{139}. But more gradual and least peaked dosing of nicotine occurs for SLT use, although the blood concentration of nicotine remains similar for a daily SLT user and a smoker \textsuperscript{140}. On the other hand, rapid dosing of nicotine occurs with smoking and this has the potential to result in much more intense cardiovascular stimulation \textsuperscript{141}. In addition, the dose range of nicotine in the selected SLT products in this study might not be within the range of cardio-toxicity. Finally, SLT products do not contain carbon monoxide and polycyclic aromatic hydrocarbons, which are known to contribute to the cardiovascular effects of smoking \textsuperscript{122, 141}. A significant association between gul use and CHD may be due to the higher nicotine concentration in the product itself along with the rapid
absorption from buccal cavity to cause cardiovascular effects. It may also be due to other additives in gul having cardiovascular effects. Further studies need to confirm these hypotheses.

It was beyond the scope of this study to verify the self-reported diagnosis of non-CHD among the community controls by a qualified physician. Fatal CHD cases were not included in this study, because hospital death registers in Bangladesh are not well developed. In addition, collection of SLT exposure data from family members of deceased individuals would be less reliable compared to data collected from the users themselves. Reporting of the stratified analyses with each SLT product in this study has the potential to be biased as we had relatively small number of specific SLT users. We could not measure the amount of different SLT use from the study participants, as there are no standard pack sizes unlike snus or snuff. This limited us from including the amount during calculation of dose-response relationship between SLT use and CHD. However, as there was no association between SLT use and CHD, this missing information did not affect the result of this study. There is a chance of having interviewer-bias in this study, which can happen to any epidemiological study. We tried to minimise that bias as much as possible by the regular presence of the first author in the field-sites during data collection. Since our subjects were recruited from within Dhaka, our results may not be generalisable to the rural areas of Bangladesh. We attempted to measure and adjust for as many possible confounding variables as possible. Importantly, this included hypertension as previously discussed. However, it was not possible to measure body mass index (BMI) because urban dwellers in Bangladesh usually do not entertain the researchers to collect data on height and weight at community settings.
This study has implications for tobacco control policy. There is an ongoing debate regarding the use of SLT products as a safer alternative to active smoking and as a possible mechanism to encourage smoking cessation \(^{100}\). On the other hand, there is a concern that SLT use may potentiate tobacco smoking \(^{142}\). As tobacco control policies vary strikingly between countries \(^{47}\), there is the potential of introducing Western SLT products as a harm-reduction agent into developing countries of South Asia \(^{44}\). Such products may contain ingredients, which could have deleterious effects on CHD and other health conditions. In addition, SLT products and nicotine concentration also differ in other South Asian countries such as in India or Pakistan \(^{1,143}\).

This study did not find an association between SLT use in general and CHD among non-smoking Bangladeshi adults. This is the first large scale case-control study assessing the association between SLT use and CHD from a South Asian perspective. Despite the fact that the current study did not find an association between different Bangladeshi SLT products and CHD except *gul*, SLT use has an established risk for development of cancers and of dental diseases. Tobacco control campaigns should focus on these SLT-related diseases. Given the fact that the burden of tobacco-related illnesses are more among people of lower socio-economic status \(^{22}\), as well as limited resources for health promotion activities in developing countries, policies supporting non-use of any form of tobacco are justified. Further research on the association between *gul* use and CHD in Bangladesh, along with SLT use and CHD in other parts of the subcontinent where SLT products may differ will guide public health policy and interventions to prevent SLT-related diseases. Because SLT use is not harmless, the strategic focus should be upon controlling both smoking and SLT use in Bangladesh.
CHAPTER 4

Why do Bangladeshi people use smokeless tobacco products?
Chapter outline

This chapter presents the manuscript that describes the perceptions of SLT use among non-smoking Bangladeshi adults. It addresses the second research question:

- What are the perceptions of Bangladeshi adults about the health effects of SLT use?

It describes the perceptions of Bangladeshi adults in general, as well as compares the perceptions between SLT users and non-users of SLT products. This manuscript was submitted to Asia Pacific Journal of Public Health on 1st July 2011 and is awaiting a response:

Rahman MA, Mahmood MA, Spurrier N, Rahman M, Choudhury SR, Leeder S. Why do Bangladeshi people use smokeless tobacco products?

Although the original manuscript was formatted according to the specific journal instruction, I have followed a consistent reference style throughout the entire thesis. Reference numbers are also chronologically arranged from the beginning to the end of this thesis. In addition, the table and figure numbers are also not based on each manuscript separately; rather they are sequenced chronologically in this thesis.

Rationale for developing this manuscript

SLT products are commonly used by South Asian population as a long standing cultural tradition. A quarter of Bangladeshi adults use different SLT products. There is no difference in usage between men and women. Understanding perceptions about the effects of SLT use on health would guide the tobacco control communities to focus on the specific issues. Therefore, this manuscript explores the perceptions about health effects of SLT use among Bangladeshi population.
Rationale for choosing *Asia Pacific Journal of Public Health*

*Asia Pacific Journal of Public Health* is a peer-reviewed journal that publishes articles on different public health issues in the Asia-Pacific region. Considering the focus on public health research from Asia, this regional journal was selected for this manuscript.

**Authors’ contributions**

MAR, NS and MAM discussed the need for and the overall constructs and concepts of the study design. MR, SRC and SL also contributed in the design of the study. MAR collected data from field sites, analysed and interpreted data, and finally, prepared the draft manuscript. NS, MAM, MR, SRC and SL reviewed drafts of the manuscript, provided feedback and incorporated their inputs. All of the authors read and approved the final version of the manuscript.
Statement of authorship

Why do Bangladeshi people use smokeless tobacco products?
Asia Pacific Journal of Public Health (Submitted on July 01, 2011)

Muhammad Aziz Rahman (candidate)
Discussed the need for and the overall constructs and concepts of the study design with Nicola Spurrier and Mohammad Afzal Mahmood. Collected data from field sites, analysed and interpreted data. Prepared the draft manuscript, reviewed based on co-authors’ inputs, submitted to the journal, and acted as a corresponding author.

Signed............................................................................. Date....................................

Mohammad Afzal Mahmood
My contribution to this paper involved: Discussed the need for and the overall constructs and concepts of the study design. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed............................................................................. Date....................................

Nicola Spurrier
My contribution to this paper involved: Discussed the need for and the overall constructs and concepts of the study design. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed............................................................................. Date....................................
Mahmudur Rahman
My contribution to this paper involved: Contributed in the design and provided support for the field activities in Bangladesh. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

(Signature is included in the appendix VI)

Sohel Reza Choudhury
My contribution to this paper involved: Contributed in the design and provided support for the field activities in Bangladesh. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

(Signature is included in the appendix VI)

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My contribution to this paper involved: Contributed in the design of the study. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

(Signature is included in the appendix VI)
Why do Bangladeshi people use smokeless tobacco products?

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Abstract

Despite scientific evidence about harmful effects of smokeless tobacco (SLT), it is widely used in Bangladesh. This study explored perceptions about health effects of SLT use. Semi-structured interviews were conducted with 1812 non-smoking adults. About 40% participants were current SLT users or had used SLT in the past. Family members’ influence was the main factor for initiation. The participants believed that people continued using SLT due to addiction (52%) and as a part of their lifestyle (23%). The majority of participants (77%) did not mention any benefit, but SLT users considered SLT as a remedy for toothache (p<0.05). Almost all participants mentioned that SLT was harmful and causes heart disease, cancer, and tuberculosis. Doctors’ advice was the common motivating factor to quit. Health promotion interventions should highlight adverse effects of SLT use which would outweigh the perceived benefits, and should consider addressing the role of family for SLT initiation and use.

Keywords

Smokeless tobacco, chewing tobacco, perceptions of smokeless tobacco use, perceptions of tobacco use, Bangladesh
Introduction

Chewing betel-leaf, known as paan in the sub-continent, is a cultural tradition of Bangladeshi people extending back over centuries. Smokeless tobacco (SLT) products are added to betel-leaf during chewing by many Bangladeshi adults. Prevalence of SLT use is 27% (26 million adult people) with a similar distribution across genders in Bangladesh. Several epidemiological studies showed that SLT use is associated with oral and dental diseases, cancers, cardiovascular diseases, hypertension, diabetes, poor reproductive outcomes, elevated all-cause mortality, and addiction. Studies from India and Pakistan report that many people believe that some of the SLT products were beneficial to health, relieving toothache, headache and stomach-ache.

In Bangladesh, tobacco studies focused on prevalence of tobacco use, association between tobacco use and cardiovascular disease, and other tobacco-related issues such as socio-demographic characteristics of tobacco users or socio-economic determinants of tobacco use. Two studies have explored perceptions of tobacco use among Bangladeshi adults thus far; one study did not report perceptions separately among SLT users, and the other study only explored perceived health effects of SLT use but not the perceived benefits or the initiation factors of SLT use.

Understanding perceptions is important as they are strongly associated with behavior. The Health Belief Model (HBM) hypothesises that perceived susceptibility, perceived severity of a disease, and perceived benefits outweighing costs are all prelude to healthy behavior change. According to this model, SLT
users would be more likely to change their chewing habits if they perceived themselves as vulnerable to diseases as a result, and if they perceived that quitting of SLT would assure better health \(^{148}\). A cohort study of current smokers from USA, UK, Canada and Australia reported that perceived benefits from smoking was large enough to inhibit quitting \(^{149}\). Therefore, it is important to identify whether perceived benefits of SLT use outweigh the harmful effects on health.

The aim of this study was to describe the patterns of SLT use among the Bangladeshi adults, and to explore their perceptions about the effects of SLT use on health.

**Methods**

**Study design and study sites**

This study was a component of a large case-control study that explored the association between CHD and use of SLT products among non-smoking Bangladeshi adults. In line with the protocol of the case-control study, we collected data from CHD-positive individuals and CHD-negative individuals. CHD-positive individuals were recruited from cardiac inpatient facilities of the National Institute of Cardiovascular Diseases (NICVD) and the National Heart Foundation Hospital and Research Institute (NHFH&RI), Dhaka, Bangladesh. CHD-negative individuals were recruited from cardiac outpatient facilities of the same hospitals and from the neighbourhood households of CHD-positive individuals within Dhaka City Corporation (DCC) areas.
**Study population**
Inclusion criteria were: age 40-75 years, non-smoker, residence within DCC areas, and well enough to undertake a 20 minute interview. Non-smokers were defined as either (i) never smokers or (ii) ex-smokers who had not smoked a single puff in the past 10 years. Selection criteria for CHD-positive and CHD-negative individuals will be reported elsewhere. For this study, we re-classified the study participants into SLT users and SLT non-users.

**Sample size**
A total of 1812 participants were interviewed for the original study and formed the sample for this study. It included 302 CHD-positive individuals and 1208 CHD-negative individuals.

**Data collection**
Data were collected through semi-structured interviews by four trained interviewers during January-July 2010 in Bangladesh. Interviewers described the study objectives prior to obtaining written consent from each study participant. Interviewers collected information on the following variables:

**Socio-demographic variables**
Information on age, sex, residence, marital status, highest level of education achieved, primary occupation and monthly house-rent were collected from the participants.
Use of SLT products

Detailed information on SLT use such as current use and quitting, types of SLT products used, frequency and duration of SLT use for current users, and duration since stopped using SLT products for quitters was collected. Betel-leaf or areca-nut alone was not included as a SLT product, as they do not contain tobacco. If a respondent used any SLT product with/without betel-leaf or areca-nut in the last one year, he/she was categorized as a current SLT user. If a respondent stopped using SLT products during the past twelve months, he/she was categorized as a quitter of SLT products. We categorized frequency into light use (less than once a day) and heavy use (at least once a day), duration into short duration (<10 years) and long duration (>10 years).

Perceptions of SLT use

Participants’ perceptions about health effects of SLT use were collected through a semi-structured questionnaire. Some of the questions were chosen from prior tobacco research in Bangladesh⁶⁶,⁹⁰, and perception studies in India⁵⁹ and Pakistan⁹¹. Irrespective of usage status, participants were asked to offer possible reasons as to why Bangladeshi adults would use SLT products. All participants were interviewed regarding their perceptions of beneficial and harmful effects of SLT use on health. Only the SLT users, either current or past, were asked regarding the factors, persons, or events that influenced them to start using SLT. They were also asked whether they had ever tried to quit, reasons for quitting attempts or successfully quitting SLT use, and an estimate of weekly or daily expenditure on SLT products.
Data analysis

Descriptive statistics were used to describe the socio-demographic variables (age, sex, residence, marital status, education, occupation and monthly house-rent) and main exposure variable (prevalence, types, frequency and duration of SLT use) among the study participants. Open ended responses were recorded and categorized under each item of perceptions. First, the perceptions among all participants were analysed, then the differences in perceptions between SLT users and SLT non-users were analysed. We also compared the differences in perceptions between CHD-positive individuals and CHD-negative individuals. For each item of perceptions, SLT users and SLT non-users were compared using cross-tabulations. McNemar’s chi-squared ($\chi^2$) tests were used when the frequency in all of the cells of the cross-tabulation was $\geq 5$ and Fisher’s exact tests were used otherwise, to determine statistical significance at the 0.05 level.

Results

Study participants

Out of 1920 eligible participants, 1812 (94%) took part in this study. The mean age of participants was 53 years ($\pm 8.5$ years) and 70% were aged 40-57 years. Half of the participants were women. More than two-thirds (78%) were married and 76% had completed formal education. The majority (81%) of female participants were housewives, whereas half (47%) of the male participants were either government or private service holders. Based on the monthly house-rent, half (51%) of participants were categorized as middle socio-economic group (monthly house rent 5,000-10,000 Bangladesh Taka) (Table 7).
<table>
<thead>
<tr>
<th>Variables</th>
<th>Total, N(%)</th>
<th>SLT users, n(%)</th>
<th>SLT non-users, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total study participants</td>
<td>1812</td>
<td>704</td>
<td>1108</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>53.0 (±8.5)</td>
<td>54.8 (±8.5)</td>
<td>51.8 (±8.3)</td>
</tr>
<tr>
<td>Age-groups (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-48</td>
<td>635 (35.0)</td>
<td>179 (25.4)</td>
<td>456 (41.2)*</td>
</tr>
<tr>
<td>49-57</td>
<td>641 (35.4)</td>
<td>269 (38.2)</td>
<td>372 (33.6)</td>
</tr>
<tr>
<td>58-66</td>
<td>405 (22.4)</td>
<td>180 (25.6)</td>
<td>225 (20.3)*</td>
</tr>
<tr>
<td>67-75</td>
<td>131 (7.2)</td>
<td>76 (10.8)</td>
<td>55 (5.0)*</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>912 (50.3)</td>
<td>400 (56.8)</td>
<td>512 (46.2)*</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>5 (0.3)</td>
<td>2 (0.3)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Married (and living with spouse)</td>
<td>1414 (78.1)</td>
<td>484 (68.9)</td>
<td>930 (83.9)*</td>
</tr>
<tr>
<td>Married (spouse working overseas)</td>
<td>90 (5.0)</td>
<td>43 (6.1)</td>
<td>47 (4.2)</td>
</tr>
<tr>
<td>Divorced</td>
<td>4 (0.2)</td>
<td>1 (0.1)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Widowed</td>
<td>282 (15.6)</td>
<td>165 (23.5)</td>
<td>117 (10.6)*</td>
</tr>
<tr>
<td>Separated</td>
<td>16 (0.9)</td>
<td>8 (1.1)</td>
<td>8 (0.7)</td>
</tr>
<tr>
<td>Highest level of education achieved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>204 (11.3)</td>
<td>143 (20.4)</td>
<td>61 (5.5)*</td>
</tr>
<tr>
<td>Can sign names</td>
<td>212 (11.7)</td>
<td>122 (17.4)</td>
<td>90 (8.1)*</td>
</tr>
<tr>
<td>Literate</td>
<td>12 (0.7)</td>
<td>7 (1.0)</td>
<td>5 (0.5)</td>
</tr>
<tr>
<td>Primary</td>
<td>527 (29.1)</td>
<td>248 (35.3)</td>
<td>279 (25.2)*</td>
</tr>
<tr>
<td>Secondary</td>
<td>239 (13.2)</td>
<td>73 (10.4)</td>
<td>166 (15.0)*</td>
</tr>
<tr>
<td>Higher-secondary</td>
<td>197 (10.9)</td>
<td>49 (7.0)</td>
<td>148 (13.4)*</td>
</tr>
<tr>
<td>Above higher-secondary</td>
<td>418 (23.1)</td>
<td>60 (8.6)</td>
<td>358 (32.3)*</td>
</tr>
<tr>
<td>Primary occupation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Service holder</td>
<td>558 (30.8)</td>
<td>188 (26.7)</td>
<td>370 (33.4)*</td>
</tr>
<tr>
<td>Businessmen</td>
<td>262 (14.5)</td>
<td>89 (12.7)</td>
<td>173 (15.6)</td>
</tr>
<tr>
<td>Housewife</td>
<td>741 (40.9)</td>
<td>323 (46.0)</td>
<td>418 (37.7)*</td>
</tr>
<tr>
<td>Retired</td>
<td>235 (13.0)</td>
<td>94 (13.4)</td>
<td>141 (12.7)</td>
</tr>
<tr>
<td>Socio-economic status (SES) by monthly house-rent (HR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower SES (HR &lt;5000 BDT)</td>
<td>656 (36.2)</td>
<td>367 (52.1)</td>
<td>289 (26.1)*</td>
</tr>
<tr>
<td>Middle SES (HR 5000-10000 BDT)</td>
<td>930 (51.3)</td>
<td>288 (40.9)</td>
<td>642 (57.9)*</td>
</tr>
<tr>
<td>Higher SES (HR &gt;10000 BDT)</td>
<td>226 (12.5)</td>
<td>49 (7.0)</td>
<td>177 (16.0)*</td>
</tr>
</tbody>
</table>

* indicates which categories show a statistically significant (p<0.01) difference using chi-squared tests between SLT users and SLT non-users
Use of SLT products

Amongst the 1812 participants, 704 (39%) were current SLT users or had used SLT in the past. The majority (92%) of them were current SLT users. Use of any one SLT product exclusively was more common compared to the use of more than one SLT product, which suggests some degree of product loyalty. Amongst individual types of SLT products, *jarda* was used most commonly (64%) followed by *sada-pata* (6%) and *gul* (7%). The majority of exclusive *jarda*, *sada-pata* and *gul* consumers were heavy users and long-duration users (Table 8).

Table 8: Status of smokeless tobacco (SLT) use among the study participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>SLT users, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total SLT users</td>
<td>704</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>648 (92.0)</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>56 (8.0)</td>
</tr>
<tr>
<td>Current users of any one SLT product</td>
<td></td>
</tr>
<tr>
<td><em>Jarda</em> (0.96% nicotine)</td>
<td>448 (63.6)</td>
</tr>
<tr>
<td><em>Sada-pata</em> (1.97% nicotine)</td>
<td>44 (6.3)</td>
</tr>
<tr>
<td><em>Gul</em> (5.48% nicotine)</td>
<td>49 (7.0)</td>
</tr>
<tr>
<td>Current users of any two SLT products together</td>
<td></td>
</tr>
<tr>
<td><em>Jarda</em> and <em>sada-pata</em></td>
<td>22 (3.1)</td>
</tr>
<tr>
<td><em>Jarda</em> and <em>gul</em></td>
<td>79 (11.2)</td>
</tr>
<tr>
<td><em>Sada-pata</em> and <em>gul</em></td>
<td>4 (0.6)</td>
</tr>
<tr>
<td>Current users of all three SLT products together</td>
<td></td>
</tr>
<tr>
<td><em>Jarda</em>, <em>sada-pata</em> and <em>gul</em></td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Heavy use (at least once a day) of SLT products</td>
<td></td>
</tr>
<tr>
<td><em>Jarda</em> (0.96% nicotine)</td>
<td>406 (57.7)</td>
</tr>
<tr>
<td><em>Sada-pata</em> (1.97% nicotine)</td>
<td>42 (6.0)</td>
</tr>
<tr>
<td><em>Gul</em> (5.48% nicotine)</td>
<td>45 (6.4)</td>
</tr>
<tr>
<td>Long duration use (&gt;10 years) of SLT products</td>
<td></td>
</tr>
<tr>
<td><em>Jarda</em> (0.96% nicotine)</td>
<td>261 (37.1)</td>
</tr>
<tr>
<td><em>Sada-pata</em> (1.97% nicotine)</td>
<td>35 (5.0)</td>
</tr>
<tr>
<td><em>Gul</em> (5.48% nicotine)</td>
<td>28 (4.0)</td>
</tr>
</tbody>
</table>
Comparing socio-demographic variables between SLT users and SLT non-users

Table 7 shows that there was a statistically significant difference (p<0.05) between SLT users and SLT non-users in terms of age, gender, marital status, highest level of education achieved, primary occupation and monthly house-rent. SLT users were more likely to be from older age groups, women, widowed, less educated, housewives and lower socio-economic groups compared to SLT non-users (Table 7).

Perceptions of SLT use

Reasons for using SLT products by Bangladeshi adults

Half (52%) of the participants, irrespective of their status of SLT use, believed that ongoing use of SLT products was due to addiction. Another 23% believed that SLT users exhibited a lifestyle habit. Table 9 shows the differences of perceptions between SLT users and SLT non-users. SLT users were more likely (p<0.05) to believe that the common reasons for using SLT products were family tradition, to get relief from toothache, to increase the taste of betel chewing, to give a good taste or to enhance taste in general. However, SLT users were less likely (p<0.05) to believe that Bangladeshi adults use SLT products due to addiction, curiosity, influence of bad companions, or lack of awareness of harmful effects.

Perceived harmful effects of SLT use

Almost all (97%) participants considered that SLT products were harmful to health. There was no difference in response between SLT users and SLT non-users (Table 9). Many participants considered that SLT use caused heart disease (40%), cancer
(39%), tuberculosis (20%), lung disease (14%) and hypertension (10%). However, compared to non-users, SLT users were less likely (p<0.05) to believe that these diseases were associated with SLT use. SLT users were more likely to believe that diseases associated (p<0.05) with SLT use included gastric problems, visual impairment, and dizziness compared to non-users. The harmful effects of SLT use other than diseases were wasting money, harmful to the environment (users spitting chewed betel-leaf and/or SLT products), social embarrassment, family conflict and religious beliefs (SLT products are addictive in nature and addiction is prohibited in Islam; chewing SLT products stains tongue and teeth as well as produces bad breath which are difficult to eliminate during ablution for performing prayers). However, SLT users were less likely (p<0.05) to believe that these issues were associated with SLT use compared to non-users (Table 9).

**Perceived benefits of SLT use**

The majority (77%) of participants believed that there was no benefit to use SLT products. However, SLT users were less likely (p<0.05) to believe this compared to non-users. Users believed that SLT use helped them in the following ways: to relieve toothache (11%), to enhance taste perceptions (6%), to help in digestion (3%), to make the teeth harder (3%), and to relieve anxiety (1%) (Table 9).

**Factors influencing initiation of SLT use**

A quarter (25%) of SLT users mentioned that they started using SLT products primarily due to influence from parents or siblings. They were attracted by the flavour of SLT products as well as chewing habits of family members. Users also tried SLT products out of curiosity. Later on, they believed that they became habituated to those products. Another 17% of SLT users were influenced by relatives or
neighbours, 16% were influenced by grandparents or parents-in-laws or teachers, and 14% initiated using those products to get relief from toothache. Other factors for initiation of SLT use are mentioned in Table 10. Interestingly, 5% of SLT users started using SLT products following smoking cessation, as they believed that SLT helped to decrease smoking addiction. As use of SLT is a Bangladeshi cultural tradition and SLT is served to guests in cultural celebrations, 3% SLT users started using SLT at such occasions. Sometimes older family members such as mother and mother-in-laws advised the female respondents (2%) to use SLT products with betel leaf to get relief from pregnancy symptoms of anorexia, nausea and vomiting. A few female participants (<1%) reported that advice from mother-in-laws included using betel nut to make a wife more attractive to her husband.

Factors influencing quitting of SLT

Amongst the 704 SLT users, 56 (8%) had successfully quit SLT use after using it for at least two years. SLT quitters mentioned two main reasons for quitting: advice from doctors (36%) and development of certain health problems (39%). Health problems included abdominal pain, dizziness, loss of teeth and throat problems. Other reasons given by the quitters were self-motivation and advice from family members. In contrast, many more SLT users (33%) reported unsuccessful attempts to quit SLT products. They cited two main incentives for their quitting attempts: self-motivation (30%) and advice from doctors (23%). Other factors which motivated them to attempt quitting are mentioned in Table 10.
Table 9: Perceptions of smokeless tobacco (SLT) use among the study participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total, N(%)</th>
<th>SLT users, n(%)</th>
<th>SLT non-users, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total study participants</td>
<td>1812</td>
<td>704</td>
<td>1108</td>
</tr>
<tr>
<td>In your opinion, why do Bangladeshi people use SLT products?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addiction</td>
<td>933 (51.5)</td>
<td>336 (47.7)</td>
<td>597 (53.9)*</td>
</tr>
<tr>
<td>As a lifestyle habit</td>
<td>421 (23.2)</td>
<td>164 (23.3)</td>
<td>257 (23.2)</td>
</tr>
<tr>
<td>Family tradition</td>
<td>164 (9.1)</td>
<td>77 (10.9)</td>
<td>87 (7.9)*</td>
</tr>
<tr>
<td>Curiosity</td>
<td>140 (7.7)</td>
<td>43 (6.1)</td>
<td>97 (8.8)*</td>
</tr>
<tr>
<td>Relief from toothache</td>
<td>118 (6.5)</td>
<td>80 (11.4)</td>
<td>38 (3.4)**</td>
</tr>
<tr>
<td>Peer influence</td>
<td>98 (5.4)</td>
<td>25 (3.6)</td>
<td>73 (6.6)**</td>
</tr>
<tr>
<td>SLT increases taste of betel chewing</td>
<td>88 (4.9)</td>
<td>73 (10.4)</td>
<td>15 (1.4)**</td>
</tr>
<tr>
<td>Individual's choice</td>
<td>70 (3.9)</td>
<td>21 (3.0)</td>
<td>49 (4.4)</td>
</tr>
<tr>
<td>SLT tastes good</td>
<td>66 (3.6)</td>
<td>34 (4.8)</td>
<td>32 (2.9)*</td>
</tr>
<tr>
<td>Relief from anxiety</td>
<td>61 (3.4)</td>
<td>29 (4.1)</td>
<td>32 (2.9)</td>
</tr>
<tr>
<td>SLT increases oral taste</td>
<td>60 (3.3)</td>
<td>37 (5.3)</td>
<td>23 (2.1)**</td>
</tr>
<tr>
<td>Lack of awareness of harmful effects</td>
<td>60 (3.3)</td>
<td>4 (0.6)</td>
<td>56 (5.1)**</td>
</tr>
<tr>
<td>SLT users feel good, specifically following any meal</td>
<td>41 (2.3)</td>
<td>19 (2.7)</td>
<td>22 (2.0)</td>
</tr>
<tr>
<td>Bangladeshi culture and tradition for hospitality, especially in rural areas</td>
<td>19 (1.0)</td>
<td>5 (0.7)</td>
<td>14 (1.3)</td>
</tr>
<tr>
<td>What do you think of SLT products, are they beneficial or harmful to health?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Considered SLT as harmful to health</td>
<td>1751 (96.6)</td>
<td>664 (94.3)</td>
<td>1087 (98.1)</td>
</tr>
<tr>
<td>Are you aware of any disease, which is associated with the use of SLT products?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>719 (39.7)</td>
<td>235 (33.4)</td>
<td>484 (43.7)**</td>
</tr>
<tr>
<td>Cancer</td>
<td>715 (39.5)</td>
<td>241 (34.2)</td>
<td>474 (42.8)**</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>365 (20.1)</td>
<td>105 (14.9)</td>
<td>260 (23.5)**</td>
</tr>
<tr>
<td>Lung disease</td>
<td>259 (14.3)</td>
<td>74 (10.5)</td>
<td>185 (16.7)**</td>
</tr>
<tr>
<td>Hypertension</td>
<td>178 (9.8)</td>
<td>50 (7.1)</td>
<td>128 (11.6)**</td>
</tr>
<tr>
<td>Gastric problem</td>
<td>136 (7.5)</td>
<td>72 (10.2)</td>
<td>64 (5.8)**</td>
</tr>
<tr>
<td>Condition</td>
<td>SLT Users</td>
<td>Non-SLT Users</td>
<td>Both Users</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------</td>
<td>---------------</td>
<td>------------</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>132 (7.3)</td>
<td>35 (5.0)</td>
<td>97 (8.8)**</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>133 (7.3)</td>
<td>75 (10.7)</td>
<td>58 (5.2)**</td>
</tr>
<tr>
<td>Dizziness</td>
<td>128 (7.1)</td>
<td>66 (9.4)</td>
<td>62 (5.6)**</td>
</tr>
<tr>
<td>Cough</td>
<td>122 (6.7)</td>
<td>37 (5.3)</td>
<td>85 (7.7)*</td>
</tr>
<tr>
<td>Asthma</td>
<td>111 (6.1)</td>
<td>34 (4.8)</td>
<td>77 (6.9)</td>
</tr>
<tr>
<td>Dental problem</td>
<td>109 (6.0)</td>
<td>35 (5.0)</td>
<td>74 (6.7)</td>
</tr>
</tbody>
</table>

What do you consider to be the other negative aspects of using SLT products?

<table>
<thead>
<tr>
<th>Aspect</th>
<th>SLT Users</th>
<th>Non-SLT Users</th>
<th>Both Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wasting money</td>
<td>126 (7.0)</td>
<td>33 (4.7)</td>
<td>93 (8.4)**</td>
</tr>
<tr>
<td>Harmful for the environment (i.e. through spitting)</td>
<td>42 (2.3)</td>
<td>3 (0.4)</td>
<td>39 (3.5)**</td>
</tr>
<tr>
<td>Social embarrassment</td>
<td>28 (1.5)</td>
<td>4 (0.6)</td>
<td>24 (2.2)**</td>
</tr>
<tr>
<td>Family conflict</td>
<td>20 (1.1)</td>
<td>2 (0.3)</td>
<td>18 (1.6)**</td>
</tr>
<tr>
<td>Not permitted in Islam</td>
<td>20 (1.1)</td>
<td>6 (0.9)</td>
<td>14 (1.3)</td>
</tr>
</tbody>
</table>

What do you consider to be the benefits of using SLT products?

<table>
<thead>
<tr>
<th>Benefit</th>
<th>SLT Users</th>
<th>Non-SLT Users</th>
<th>Both Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>No benefits</td>
<td>1402 (77.4)</td>
<td>439 (62.4)</td>
<td>963 (86.9)**</td>
</tr>
<tr>
<td>Relieves toothache</td>
<td>93 (5.1)</td>
<td>78 (11.1)</td>
<td>15 (1.4)**</td>
</tr>
<tr>
<td>Increases oral taste</td>
<td>47 (2.6)</td>
<td>45 (6.4)</td>
<td>2 (0.2)**</td>
</tr>
<tr>
<td>Helps in digestion</td>
<td>24 (1.3)</td>
<td>20 (2.8)</td>
<td>4 (0.4)**</td>
</tr>
<tr>
<td>Teeth become hard</td>
<td>22 (1.2)</td>
<td>20 (2.8)</td>
<td>2 (0.2)**</td>
</tr>
<tr>
<td>Relieves anxiety</td>
<td>18 (1.0)</td>
<td>9 (1.3)</td>
<td>9 (0.8)</td>
</tr>
</tbody>
</table>

* indicates which categories show a statistically significant (p<0.01) difference using chi-squared tests between SLT users and SLT non-users

** indicates p<0.01
Table 10: Experience of smokeless tobacco (SLT) users

<table>
<thead>
<tr>
<th>Variables</th>
<th>SLT users, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total SLT users</td>
<td>704</td>
</tr>
<tr>
<td>How did you start using SLT products for the first time in your life?</td>
<td></td>
</tr>
<tr>
<td>Advised by family members (parents, siblings)</td>
<td>179 (25.4)</td>
</tr>
<tr>
<td>Advised by relatives or neighbours</td>
<td>120 (17.0)</td>
</tr>
<tr>
<td>Advised by elders (grandparents, parents-in-law, teachers)</td>
<td>115 (16.3)</td>
</tr>
<tr>
<td>To get relief from toothache</td>
<td>99 (14.1)</td>
</tr>
<tr>
<td>Advised by peers</td>
<td>56 (8.0)</td>
</tr>
<tr>
<td>Started by self</td>
<td>50 (7.1)</td>
</tr>
<tr>
<td>Advised by spouse</td>
<td>46 (6.5)</td>
</tr>
<tr>
<td>Advised by colleagues</td>
<td>33 (4.7)</td>
</tr>
<tr>
<td>Start using SLT following quit of smoking</td>
<td>39 (4.5)</td>
</tr>
<tr>
<td>Started using occasionally at different occasions</td>
<td>24 (3.4)</td>
</tr>
<tr>
<td>During pregnancy, to get relief from anorexia, nausea and vomiting</td>
<td>14 (2.0)</td>
</tr>
<tr>
<td>Influenced from others using those</td>
<td>12 (1.7)</td>
</tr>
<tr>
<td>Attracted by the smell of <em>jarda</em></td>
<td>12 (1.7)</td>
</tr>
<tr>
<td>Out of curiosity</td>
<td>12 (1.7)</td>
</tr>
<tr>
<td>Have you ever tried to quit using SLT products?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>232 (33.0)</td>
</tr>
<tr>
<td>Why did you try to quit using SLT products?</td>
<td></td>
</tr>
<tr>
<td>Self motivation</td>
<td>69 (29.7)</td>
</tr>
<tr>
<td>Advice from doctors</td>
<td>53 (22.8)</td>
</tr>
<tr>
<td>Other physical illness</td>
<td>17 (7.3)</td>
</tr>
<tr>
<td>Advice from family members</td>
<td>14 (6.0)</td>
</tr>
<tr>
<td>Advice from spouse</td>
<td>10 (4.3)</td>
</tr>
<tr>
<td>Advice from children</td>
<td>8 (3.4)</td>
</tr>
<tr>
<td>For religious awareness</td>
<td>6 (2.6)</td>
</tr>
<tr>
<td>Weakness</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>During a surgery</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Financial constraints</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Dental problem</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Decreased eyesight</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Realized that it is a wastage of money</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>How much do you spend a week to purchase SLT products?</td>
<td></td>
</tr>
<tr>
<td>Range of expenses in BDT (=USD)</td>
<td>1-1050 (0.01-15)</td>
</tr>
<tr>
<td>Mean expenses in BDT (=USD)</td>
<td>94 (1.34)</td>
</tr>
</tbody>
</table>
Costs of SLT products

Costs for SLT use depended on the products used by participants. *Gul*, which is used alone usually, was relatively cheaper than other SLT products. On the other hand, jarda and sada-pata are usually used as ingredients to betel-leaf chewing. Hence total costs for these products are greater compared to the use of gul. The minimum weekly expense for SLT use in this study was only 1.00 Bangladesh Taka (≈0.01 US$), for those who used gul alone 2-3 times a day. Alternately, the maximum weekly expense for SLT use was 1050.00 Bangladesh Taka (≈15 US$) for those who used jarda alone more than four times a day (Table 10). The average weekly income of Bangladeshi people is about 46 US$ and uneducated people earn 21 US$ or less per week on an average. Thus SLT use represents an estimate of 0.05-33% on an average weekly income in this study.

Comparing perceptions of SLT use between CHD positive individuals and CHD negative individuals

There was no difference between CHD-positive and CHD-negative individuals regarding the reasons for using SLT products by Bangladeshi adults, perceived harmful effects, and perceived benefits of SLT use (analyses not shown). The only difference was that CHD-positive SLT users were more likely (p<0.05) to start using SLT products due to influence from peers and attempted to quit due to religious awareness compared to CHD-negative SLT users (analyses not shown).

Discussion

Addiction and lifestyle habit were cited as the main reasons for continued use of SLT products, and this is consistent with the effects of nicotine in SLT products. A study reported that African traditional healers, who were regular users of
SLT products, stated that almost all of them strongly believed that those products were addictive in nature. A study from Pakistan revealed similar opinions about the addictive nature of SLT products.

In this study, almost all participants believed that use of SLT products were harmful to health, consistent with the results of the recent Global Adult Tobacco Survey (GATS) in Bangladesh. GATS reported that 93% adults perceived SLT products could cause serious illness. SLT use was perceived to be associated with heart disease, cancer, tuberculosis, lung disease and hypertension in this study, although there was a difference between SLT users and SLT non-users. This disease specific perception difference could be due to differences in the level of awareness, as SLT users were less educated and mostly from lower SES compared to non-users in this study. GATS also reported that Bangladeshi people believed SLT products could cause oral cancer, heart attack and stroke. Heart disease and lung disease were also perceived as SLT-related diseases by Pakistani SLT users. Oral cancer was perceived to be a SLT-related disease by highly educated professionals interviewed in the USA. This group perceived SLT use to be a higher risk in this regard than smoking cigarettes. These findings are in contrast to the findings of a study in South Africa where the majority of the respondents considered SLT use to be harmless. Health education campaigns in Bangladesh should start with the assumption that many people are already aware that SLT is harmful. People need to be informed about the exact nature of the threat for SLT use, along with seriousness and severity of the SLT-related diseases.
Although the majority of study participants did not mention any benefit of using SLT products, relieving toothache was one common benefit mentioned by some SLT users. Dental health is often neglected in Bangladesh and in other developing countries in general. Lack of awareness regarding oral health, financial constraints, and scarcity of dental services result in high rates of dental diseases. It is common for Bangladeshi adults, specifically in rural areas to rely on traditional remedies and herbal treatments. Studies from India and South Africa also have found that SLT products were used to aide relief of toothache.

The principal initiating factor for using SLT products was influence from family members in this study. Gupta et al. reported that the perceived medicinal benefits of SLT use in some cases led to “advice for initiating tobacco use from adults to non-users and even children.” Generally, advice from older family members is respected within the socio-cultural context of Bangladesh. This may explain why SLT initiation occurred on recommendation by other family members in this study. This finding also reflects the cultural acceptability of betel-leaf and/or SLT use in Bangladesh as in other areas of the subcontinent. In contrast, smoking is not socially acceptable and smokers do not tend to smoke in front of elders in Bangladesh.

In this study, advice from doctors was the common factor reported for successful quitting as well as for making a quitting attempt amongst SLT users. A previous study from Bangladesh also identified three major factors for permanent quitting of tobacco use: self-restraint, supports from family members or friends, and advice from doctors. Self-motivation (i.e. ideas about self control) was also identified as another factor for quitting attempt in this study. Similar findings have been reported
from other studies $^{91, 154}$. These are important findings as they point to the need for defining health education campaigns, which should not only target the individuals but also involve family members. The campaigns need to consider that betel-leaf use is regarded as a cultural phenomenon by many Bangladeshis, but not SLT products. Providing specific messages regarding the harmful effects of SLT use in tobacco campaigns would more likely sensitize SLT users, as well as family members to change their habit of using SLT products.

Weekly expenditure for SLT use varied according to the types of SLT products used in this study. One study from Bangladesh reported that average tobacco-related (both smoking and SLT) expenditure for an adult was 50-75 Bangladesh Taka ($\approx 0.71-1.07$ US$) per week $^{17}$. Although expenses for SLT products are presumably lower than that associated with cigarette smoking, Bangladeshi tobacco users have been estimated to spend approximately 4.5% of total monthly household expenditure on tobacco use which is a significant burden for people of lower socio-economic status $^{22}$. While increasing taxation on cigarettes is associated with decreased prevalence of smoking and people from lower socio-economic groups are more responsive to price $^{155}$, there is no policy for regulating price of SLT products in Bangladesh. Along with the socio-cultural acceptability of SLT usage, cheap prices of SLT products could be one of the important factors for increased prevalence of SLT use in Bangladesh.

Strengths of this study include exploring perceptions of SLT use among Bangladeshi population involving a large sample of non-smoking adults. Some of the issues explored in this study included the fact that whilst most participants were aware regarding harmful effects of SLT use in general, specific disease-
related awareness was not strong among the SLT users. Awareness raising campaigns should focus on SLT-related diseases which are consistently associated with use of SLT products such as oral diseases and cancers. Smokers have many functional strong positive beliefs for smoking which inhibit them to quit smoking. In contrast, SLT users in this study did not have similar strong positive beliefs for SLT use. We could utilize this opportunity to create awareness among Bangladeshi adults by focusing on the adverse effects of SLT use, which would outweigh the benefits of using SLT products. Family members had an important role to assist in quitting SLT use, which indicates the need to involve family members in tobacco control activities. Advice from doctors was another important influencing factor for quitting SLT products. Hence, it is important to involve physicians in tobacco control activities, as physicians are influential and may be able to help convince the general public for tobacco quitting. Mass media campaigns should highlight adverse effects of SLT use along with smoking-related harm. In terms of limitations, the data were collected from urban areas of Bangladesh; perceptions may differ among rural populations due to variation of education level and exposure to media.

Conclusions

This is the first study from Bangladesh, reporting comprehensive perception data of SLT use among non-smoking adults. Findings of this study could be considered for formulating future tobacco control activities in Bangladesh. Awareness campaigns should highlight adverse effects of SLT use which would outweigh the perceived benefits, and should focus on specific SLT-related diseases. The campaigns should also alert people regarding the influence of families and friends in introducing SLT products to their kin.
CHAPTER 5

Hospital controls vs. community controls: choice for a case-control study in Bangladesh
Chapter outline

Chapter 5 presents the manuscript that addresses the control selection issue which is inferred from the case-control study. It addresses the third research question:

- Does using hospital controls or community controls in a case-control study in Bangladesh give different results?

It compares hospital controls with community controls in terms of socio-demographic variables, risk factors for CHD, and SLT use. Based on the findings, the manuscript indicates an inference regarding the selection of controls for a case-control study.

This manuscript is submitted to *Epidemiologic Perspectives and Innovations* journal on 13th October 2011 and is awaiting a response:

Rahman MA, Spurrier N, Mahmood MA, Rahman M, Choudhury SR, Leeder S. Hospital controls vs. community controls: choice for a case-control study in Bangladesh.

Although the original manuscript was formatted according to the specific journal instruction, I have followed a consistent reference style throughout the entire thesis and the reference numbers are also chronologically arranged from the beginning to the end of this thesis. In addition, the table and figure numbers are also not based on each manuscript separately; rather they are sequenced chronologically in this thesis.

Rationale for developing this manuscript

Hospital controls and community controls can potentially differ in a number of ways, which have the possibility of introducing bias in a case-control study. Whilst there is a theoretical possibility of bias using hospital controls in a case-control study, there are limited studies to support this hypothesis. Therefore, this manuscript explores the
difference in results of a case-control study using both hospital controls and community controls.

**Rationale for choosing *Epidemiologic Perspectives and Innovations* journal**

*Epidemiologic Perspectives and Innovations* is an open access peer-reviewed journal that publishes articles on epidemiologic research methods, applications, critical overviews, teaching tools, perspectives, and other analytic work. Considering the focus on epidemiologic research methods and open accessibility, this journal was selected for this particular manuscript.

**Authors’ contributions**

MAR, NS and MAM discussed the need for and the overall constructs and concepts of the study design. MR, SRC and SL also contributed in the design of the study. MAR collected data from field sites, analysed and interpreted data, and finally, prepared the draft manuscript. NS, MAM, MR, SRC and SL reviewed drafts of the manuscript, provided feedback and incorporated their inputs. All of the authors read and approved the final version of the manuscript.
Statement of authorship

Hospital controls vs. community controls: choice for a case-control study in Bangladesh

*Epidemiologic Perspectives and Innovations* (Submitted on October 13, 2011)

Muhammad Aziz Rahman (candidate)
Discussed the need for and the overall constructs and concepts of the study design with Nicola Spurrier and Mohammad Afzal Mahmood. Collected data from field sites, analysed and interpreted data. Prepared the draft manuscript, reviewed based on co-authors’ inputs, submitted to the journal, and acted as a corresponding author.

Signed............................................................................. Date....................................

Nicola Spurrier
My contribution to this paper involved: Discussed the need for and the overall constructs and concepts of the study design. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed............................................................................. Date....................................

Mohammad Afzal Mahmood
My contribution to this paper involved: Discussed the need for and the overall constructs and concepts of the study design. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed............................................................................. Date....................................
Mahmudur Rahman
My contribution to this paper involved: Contributed in the design and provided support for the field activities in Bangladesh. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

(Signature is included in the appendix VI)

Sohel Reza Choudhury
My contribution to this paper involved: Contributed in the design and provided support for the field activities in Bangladesh. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

(Signature is included in the appendix VI)

Stephen Leeder
My contribution to this paper involved: Contributed in the design of the study. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

(Signature is included in the appendix VI)
Hospital controls vs. community controls: choice for a case-control study in Bangladesh

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3 NHFH&RI (National Heart Foundation Hospital & Research Institute), Dhaka, Bangladesh
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Abstract

Background
Hospital controls and community controls can differ in a number of ways with the potential to introduce bias in case-control studies. We aimed to determine whether hospital controls could be used in case-control studies with minimal bias, where resource constraints limit recruitment of community controls.

Methods
Hospital controls and community controls were compared in terms of socio-demographic and risk factor variables in a study of smokeless tobacco (SLT) use and coronary heart disease (CHD) in Bangladesh in 2010. Incident cases of CHD were selected from two cardiac hospitals. Hospital controls were selected from outpatient departments of the same hospitals. Community controls were selected from neighbourhoods matched to those of CHD cases. Four community controls and one hospital control were matched to each case on age and gender.

Results
The study enrolled 302 cases, 302 hospital controls, and 1208 community controls. Distribution of age, gender, marital status, occupation, and socio-economic status was similar between hospital controls and community controls. Compared to community controls, hospital controls were more educated, had higher rates of hypertension and reported more family history of heart diseases. On the other hand, they reported relatively less physical activity (p<0.05). Current use of SLT was higher amongst community controls (38%) compared to hospital controls (32%), but this was not a statistically significant difference (adjusted OR 0.81, 95% CI 0.58-1.12). Current use of SLT was not associated with an increased risk of CHD when data from community controls were used (adjusted OR 0.87, 95% CI 0.63 to 1.19,
p>0.05), nor when data from hospital controls were used (adjusted OR 1.00, 95% CI 0.63 to 1.60, p>0.05).

Conclusions
There were significant differences between the two groups of controls but only on confounding variables which could be measured and adjusted for during multivariate analyses. For comparable future studies in resource-scarce settings, it is possible to enrol hospital controls with careful planning which are similar to potential community controls, whilst minimising selection bias.

Keywords
Choice of controls, hospital controls, community controls, case-control study, smokeless tobacco, coronary heart disease, Bangladesh
Introduction

Selection of an appropriate control is crucial in a case-control study to avoid selection bias. Controls should be selected from the same source population from where the cases are selected, be free from the disease of interest, and be independent of the exposure variable of the study. Controls are generally selected from a hospital or community setting.

Hospital controls and community controls can potentially differ in a number of ways, which may introduce bias into a case-control study. The distribution of the exposure variable can differ between hospital controls and community controls. The distribution of confounding variables also may differ between hospital controls and community controls. This is because hospital controls are more likely to have co-morbidities which have resulted in their hospital appointment or hospitalisation. If the disease of a hospital control (e.g. hypertension) is due to the main exposure variable (e.g. smokeless tobacco), the estimated odds ratios (ORs) are likely be biased (Berkson’s bias). In this instance, ORs would be decreased towards null if hospital controls are used.

Hospital controls undergo similar diagnostic procedures as cases to screen out the disease of interest in hospital settings, whereas this selection procedure is generally lacking for community controls. The later can result in the introduction of misclassification bias in a case-control study. In addition, refusal rates are usually high among community controls as they are less motivated and may have less time to participate in a research project. The distribution of exposure variables may systematically differ between respondents and non-respondents, which could lead to
bias. If the distribution of the exposure variable is high among the respondent community controls, the estimated ORs are likely to be decreased towards null.

Hospital controls are also more likely to be selected from the same source population from where the cases were selected compared to community controls, thus are more likely to be closely matched on important confounders.

Cases as well as hospital controls may recall exposure history in a more detailed manner compared to community controls because they have been exposed to medical history taking (often several times). Therefore, the association of risk is likely to be under-estimated if hospital controls are used. In addition, healthcare seeking behaviour is likely to be comparable between cases and hospital controls, as both groups have accessed a hospital service. Finally, hospital controls are easily accessible, convenient to select and conduct interviews with, and overall require less financial resources for recruitment compared to community controls.

Whilst there is a theoretical possibility of bias using hospital controls in a case-control study, there are limited studies to support this hypothesis. Neupane et al. reported the difference between hospital controls and community controls in a case-control study assessing the risk factors for community-acquired pneumonia (CAP). Hospital controls yielded weaker associations for CAP compared to community controls in that study, and the authors indicated the preference for community controls for a case-control study if the response rate was likely to be high. Similarly, another case-control study of hepatocellular carcinoma with both groups of controls reported a preference for community controls, as the reported ORs using
hospital controls were underestimated \(^{163}\). On the other hand, another US study exploring the association of different risk factors and CHD did not find any difference between hospital and community control groups, suggesting that studies of CHD could utilize hospital controls \(^{161}\).

We had the opportunity to enrol both hospital controls and community controls in a large case-control study recently conducted in Bangladesh exploring the association between smokeless tobacco (SLT) use and coronary heart disease (CHD). Considering the financial implications to recruit community controls, this issue is of particular importance for a resource-poor developing country where funding for research is scarce. The aim of the analyses presented in this paper was to assess possible selection bias inherent in selecting controls for a case-control study by comparing hospital controls and community controls in terms of socio-demographic variables, the exposure variable of interest and potential confounding variables. This would allow a more informed decision as to whether hospital controls could be used in case-control studies where resource constraints limit recruitment of community controls.

**Methods**

**Study settings**

A matched case-control study was conducted in 2010. Data were collected through structured interviews by four trained interviewers. CHD cases were recruited from inpatient facilities of the National Institute of Cardiovascular Diseases (NICVD) and the National Heart Foundation Hospital and Research Institute (NHFH&RI), Dhaka, Bangladesh. Hospital controls were recruited from cardiac outpatient facilities and
community controls were recruited from the neighbourhood households of CHD cases within Dhaka City Corporation (DCC) areas.

**Study population**

Inclusion criteria were: age 40-75 years, non-smokers, residence within DCC areas, and well enough to undertake a 20 minute interview. Non-smokers were defined as either (i) never smokers or (ii) ex-smokers who had not smoked a single puff in the past 10 years. CHD patients admitted to the two hospitals and diagnosed as incident cases of CHD (diagnosis for the first time within the last one-year) by hospital cardiologists, were selected as cases. Either angina and/or myocardial infarction were included in the definition of CHD for the purpose of this study.

Patients, who attended cardiac outpatient facilities of the same hospitals and were diagnosed as not suffering from CHD by hospital cardiologists, were selected as hospital controls. It should be noted that unlike a developed country, patients can visit tertiary cardiac outpatient facilities by themselves in Bangladesh, without having a referral from a general practitioner or primary health care provider. In fact, this is the case for most patients. Due to the resource limitations of this study, we were only able to recruit hospital controls from cardiac outpatient facilities. There included a hypertension clinic at NHFH&RI, which operates twice a week. While patients with known hypertension attend the clinic for treatment and follow-up, other individuals self refer for hypertension screening. About two-thirds (64%) of the hospital controls were selected from the hypertension clinic of NHFH&RI, which was the main source of recruiting controls from that hospital. This poses a risk of potential bias because SLT use is known to be associated with hypertension. Diagnoses of hospital
controls included hypertension (62%), non-specific chest pain (48%), and gastric acidity (13%). Some patients were not assigned a diagnosis, and symptoms of palpitation (10%) or breathlessness (8%) were given in the case-notes. Each hospital control was matched with a corresponding case by age (±5 years) and sex.

Neighbourhood residents of the CHD cases, who had no self-reported cardiac disease (“Have you ever been told by a doctor or health-care worker that you have heart disease?”), were selected as community controls. Interviewers travelled to the residence of a CHD case and door knocked on the next house in the apartment block or in the street until an eligible control for that case was located. Control subjects were matched by age (±5 years), sex and socio-economic status (SES) (monthly house-rent used as a proxy for SES) to the corresponding case. Hospital controls were not matched with cases for SES. This was because of the practical issue of interviewing hospital controls in outpatient areas. This was a public space and we felt that it would be culturally inappropriate to ask such personal questions like house-rent. In addition, that setting was very busy and the research assistants did not have the luxury of same time as they did in private dwellings for community controls. If a suitable control subject could not be located in a suburb of the CHD case, the next adjacent suburb was used (this happened in 28% of cases).

Data collection
A structured interview was used to measure socio-demographic, exposure and confounding variables. Socio-demographic items included age, gender, marriage, residence, education, occupation and monthly house-rent. The SLT use questionnaire which included items regarding current and past use, as well as types
of SLT products used. If a respondent used any SLT product with/without betel-leaf or areca-nut in the last one year, he/she was categorized as a current SLT user. If a respondent ceased using SLT products for at least last twelve months, he/she was categorized as a past SLT user. If a respondent was not using any SLT product currently or in the past, he/she was categorized as never a tobacco user (as they were also non-smokers according to the participant selection criteria).

To determine the potential confounding effects in the association between SLT use and CHD, information on other known risk factors for CHD were collected. These included self-reported history of hypertension, diabetes, family history of heart diseases, level of physical activity, current use of hormonal contraceptives among female participants, exposure to indoor smoking, and stressful life events within the past year. Some of these selected risk factors have been included in prior tobacco research in Bangladesh 18, 19.

Interviewers described the study objectives prior to obtaining written consent from each study participant. Reasons for non-participation were documented. Categorization of CHD cases according to the case definition was undertaken by the first author and selection of the majority of controls was done in his presence. The author trained the interviewers and undertook regular supervision of all data collection activities. In addition, the first author re-interviewed four cases (1%), 24 community controls (2%) and six hospital controls (2%) to ensure that interviewers were obtaining data in the intended manner.
Sample size

Sample size for this case-control study was calculated using Epi-info version 3.5.1. Considering 95% confidence intervals, 80% power of the study, control: case ratio of 4:1, correlation for matched design 0.1, an expected frequency of exposure (SLT) among controls of 25% \(^{22}\), a clinically significant odds ratio considered to be 1.5 \(^{19,83}\), 302 cases and 1,208 controls were required for this study. Additionally, one hospital control was selected for each case.

Data analysis

Analyses were performed with STATA version 10. Initially, categorical variables were described as proportions for socio-demographic variables, SLT use, and risk factors for CHD. These variables were then compared between hospital controls and community controls. To determine the association between SLT use and CHD, cases and each group of controls were compared using cross-tabulations. Similarly, to determine the association between SLT use and choice of controls, hospital controls and community controls were compared using cross-tabulations. To statistically compare cases and controls as well as hospital controls and community controls, we used McNemar’s chi-squared (\(\chi^2\)) tests when the frequency in all of the cells of the cross-tabulation was \(\geq 5\) and Fisher’s exact test otherwise. Univariate conditional logistic regression models were fitted to determine the strength of the association between SLT use and CHD, with the effect of SLT use expressed as a matched odds ratios (ORs) with 95% confidence intervals (CIs). Then multivariate conditional logistic regression models were fitted to adjust for potential confounding variables. Confounding variables were identified initially using a \(\chi^2\) test relating the variables to CHD. If the p-value from the \(\chi^2\) test was less than 0.20 and there was no
missing data for the confounder, that variable was included into the final multivariate analysis. The adjusted ORs with 95% CIs were used to report the association between SLT use and CHD, and the association between SLT use and choice of controls. To determine whether the inclusion of ex-smokers could have biased the results, analyses were conducted separately for never-smokers, ex-smokers, and combining both groups.

Ethics

The protocol for this project was approved by The University of Adelaide Human Research Ethics Committee, Australia (H-117-2009) and the local ethics committee of Bangladesh Medical Research Council, Bangladesh (BMRC/NREC/2007-2010/125).

Results

Study participants

Eligible participants included 311 hospital cases, 1293 community controls and 316 hospital controls. Nine potential hospital cases (3%), 85 potential community controls (7%), and 14 potential hospital controls (4%) did not consent to participate. Thus, the overall response rate was 94%. Results for the remaining 302 CHD cases, 1208 community controls and 302 hospital controls are presented in this paper.

Socio-demographic variables

Mean age of the hospital controls was 52 (±8.4) years and the community controls was 53 (±8.5) years. Hospital controls and community controls had similar distribution of age and gender, as they were matched by these variables. There was
a significant difference (p<0.05) between hospital controls (81%) and community controls (74%) regarding highest level of education achieved. Half of the controls were categorized as middle SES. There was no difference between hospital controls and community controls according to marital status, primary occupation and SES (Table 11).

Risk factors for CHD

More than two-thirds of the hospital controls (67%) were hypertensive compared to one-third (34%) of the community controls (p<0.05). This is a result of recruiting hospital controls from the hypertension clinic of NHFH&RI. There was also a significant difference (p<0.05) between hospital controls (27%) and community controls (22%) regarding reporting a positive family history of heart diseases. Two-thirds of the community controls (65%) undertook physical activity besides their regular work for at least 30 minutes per week that made them huff and puff compared to half of the hospital controls (p<0.05). There was no difference between hospital controls and community controls regarding reporting of diabetes, use of hormonal contraceptives by female respondents, exposure to indoor smoking, and occurrence of acute psycho-social stress within last one year (Table 11).

Use of SLT products

Current use of SLT was more common among community controls (38%) compared to hospital controls (32%) among the total participants, and when data were analysed separately for never-smokers and ex-smokers (Table 12). For the total sample, jarda (0.96% nicotine) was more commonly used than sada-pata (0.18-6.04% nicotine) and gul (5.48% nicotine). There was no difference in current use of
jarda, sada-pata and gul between hospital controls and community controls. (Data not shown)

Univariate analyses did not show any difference between current SLT use and choice of controls. When multivariate analyses were undertaken, there was also no statistically significant association between current SLT use and choice of controls, when total participants were used (adjusted OR 0.81, 95% CI 0.58-1.12), or when never-smokers were used (adjusted OR 0.94, 95% CI 0.63-1.40), or when ex-smokers were used (adjusted OR 0.78, 95% CI 0.38-1.59). When cases and controls were compared, there was no statistically significant association between current SLT use and CHD, when community controls were used (adjusted OR 0.87, 95% CI 0.63-1.19), or hospital controls were used (adjusted OR 1.00, 95% CI 0.63-1.60) (Table 13). Use of individual SLT products was also not associated with choice of controls, when data were analysed separately for never-smoker or ex-smoker participants, and for current use, quitting or ever use of SLT products.
Table 11: Socio-demographic and risk factor variables for coronary heart disease (CHD) among the study participants

<table>
<thead>
<tr>
<th>Socio-demographic variables</th>
<th>Total, N (%)</th>
<th>Cases, n(%)</th>
<th>Hospital controls, n(%)</th>
<th>Community Controls, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total study participants</td>
<td>1812</td>
<td>302</td>
<td>302</td>
<td>1208</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>53.0 (±8.5)</td>
<td>53.5 (±8.5)</td>
<td>51.9 (±8.4)</td>
<td>53.1 (±8.5)</td>
</tr>
<tr>
<td>Age-groups (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-48</td>
<td>635 (35.0)</td>
<td>95 (31.5)</td>
<td>121 (40.1)</td>
<td>419 (34.7)</td>
</tr>
<tr>
<td>49-57</td>
<td>641 (35.4)</td>
<td>109 (36.1)</td>
<td>102 (33.8)</td>
<td>430 (35.6)</td>
</tr>
<tr>
<td>58-66</td>
<td>405 (22.4)</td>
<td>72 (23.8)</td>
<td>61 (20.2)</td>
<td>272 (22.5)</td>
</tr>
<tr>
<td>67-75</td>
<td>131 (7.2)</td>
<td>26 (8.6)</td>
<td>18 (6.0)</td>
<td>87 (7.2)</td>
</tr>
<tr>
<td>Male participants</td>
<td>900 (49.7)</td>
<td>150 (49.7)</td>
<td>150 (49.7)</td>
<td>600 (49.7)</td>
</tr>
<tr>
<td>Married (and living with spouse)</td>
<td>1414 (78.0)</td>
<td>232 (76.8)</td>
<td>243 (80.5)</td>
<td>939 (77.8)</td>
</tr>
<tr>
<td>Highest level of education achieved</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>204 (11.3)</td>
<td>34 (11.3)</td>
<td>19 (6.3)</td>
<td>151 (12.5)</td>
</tr>
<tr>
<td>Can sign names</td>
<td>212 (11.7)</td>
<td>27 (8.9)</td>
<td>35 (11.6)</td>
<td>150 (12.4)</td>
</tr>
<tr>
<td>Primary</td>
<td>527 (29.1)</td>
<td>95 (31.5)</td>
<td>94 (31.2)</td>
<td>338 (28.0)</td>
</tr>
<tr>
<td>Secondary</td>
<td>239 (13.2)</td>
<td>44 (14.6)</td>
<td>42 (14.0)</td>
<td>153 (12.7)</td>
</tr>
<tr>
<td>Higher-secondary</td>
<td>197 (10.9)</td>
<td>33 (10.9)</td>
<td>48 (15.9)</td>
<td>116 (9.6)</td>
</tr>
<tr>
<td>Above higher-secondary</td>
<td>418 (23.1)</td>
<td>66 (21.9)</td>
<td>62 (20.6)</td>
<td>290 (24.0)</td>
</tr>
<tr>
<td>Primary occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Service holder</td>
<td>558 (30.8)</td>
<td>87 (28.8)</td>
<td>102 (33.8)</td>
<td>369 (30.6)</td>
</tr>
<tr>
<td>Businessmen</td>
<td>262 (14.5)</td>
<td>42 (13.9)</td>
<td>40 (13.2)</td>
<td>180 (14.9)</td>
</tr>
<tr>
<td>Housewife</td>
<td>741 (40.9)</td>
<td>126 (41.7)</td>
<td>120 (39.7)</td>
<td>495 (41.0)</td>
</tr>
<tr>
<td>Retired</td>
<td>235 (13.0)</td>
<td>47 (15.6)</td>
<td>39 (12.9)</td>
<td>149 (12.3)</td>
</tr>
<tr>
<td>Socio-economic status (SES) by monthly house-rent (HR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower SES (HR &lt;5000 BDT)</td>
<td>656 (36.2)</td>
<td>109 (36.1)</td>
<td>114 (37.7)</td>
<td>433 (35.8)</td>
</tr>
<tr>
<td>Middle SES (HR 5000-10000 BDT)</td>
<td>930 (51.3)</td>
<td>152 (50.3)</td>
<td>158 (52.3)</td>
<td>620 (51.3)</td>
</tr>
<tr>
<td>Higher SES (HR &gt;10000 BDT)</td>
<td>226 (12.5)</td>
<td>41 (13.6)</td>
<td>30 (9.9)</td>
<td>155 (12.8)</td>
</tr>
<tr>
<td>Presence of other risk factors for CHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>796 (43.9)</td>
<td>180 (59.6)</td>
<td>203 (67.2)</td>
<td>413 (34.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>446 (24.6)</td>
<td>129 (42.7)</td>
<td>73 (24.2)</td>
<td>244 (20.2)</td>
</tr>
<tr>
<td>Family history of heart disease</td>
<td>421 (23.2)</td>
<td>94 (31.5)</td>
<td>79 (27.2)</td>
<td>248 (21.5)</td>
</tr>
<tr>
<td>Performed physical activities</td>
<td>1116 (61.6)</td>
<td>179 (59.5)</td>
<td>149 (50.2)</td>
<td>788 (65.3)</td>
</tr>
<tr>
<td>Use of hormonal contraceptives</td>
<td>60 (3.3)</td>
<td>9 (3.0)</td>
<td>10 (3.3)</td>
<td>41 (3.4)</td>
</tr>
<tr>
<td>Exposure to indoor smoking</td>
<td>321 (17.7)</td>
<td>58 (19.2)</td>
<td>45 (14.9)</td>
<td>218 (18.0)</td>
</tr>
<tr>
<td>Acute psycho-social stress#</td>
<td>434 (24.0)</td>
<td>94 (31.1)</td>
<td>75 (24.8)</td>
<td>265 (21.9)</td>
</tr>
</tbody>
</table>

Superscripts indicate which categories show a statistically significant (p<0.05) difference using chi-squared tests between hospital controls and community controls: same letter indicates no difference, different letter indicates a difference.

# Such an incident that caused mental agony, sorrow, unhappiness or anxiety within last one year, like death of family members, divorce, separation, sudden job loss, unemployment, financial loss etc.
Table 12: Status of smokeless tobacco (SLT) use according to smoking exposure among the study participants

<table>
<thead>
<tr>
<th>Smokeless tobacco use</th>
<th>Total, N (%)</th>
<th>Cases, n(%)</th>
<th>Hospital controls, n(%)</th>
<th>Community Controls, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total study participants (non-smokers)</td>
<td>1812</td>
<td>302</td>
<td>302</td>
<td>1208</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>1292 (71.3)</td>
<td>203 (67.2)</td>
<td>225 (74.5)\textsuperscript{a}</td>
<td>864 (71.5)\textsuperscript{a}</td>
</tr>
<tr>
<td>Ex-smokers (quit &gt;10 years ago)</td>
<td>520 (28.7)</td>
<td>99 (32.8)</td>
<td>77 (25.5)\textsuperscript{a}</td>
<td>344 (28.5)\textsuperscript{a}</td>
</tr>
<tr>
<td>Non-smokers (total study participants)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever users of SLT products</td>
<td>701 (38.7)</td>
<td>118 (39.1)</td>
<td>101 (33.4)\textsuperscript{a}</td>
<td>482 (39.9)\textsuperscript{b}</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>648 (35.8)</td>
<td>99 (32.8)</td>
<td>95 (31.5)\textsuperscript{a}</td>
<td>454 (37.6)\textsuperscript{b}</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>53 (2.9)</td>
<td>19 (6.3)</td>
<td>6 (2.0)\textsuperscript{a}</td>
<td>28 (2.3)\textsuperscript{a}</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>1292</td>
<td>203</td>
<td>225</td>
<td>864</td>
</tr>
<tr>
<td>Ever users of SLT products</td>
<td>444 (34.4)</td>
<td>60 (29.6)</td>
<td>71 (31.6)\textsuperscript{a}</td>
<td>313 (36.2)\textsuperscript{a}</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>418 (32.4)</td>
<td>51 (25.1)</td>
<td>68 (30.2)\textsuperscript{a}</td>
<td>299 (34.6)\textsuperscript{a}</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>26 (2.0)</td>
<td>9 (4.4)</td>
<td>3 (1.3)\textsuperscript{a}</td>
<td>14 (1.6)\textsuperscript{a}</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>520</td>
<td>99</td>
<td>77</td>
<td>344</td>
</tr>
<tr>
<td>Ever users of SLT products</td>
<td>257 (49.4)</td>
<td>58 (58.6)</td>
<td>30 (39.0)\textsuperscript{a}</td>
<td>169 (49.1)\textsuperscript{a}</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>230 (44.2)</td>
<td>48 (48.5)</td>
<td>27 (35.1)\textsuperscript{a}</td>
<td>155 (45.1)\textsuperscript{a}</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>27 (5.2)</td>
<td>10 (10.1)</td>
<td>3 (3.9)\textsuperscript{a}</td>
<td>14 (4.1)\textsuperscript{a}</td>
</tr>
</tbody>
</table>

Superscripts indicate which categories show a statistically significant (p<0.05) difference using chi-squared tests between hospital controls and community controls; same letter indicates no difference, different letter indicates a difference.
Table 13: Univariate and multivariate matched analysis showing association between coronary heart disease and use of smokeless tobacco, as well as association between smokeless tobacco use and choice of controls (by smoking status of the participants)

<table>
<thead>
<tr>
<th></th>
<th>Cases vs. hospital controls</th>
<th>Cases vs. community controls</th>
<th>Hospital controls vs. community controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases, n(%)</td>
<td>Hospital Controls, n(%)</td>
<td>OR</td>
</tr>
<tr>
<td>Never users of any tobacco (Reference)</td>
<td>302</td>
<td>302</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-smokers (total study participants)</td>
<td>302</td>
<td>118 (39.1)</td>
<td>101 (33.4)</td>
</tr>
<tr>
<td>Ever users of SLT products</td>
<td>203</td>
<td>203</td>
<td>0.30</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>302</td>
<td>99 (32.8)</td>
<td>95 (31.5)</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>203</td>
<td>19 (6.3)</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>302</td>
<td>101 (33.4)</td>
<td>101 (33.4)</td>
</tr>
<tr>
<td>Ever users of SLT products</td>
<td>302</td>
<td>203</td>
<td>0.30</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>302</td>
<td>99 (32.8)</td>
<td>95 (31.5)</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>302</td>
<td>19 (6.3)</td>
<td>6 (2.0)</td>
</tr>
</tbody>
</table>

The variables that were significant (p<0.20) during initial univariate analysis, were selected as confounders and adjusted during multivariate analysis

* Adjusted for: age, marital status, hypertension, diabetes, indoor smoking exposure and acute psycho-social stress; matched for: age and sex

§ Adjusted for: age, hypertension, diabetes and acute psycho-social stress; matched for: age, sex, residential areas and socio-economic status

¶ Adjusted for: age, marital status and hypertension; matched for: age and sex
Discussion

In this study, we found a significant difference between hospital controls and community controls for highest level of education achieved, presence of hypertension, positive family history of heart disease, and level of physical activity. There was no statistically significant difference between the two groups of controls for use of SLT. Findings regarding the association between SLT use and CHD did not change using either hospital controls or community controls.

Hospital controls were more educated compared to community controls. Whilst the hospitals involved are public health care facilities, factors such as distance from residence, transport facilities, convenience, affordability of treatment, and previous experience of hospital visit may impact on accessing hospital services. Individuals who are more highly educated may have greater levels of health literacy and be more health conscious compared to less educated people in Bangladesh\textsuperscript{165}. The higher prevalence of hypertension among hospital controls was primarily due to recruiting from the hypertension clinic of one hospital. In addition, literate people are more likely to be aware of hypertension compared to poorly-educated people within Bangladesh context\textsuperscript{166}. Hospital controls reported more positive family history of heart diseases, which may be due to repeated exposure to medical history taking. Hospital controls possibly perform less physical activity as they belong to an unwell population group and that most of them were considered to be hypertensive or under treatment for hypertension. In addition, there may be other unmeasured health problems which prevented them undertaking physical activity.
Prevalence of SLT use was slightly higher among community controls compared to hospital controls in this study, although the difference was not statistically significant. A previous study from Bangladesh by the first author also reported a similar finding. In that study (n=207), prevalence of SLT use among hospital patients were less (22%) than that compared to the general population (32%). On the other hand, prevalence of SLT use among hospital controls in the present study is similar to the prevalence of the general source population. For example, the SLT prevalence in Bangladesh was reported to be 30% in the Behaviour Risk Factor Surveillance study and 27% by the recent Global Adult Tobacco Survey (GATS). However, the reported prevalence of SLT use in the current study, where urban inhabitants were the study participants, would not necessarily be the same in other areas of Bangladesh, as some studies reported higher prevalence of SLT use in rural areas than urban settings in Bangladesh.

Community controls reported that they were free from any SLT-related diseases, but not the hospital controls. In fact, hospital controls were hypertensive or being treated for hypertension and studies have reported a significant association between SLT use and hypertension. As mentioned earlier, this is an example of Berkson’s bias, which has the potential to decrease the reported ORs towards null. However, in practical terms these were the only readily available source of hospital controls in this instance. This is the most important limitation of the present study, but provides a useful example of this phenomenon. On the other hand, there might be under-reporting of hypertension by community controls resulting in an over-estimation of the reported ORs when data were analysed using community controls. Because hypertension is an important potential confounder, it was adjusted for using...
multivariate analyses. Use of SLT is known to be associated with premalignant oral lesions, many cancers (oral, laryngeal, pharyngeal, oesophageal, lung and pancreatic), diabetes, asthma, and poor reproductive outcomes \(^{100}\). Although community controls were screened out by self-reporting, hospital controls were screened out by hospital cardiologists; and none of them had any reported diagnosis of these diseases. In addition, the difference in the distribution of other confounding variables between hospital controls and community controls was also addressed by adjustment during multivariate analyses.

The difference in screening procedure to select controls from hospitals and communities might have resulted in inclusion of undiagnosed CHD cases in community controls. In this event, it is likely that the reported ORs using community controls were over-estimated in this study. Refusal rate was also low and similar between hospital controls and community controls, which indicates that the reported ORs were unlikely to have been affected by this issue. The ORs calculated using hospital controls in the current study might be underestimated due to the recall of exposure history. However, we addressed this issue during data collection by defining a time-frame of twelve months within the last one year for current use and quitting of SLT products. It is difficult to compare the health care seeking behaviour between hospital controls and community controls. Although there could be a difference in perceptions of health care seeking, having the availability of free and accessible medical care at the public cardiac hospital in this study partially minimises this difference. Other issues of accessibility as mentioned earlier should also be considered.
We did not find any difference in the association between SLT use and CHD utilizing either group of controls. Findings of our study are also supported by earlier case-control\textsuperscript{13, 14, 122, 123} as well as cohort studies\textsuperscript{118-120}. However, all of these four Swedish case-control studies, included controls from population registers and none of them included both groups of controls. The INTERHEART study\textsuperscript{80} included both groups of controls, but did not report the results separately for each group.

It was beyond the scope of this study to verify the self-reported diagnosis of non-CHD among the community controls by a qualified physician. In addition, we could not include four hospital controls for each case as we did for community controls due to budget limitations. This will have reduced the power of the study when only hospital controls were included in the analyses. Studies with similar number of controls per case in each group could be designed in future to have a comprehensive interpretation regarding this issue.

**Conclusions**

We found a significant difference between hospital controls and community controls, in terms of confounding variables but not in terms of exposure variable. The confounders could be measured and adjusted for statistically during multivariate analyses. Most importantly, there was no difference in the results regarding the association between SLT use and CHD using either group of controls in this study. This is the first case-control study in a larger scale from South Asian context, reporting the comparison between two groups of controls. Results of a study would be more credible if the exposure of cases could be compared to both hospital controls and community controls\textsuperscript{159, 161}, thus allowing for an appreciation and
balance of all possible positive and negative biases. However, considering the budget constraints for any public health research in resource-scarce settings like South Asia, researchers should only consider selecting hospital controls for a case-control study if potential confounders are carefully considered, measured and adjusted for.
CHAPTER 6

Rose Angina Questionnaire: validation with cardiologists’ diagnoses to detect coronary heart disease in Bangladesh
Chapter outline

Chapter 6 presents the manuscript that addresses the utility of the RAQ to detect CHD among Bangladeshi population. It addresses the forth research question:

- What is the utility of the Rose Angina Questionnaire (RAQ) for detecting CHD among Bangladeshi adults?

It describes the accuracy of the RAQ for detecting CHD by comparing with the diagnoses made by the cardiologists. This manuscript is submitted to The Southeast Asian Journal of Tropical Medicine and Public Health on 17th November 2011 and is awaiting a response:

  Rahman MA, Spurrier N, Mahmood MA, Rahman M, Choudhury SR, Leeder S. Rose Angina Questionnaire: validation with cardiologists’ diagnoses to detect coronary heart disease in Bangladesh.

Although the original manuscript was formatted according to the specific journal instruction, I have followed a consistent reference style throughout the entire thesis and the reference numbers are also chronologically arranged from the beginning to the end of this thesis. In addition, the table and figure numbers are also not based on each manuscript separately; rather they are sequenced chronologically in this thesis.

Rationale for developing this manuscript

The RAQ, being a questionnaire-based tool to detect CHD, has variable sensitivity and specificity compared with different other diagnostic tools. Sensitivity and interpretation of chest pain may differ depending on culture, education, and socioeconomic status. Therefore, it is presumed that the responses to the RAQ would differ between Western countries and South Asian countries. Studies validating the RAQ to detect CHD among South Asian populations are very limited.
Therefore, this manuscript aims to validate the RAQ to detect CHD by comparing RAQ categorization with diagnoses by cardiologists in Bangladesh.

**Rationale for choosing The Southeast Asian Journal of Tropical Medicine and Public Health**

The Southeast Asian Journal of Tropical Medicine and Public Health is a peer-reviewed journal that publishes articles focused on different public health issues of Southeast Asia. Considering the applicability of the current research to South Asian populations, this journal was selected for this particular manuscript.

**Authors’ contributions**

MAR, NS and MAM discussed the need for and the overall constructs and concepts of the study design. MR, SRC and SL also contributed in the design of the study. MAR collected data from field sites, analysed and interpreted data, and finally, prepared the draft manuscript. NS, MAM, MR, SRC and SL reviewed drafts of the manuscript, provided feedback and incorporated their inputs. All of the authors read and approved the final version of the manuscript.
Statement of authorship

Rose Angina Questionnaire: validation with cardiologists’ diagnoses to detect coronary heart disease in Bangladesh

*The Southeast Asian Journal of Tropical Medicine and Public Health*

(Submitted on November 17, 2011)

**Muhammad Aziz Rahman (candidate)**
Discussed the need for and the overall constructs and concepts of the study design with Nicola Spurrier and Mohammad Afzal Mahmood. Collected data from field sites, analysed and interpreted data. Prepared the draft manuscript, reviewed based on co-authors’ inputs, submitted to the journal, and acted as a corresponding author.

Signed............................................................................. Date....................................

**Nicola Spurrier**
My contribution to this paper involved: Discussed the need for and the overall constructs and concepts of the study design. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed............................................................................. Date....................................

**Mohammad Afzal Mahmood**
My contribution to this paper involved: Discussed the need for and the overall constructs and concepts of the study design. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed............................................................................. Date....................................
Mahmudur Rahman
My contribution to this paper involved: Contributed in the design and provided support for the field activities in Bangladesh. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

(Signature is included in the appendix VI)

Sohel Reza Choudhury
My contribution to this paper involved: Contributed in the design and provided support for the field activities in Bangladesh. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

(Signature is included in the appendix VI)

Stephen Leeder
My contribution to this paper involved: Contributed in the design of the study. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

(Signature is included in the appendix VI)
Rose Angina Questionnaire: validation with cardiologists’ diagnoses to detect coronary heart disease in Bangladesh

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Abstract

The study aimed to validate the Rose Angina Questionnaire (RAQ) for detecting coronary heart disease (CHD) by comparing RAQ categorization with diagnoses by cardiologists in Bangladesh. Patients of 40-75 years attending to two cardiac hospitals were categorized as CHD positive and CHD negative by cardiologists. CHD positive individuals were incident cases and recruited from inpatient departments, whereas CHD negative individuals were recruited from outpatient departments. The RAQ was used to reclassify these patients into CHD positive [RAQ] and CHD negative [RAQ]. The original version of the RAQ was translated into Bengali language. We included 302 CHD positive [cardiologists] and 302 CHD negative [cardiologists] individuals. Out of 604 individuals, the RAQ reclassified 194 individuals as CHD positive [RAQ] and 409 individuals as CHD negative [RAQ]. For sensitivity and specificity, out of 301 CHD positive [cardiologists] individuals, 53% were categorized as having CHD by the RAQ; and out of 302 CHD negative [cardiologists] individuals, 89% were categorized as not having CHD by the RAQ. Compared with diagnoses by cardiologists, the RAQ had positive likelihood ratio of 4.8 for detecting CHD among Bangladeshi adults. There was no difference of sensitivity and specificity when subgroup analyses were conducted by age and gender. But sensitivity of the RAQ was more among people from lower socioeconomic status compared to the higher group. The RAQ had moderate sensitivity but high specificity to detect CHD in this study. It can be used to screen individuals at risk of CHD in large scale epidemiological surveys and at primary health care settings where it is impractical to use cardiologists’ diagnoses.

Keywords

Bangladesh, coronary heart disease, Rose Angina Questionnaire.
Introduction

The Rose Angina Questionnaire (RAQ) was developed in 1962 to detect ischemic heart pain (angina pectoris and myocardial infarction) for epidemiological field-surveys. Since then, the RAQ has been used in many countries to detect coronary heart disease (CHD) in epidemiological research. Rose suggested that the sensitivity and specificity of the questionnaire may vary between countries. Since then many studies have been conducted to validate the RAQ. The chosen gold standard varied from research to research and included clinicians' diagnoses, electrocardiogram (ECG) changes, thallium scintigraphy, coronary calcification, and angiographic changes. Depending on the gold standard used, studies reported different sensitivity and specificity of the RAQ, but generally there has been high specificity (80-95%) but variable sensitivity (19-83%). The RAQ was developed originally based on responses from men only. Since then a number of studies have been conducted including both genders, and have suggested that the RAQ is suitable for use by women as well.

In the original RAQ, angina pectoris was indicated by responses to seven questions and possible myocardial infarction was indicated by response to a single question. Rose defined angina pectoris as, “a chest pain or discomfort with these characteristics: (a) the site must include either the sternum (any level) or the left arm and left anterior chest (defined as the anterior chest wall between the levels of clavicle and lower end of sternum), (b) it must be provoked by either hurrying or walking uphill (or by walking on the level, for those who never attempt more), (c) when it occurs on walking it must make the subject either stop or slacken pace, unless nitroglycerin is taken, (d) it must disappear on a majority of occasions in 10
minutes or less from the time when the subject stands still.” Possible myocardial infarction was defined as, “one or more attacks of severe pain across the front of the chest lasting for 30 minutes or longer.” The RAQ has been modified in various subsequent studies. For example, by altering the number of questions, specifying a time-period, or through translation to another language. For example, Fischbacher et al. undertook a study of UK residents and translated the RAQ into Hindi, Punjabi, Urdu, and Bengali. Other researchers have translated into Arabic, Thai, Bhasa Melayu, and Farsi.

Studies validating the RAQ to detect CHD among South Asian populations are limited. Fischbacher et al. showed that the sensitivity of the RAQ to categorize definite angina compared to physicians’ diagnoses was 21% among South Asian people (Indian, Bangladeshi, Pakistani) in UK, whereas it was 37% for people of European descent. Sensitivity and interpretation of chest pain may differ depending on culture, education, and socioeconomic status (SES). Richards et al. reported that people from lower SES had greater perceived vulnerability of chest pain and they had more Rose angina with high grade compared to affluent people. Therefore, it is presumed that the responses to the RAQ would differ between Western countries and South Asian countries.

South Asian people have an early onset of CHD and die prematurely compared to other Caucasians. Bangladesh, a developing country from South Asia, also has a huge burden of CHD. Although prevalence of CHD is 3% in Bangladesh, cardiovascular diseases are estimated to account for 27% of all deaths there. Therefore, screening people at risk of CHD is important for early intervention.
Specifically for resource-poor settings, the tool for detecting CHD should be standardized, sensitive, specific as well as low in cost. There are currently no screening tools to be used by health care providers in primary health care settings, which are accessed by the most of the Bangladeshi people. Hence the RAQ can be a useful tool to detect CHD at an early stage with a potential to arrest the progress of the disease. In addition, it can also be a useful tool to detect CHD in epidemiological studies in Bangladesh. However, studies validating the RAQ in Bangladesh are lacking. Although Bangladeshi participants were included in the previous study of Fischbacher et al.\textsuperscript{178}, all subjects were residents of the UK. Responses from native Bangladeshis may differ due to the very different socio-cultural setting. In addition, this is the only published example thus far, where the RAQ was translated into Bangladeshi language. Within the context of potential influence of socio-cultural factors, there are reports about varying RAQ performance amongst different population groups. Consequently, further studies are recommended to establish cross-cultural validity of the RAQ\textsuperscript{178}. The aim of this study was to determine the utility of the RAQ for detecting CHD among Bangladeshi adults, by comparing RAQ categorization with diagnosis by a cardiologist.

**Methods**

**Study settings**

This study was a component of a large case-control study that explored the association between CHD and use of smokeless tobacco products among non-smoking Bangladeshi adults. This study was conducted during January-July 2010 in Dhaka, Bangladesh. Data were collected through structured interviews by trained research assistants. The research assistants read out the questions and recorded
the answers on the standardised data capture sheets. Patients were recruited from the National Institute of Cardiovascular Diseases (NICVD) and the National Heart Foundation Hospital and Research Institute (NHFH&RI), Dhaka.

**Study participants**

Inclusion criteria were: age 40-75 years, non-smoker, residence within Dhaka City Corporation areas, and well enough to undertake a 20 minutes interview. Non-smokers were defined as either never smokers or ex-smokers who stopped smoking at least 10 years ago and who did not even smoke a single puff within that period.

**CHD positive [cardiologists] individuals**

These patients were admitted to cardiac inpatient facilities and diagnosed as incident cases of CHD (i.e. diagnosed for the first time within the last one-year) by a hospital cardiologist. Cardiologists diagnosed CHD using a combination of clinical judgment, classical symptoms of CHD, electrocardiogram changes, cardiac enzymes, exercise tolerance test or coronary artery angiogram. Either angina and/or myocardial infarction were included in the definition of CHD.

**CHD negative [cardiologists] individuals**

These patients attended cardiac outpatient facilities of the same hospitals and were diagnosed as not suffering from CHD by a hospital cardiologist. Cardiologists ruled out CHD based on patients’ history of illness, physical examination, results of available investigations and their clinical judgement. Diagnoses of these patients included hypertension (62%), non-specific chest pain (48%), and gastric hyper-
acidity (13%). Other patients did not have any diagnosis and only symptoms of palpitation (10%) or breathlessness (8%) were noted.

**CHD positive [RAQ] and CHD negative [RAQ] individuals**

The individuals who were considered to have experienced either angina pectoris or possible myocardial infarction using the criteria set at the RAQ, were reclassified as CHD positive [RAQ] individuals. The remaining individuals, who were not considered to have angina pectoris or possible myocardial infarction by the RAQ, were reclassified as CHD negative [RAQ] individuals. Figure 4 shows the reclassification done by the RAQ.

We recruited 302 CHD positive [cardiologists] individuals and 302 CHD negative [cardiologists] individuals based on the sample size calculations of the original case-control study. Each CHD negative [cardiologists] individual was matched with a corresponding CHD positive [cardiologists] individual by age (±5 years) and sex.

**Data collection**

*Socio-demographic variables*

Information regarding age, sex, residence, marital status, highest level of education achieved, primary occupation and monthly house-rent as a proxy for the SES was collected from the study participants.

*Risk factors for CHD*

Information on known risk factors for CHD was collected, which included self-reported history of hypertension, diabetes, family history of heart diseases, level of
Rose Angina Questionnaire

In addition to the seven questions used to indicate angina pectoris and the one specific question for possible myocardial infarction from the original RAQ, we included one additional time-period question to ensure detection of only incident cases of CHD. Incident cases are preferred to prevalent cases for a case-control study because an individual may change his/her behavior following an episode of coronary symptoms leading to biased history of exposure. Those patients meeting the criteria for a positive case of either possible myocardial infarction or angina
pectoris, with the onset of symptoms for the first time within last one-year, were categorized as incident CHD positive [RAQ] individuals. Appendix 1 shows that the possible myocardial infarction question was asked first, followed by the angina pectoris questions to ensure a logical progression through the study questionnaire.

**Bengali version of the RAQ**

The original English version of the RAQ was translated into Bengali language by the first author (MAR), who is a local native speaker from Bangladesh. Concurrently, two additional translators undertook forward-translation of the English RAQ into Bengali. Both of the additional translators were native Bengali speakers and had a good command of English. One was a medical graduate and the other held a non-medical university degree. Both independent translators were not informed of the study aims until after they had completed the translation exercise. Finally, a public health researcher from the Institute of Epidemiology, Disease Control and Research (IEDCR), Bangladesh compared the three translated versions of the RAQ. MAR and the IEDCR researcher came to a consensus regarding the Bengali questionnaire. The Bengali RAQ was back-translated into English by two additional independent translators. These additional translators were also blind to the study concepts. The back-translated English questionnaire was reviewed carefully by MAR and other Bangladeshi co-authors; it was considered identical to the original English version except for several minor grammatical errors. Appendix 2 shows the Bengali RAQ used for this study. An interviewer-administered version of the RAQ was used for this study.
**Data analysis**

Socio-demographic variables and risk factors for CHD were compared between CHD positive [cardiologists] and CHD negative [cardiologists], as well as between CHD positive [RAQ] and CHD negative [RAQ]. To statistically compare CHD positive and CHD negative individuals, we used McNemar’s chi-squared ($\chi^2$) tests when the frequency in all of the cells of the cross-tabulation was $\geq 5$ and Fisher’s exact test otherwise, to determine statistical significance at the 0.05 level. The utility of the RAQ to detect CHD compared with diagnosis done by a cardiologist was determined by calculating the number of false positives, number of false negatives, sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio with 95% confidence intervals (CIs). Likelihood ratios, which are not dependent on the prevalence of the disease in the population, are preferred to predictive values for reporting the validity of a diagnostic tool. CHD positive [RAQ] individuals were sub-categorized further into RAQ possible myocardial infarction and RAQ angina pectoris, and data were analyzed separately for each sub-category.

**Ethics statement**

Informed written consent was taken from each participant in the prescribed consent form in presence of a witness. If any participant was not literate enough to provide a signature, verbal informed consent in presence of a witness was obtained in those circumstances. The consent form described purpose and methods of the study, confidentiality of the interviews, risks and benefits of participating in the study, individuals’ rights to participate voluntarily and to withdraw from the study at any time without any consequences. The interviewers also provided an information sheet regarding the study and a complaint form with contact details of the study
coordinators. Privacy and confidentially were maintained regarding the collected data. No information that could identify any individual was used or published anywhere. The protocol for this project was approved by The University of Adelaide Human Research Ethics Committee, Australia (H-117-2009) and the local ethics committee of Bangladesh Medical Research Council, Bangladesh (BMRC/NREC/2007-2010/125).

Results

Study participants

Study participants included 302 CHD positive [cardiologists] and 302 CHD negative [cardiologists] individuals. The RAQ reclassified total participants into 194 (32%) CHD positive [RAQ] and 409 (68%) CHD negative [RAQ] individuals. Among the 194 CHD positive [RAQ] individuals, 157 (80.9%) of them considered to have had a RAQ possible myocardial infarction and the remainder (19.1%) as experiencing RAQ angina pectoris.

Mean age of participants was 53 years (standard deviation ±8.5 years). Among the 604 participants, 71% were aged 40-57 years and 50% were men. More than two-thirds (79%) were married and about half (49%) attained their education beyond the primary level. The majority (81%) of female participants were housewives, whereas 74% of male participants had a job in the Government or private sector. Based on the monthly house-rent paid by the participants, half (51%) were categorized as from middle SES group. Table 14 shows that CHD positive [cardiologists] and CHD negative [cardiologists] individuals had a similar distribution of all the above mentioned socio-demographic variables. This is consistent with the known
epidemiology of CHD in Bangladesh\textsuperscript{193}. Table 14 also shows that CHD positive [cardiologists] individuals were more likely to be diabetic compared to CHD negative [cardiologists] individuals.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Total, N(%)</th>
<th>CHD positive [cardiologists], n(%)</th>
<th>CHD negative [cardiologists], n(%)</th>
<th>CHD positive [RAQ], n(%)</th>
<th>CHD negative [RAQ], n(%)</th>
</tr>
</thead>
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<tr>
<td>Total study participants</td>
<td>604</td>
<td>302</td>
<td>302</td>
<td>194</td>
<td>409</td>
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<td><strong>Socio-demographic variables</strong></td>
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<tr>
<td>Age in years, mean(SD)</td>
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<td>54 (±8.5)</td>
<td>52 (±8.4)</td>
<td>53 (±8.6)</td>
<td>52 (±8.4)</td>
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<td>121 (40.1)</td>
<td>64 (33.0)</td>
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<td>211 (34.9)</td>
<td>109 (36.1)</td>
<td>102 (33.8)</td>
<td>67 (34.5)</td>
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<td>58-66</td>
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<td>26 (8.6)</td>
<td>18 (6.0)</td>
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<td>Male participants</td>
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<td>150 (49.7)</td>
<td>150 (49.7)</td>
<td>95 (49.0)</td>
<td>205 (50.1)</td>
</tr>
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<td>475 (78.6)</td>
<td>232 (76.8)</td>
<td>243 (80.5)</td>
<td>145 (74.7)</td>
<td>330 (80.7)</td>
</tr>
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<td>Highest level of education achieved</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>Illiterate</td>
<td>53 (8.8)</td>
<td>34 (11.3)</td>
<td>19 (6.3)</td>
<td>23 (11.9)</td>
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<td>Can sign names</td>
<td>62 (10.3)</td>
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<td>35 (11.6)</td>
<td>28 (14.4)</td>
<td>34 (8.3)</td>
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<td>Primary</td>
<td>189 (31.3)</td>
<td>95 (31.5)</td>
<td>94 (31.2)</td>
<td>58 (29.9)</td>
<td>130 (31.8)</td>
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<td>Primary occupation</td>
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<td>102 (33.8)</td>
<td>59 (30.4)</td>
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<td>42 (13.9)</td>
<td>40 (13.3)</td>
<td>29 (14.9)</td>
<td>53 (13.0)</td>
</tr>
<tr>
<td>Housewife</td>
<td>246 (40.7)</td>
<td>126 (41.7)</td>
<td>120 (39.7)</td>
<td>78 (40.2)</td>
<td>167 (40.8)</td>
</tr>
<tr>
<td>Socioeconomic status (SES) by monthly house-rent (HR)</td>
<td>86 (14.2)</td>
<td>47 (15.6)</td>
<td>39 (12.9)</td>
<td>28 (14.4)</td>
<td>58 (14.2)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Lower SES (HR&lt;5000 BDT)</td>
<td>223 (36.9)</td>
<td>109 (36.1)</td>
<td>114 (37.8)</td>
<td>80 (41.2)</td>
<td>143 (35.0)</td>
</tr>
<tr>
<td>Middle SES (HR 5000-10000 BDT)</td>
<td>310 (51.3)</td>
<td>152 (50.3)</td>
<td>158 (52.3)</td>
<td>97 (50.0)</td>
<td>213 (52.1)</td>
</tr>
<tr>
<td>Higher SES (HR &gt;10000 BDT)</td>
<td>71 (11.8)</td>
<td>41 (13.6)</td>
<td>30 (9.9)</td>
<td>17 (8.8)</td>
<td>53 (13.0)</td>
</tr>
</tbody>
</table>

Risk factors for CHD

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Yes</th>
<th>No</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>383 (63.4)</td>
<td>180 (59.6)</td>
<td>203 (67.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>202 (33.4)</td>
<td>129 (42.7)</td>
<td>73 (24.2)*</td>
</tr>
<tr>
<td>Family history of heart disease</td>
<td>173 (28.6)</td>
<td>94 (31.5)</td>
<td>79 (26.2)</td>
</tr>
</tbody>
</table>

Level of physical activities

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes</th>
<th>No</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>270 (44.7)</td>
<td>122 (40.5)</td>
<td>148 (49.0)</td>
</tr>
<tr>
<td>Mild (1-2 times/week)</td>
<td>70 (11.6)</td>
<td>47 (15.6)</td>
<td>23 (7.6)</td>
</tr>
<tr>
<td>Moderate (3-4 times/week)</td>
<td>42 (7.0)</td>
<td>22 (7.3)</td>
<td>20 (6.6)</td>
</tr>
<tr>
<td>Vigorous (&gt;5 times/week)</td>
<td>216 (35.8)</td>
<td>110 (36.5)</td>
<td>106 (35.1)</td>
</tr>
</tbody>
</table>

Use of hormonal contraceptives

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 (3.1)</td>
<td>9 (3.0)</td>
<td>10 (3.3)</td>
</tr>
</tbody>
</table>

Exposure to indoor smoking

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>103 (17.1)</td>
<td>58 (19.2)</td>
<td>45 (14.9)</td>
</tr>
</tbody>
</table>

Acute psycho-social stress

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>169 (28.0)</td>
<td>94 (31.1)</td>
<td>75 (24.8)</td>
</tr>
</tbody>
</table>

* indicates a statistically significant (p<0.05) difference using chi-squared tests between CHD positive [cardiologists] and CHD negative [cardiologists].

# indicates a statistically significant (p<0.05) difference using chi-squared tests between CHD positive [RAQ] and CHD negative [RAQ].

\* indicates a statistically significant (p<0.05) difference using chi-squared tests between CHD positive [RAQ] and CHD negative [RAQ].

\# Such an incident that caused mental agony, sorrow, unhappiness or anxiety within last one year, like death of family members, divorce, separation, sudden job loss, unemployment, financial loss etc.
Table 15: Comparing coronary heart disease detection by the Rose Angina Questionnaire with diagnoses done by hospital cardiologists, Dhaka, Bangladesh

<table>
<thead>
<tr>
<th></th>
<th>By Cardiologists' diagnosis</th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>CHD positive [cardiologists]</strong>, n(%)</td>
<td><strong>CHD negative [cardiologists]</strong>, n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By the Rose Angina Questionnaire (RAQ)</td>
<td>CHD positive [RAQ]</td>
<td>160 (53)</td>
<td>34 (11)</td>
<td>194</td>
</tr>
<tr>
<td></td>
<td>CHD negative [RAQ]</td>
<td>141 (47)</td>
<td>268 (89)</td>
<td>409</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>301</td>
<td>302</td>
<td>603</td>
</tr>
</tbody>
</table>

**Utility of the RAQ to detect CHD**

Amongst the 194 CHD positive [RAQ] individuals, 34 (17.5%) had been diagnosed as not having CHD by hospital cardiologists (false positives). On the other hand, amongst the 409 CHD negative [RAQ] individuals, 141 (34.5%) had been diagnosed as experiencing CHD by hospital cardiologists (false negatives). Table 14 shows that CHD positive [RAQ] individuals were more likely to diabetic and exposed to indoor smoking, but less likely to be hypertensive compared to CHD negative [RAQ] individuals.

Table 15 shows that amongst the 301 CHD positive [cardiologists] individuals, 160 (53.2%) were categorized as CHD positive by both cardiologists and the RAQ reflecting moderate sensitivity (95% CIs 47.5%-58.7%). Amongst the 302 CHD negative [cardiologists] individuals, 268 (88.8%) were categorized as CHD negative by both cardiologists and the RAQ reflecting high specificity (95% CIs 82.9%-92.7%). CHD positive [cardiologists] individuals were 4.7 times (95% CIs 3.4-6.6) more likely
to have positive scores on the RAQ indicative of CHD compared to CHD negative [cardiologists] individuals (positive likelihood ratio). With reference to negative likelihood ratio, CHD positive [cardiologists] individuals were 0.5 times less likely to have negative scores on the RAQ indicative of not suffering from CHD compared to CHD negative [cardiologists] individuals.

Table 16 shows that when RAQ possible myocardial infarction only was considered, the RAQ showed a similar sensitivity (50.9%, 95% CIs 45.1%-56.6%) to that of the combined results. However, it showed higher specificity (96%, 95% CIs 92.4%-97.9%) and positive likelihood ratio (12.9, 95% CIs 7.2-23.3). When RAQ angina pectoris only was considered, the RAQ showed a very low sensitivity (9%, 95% CIs 5.4%-14.7%). Table 16 also shows that sensitivity, specificity and positive likelihood ratio remained similar when subgroup analyses were conducted by gender and age groups. Sensitivity of the RAQ was more among people from lower SES compared to higher SES, but specificity was more among people from higher SES.
Table 16: Validation of the Rose Angina Questionnaire (RAQ) compared with cardiologist-diagnosis, according to types of cases, gender, age-groups and socio-economic status of the study population in Dhaka, Bangladesh

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity %</th>
<th>95% confidence intervals</th>
<th>Specificity %</th>
<th>95% confidence intervals</th>
<th>Likelihood ratio positive</th>
<th>95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All study population</strong></td>
<td>53.2</td>
<td>47.5-58.7</td>
<td>88.8</td>
<td>82.9-92.7</td>
<td>4.7</td>
<td>3.4-6.6</td>
</tr>
<tr>
<td><strong>CHD types</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible myocardial infarction</td>
<td>50.9</td>
<td>45.1-56.6</td>
<td>96.0</td>
<td>92.4-97.9</td>
<td>12.9</td>
<td>7.2-23.3</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>9.0</td>
<td>5.4-14.7</td>
<td>92.1</td>
<td>88.4-94.7</td>
<td>1.1</td>
<td>0.6-2.2</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>52.0</td>
<td>44.1-59.8</td>
<td>88.2</td>
<td>78.6-93.5</td>
<td>4.6</td>
<td>2.9-7.4</td>
</tr>
<tr>
<td>Women</td>
<td>54.3</td>
<td>46.4-62.1</td>
<td>89.4</td>
<td>80.7-94.2</td>
<td>4.9</td>
<td>3.0-7.8</td>
</tr>
<tr>
<td><strong>Age groups (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-48</td>
<td>52.6</td>
<td>42.7-62.4</td>
<td>88.2</td>
<td>76.6-94.1</td>
<td>4.5</td>
<td>2.7-7.7</td>
</tr>
<tr>
<td>49-57</td>
<td>52.8</td>
<td>43.4-61.9</td>
<td>90.3</td>
<td>79.3-95.4</td>
<td>5.4</td>
<td>2.9-10.0</td>
</tr>
<tr>
<td>58-66</td>
<td>54.2</td>
<td>42.7-65.2</td>
<td>89.0</td>
<td>72.7-65.6</td>
<td>4.7</td>
<td>2.3-9.8</td>
</tr>
<tr>
<td>67-75</td>
<td>53.9</td>
<td>35.5-71.3</td>
<td>82.9</td>
<td>26.2-96.0</td>
<td>3.2</td>
<td>1.1-9.6</td>
</tr>
<tr>
<td><strong>Socio-economic status (SES) by monthly house-rent (HR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower SES (HR &lt;5000 BDT)</td>
<td>56.9</td>
<td>47.5-65.8</td>
<td>85.8</td>
<td>73.3-92.4</td>
<td>3.6</td>
<td>2.3-5.7</td>
</tr>
<tr>
<td>Middle SES (HR 5000-10000 BDT)</td>
<td>53.3</td>
<td>45.4-61.0</td>
<td>90.1</td>
<td>81.9-94.6</td>
<td>5.3</td>
<td>3.2-8.6</td>
</tr>
<tr>
<td>Higher SES (HR &gt;10000 BDT)</td>
<td>42.5</td>
<td>28.5-57.8</td>
<td>100</td>
<td>Undefined</td>
<td>Undefined</td>
<td>Undefined</td>
</tr>
</tbody>
</table>
Discussion

This study showed that the RAQ had moderate sensitivity of 53% but high specificity of 89% to detect CHD among Bangladeshi adults compared with diagnoses done by the cardiologists. Our findings are consistent with a prior UK research although the reported sensitivity was only 21% among South-Asian population in that study\textsuperscript{178}. This difference of sensitivity may be due to the different responses regarding the location and description of the chest pain in the RAQ due to socio-cultural variations in two different research settings. In addition, variation of awareness level and exposure to media regarding heart disease may also influence the response and subsequent sensitivity.

There was no gender variation in responses, reflected by the similar sensitivity and specificity of the RAQ to detect CHD compared with diagnoses done by the cardiologists. One Indian study\textsuperscript{194}, which defined CHD as affirmative responses to the RAQ, previous history of angina/infarction and ECG changes, also showed similar prevalence of Rose angina between men and women, both in urban and rural areas. Another study comparing RAQ diagnosis with thallium scintigraphy\textsuperscript{175} also showed the similar sensitivity of the RAQ between men (44%) and women (41%), although the RAQ was more specific for men (77%) than women (56%). However, meta-analysis from 31 countries\textsuperscript{195} showed that women had higher prevalence of Rose angina compared to men, but men had higher prevalence of Rose myocardial infarction than women. This variation was unexplained\textsuperscript{195}; but more reporting by men regarding the non-exertional chest pain as occurs in myocardial infarction, might be due to sensitization of the fact that men are the predominant sufferers of CHD\textsuperscript{189}.
The RAQ performed similarly across different age-groups in this study. In an US study, the RAQ showed greater sensitivity for women below 55 years compared to the older population. There is limited research examining the response differences of the RAQ among different age groups and warrants further investigation as prevalence of CHD differs by age. In this study, the RAQ showed a greater sensitivity to detect CHD among people from lower SES than higher SES. This difference was also reported by Richards et al. Individuals from lower SES are categorized more often as having RAQ angina than more advantaged individuals. This could be partly attributable to social desirability bias with more expression of pain symptoms by the disadvantaged people.

We used the full version of the original RAQ and added a time-period to detect incident CHD cases. Similar modification was done in the Beta Blocker Heart Attack Trial, which showed the sensitivity of 59.7% and specificity of 93.6% for detecting Rose angina over 25-months of follow-up. We translated the original RAQ into Bengali for cultural adaptation following a rigorous translation process; other studies also followed the similar procedure for different languages. Although self-administered version of the RAQ could give about a two-fold higher prevalence of angina than the interviewer-administered questionnaire, interviewer-administered questionnaire is commonly used for any public health research in Bangladesh considering the literacy situation and the social context. Rose also reported that variation in the technique of administering a questionnaire and interpretation of answers by different trained interviewers did not affect the detection of angina pain. Therefore, using the full version of the RAQ, adding a time-period question to the
original RAQ, translating into Bengali language, and administering it by the interviewers did not bias our study results.

The RAQ can be used as a useful standard tool at a primary care level as well as in epidemiological research to detect CHD within South Asian context. Besides feasibility and cost involvement for utilizing ECG and cardiac enzymes as diagnostic tools for CHD, ECG has limitations as 40% CHD patients might have normal tracings at rest. Although study suggests that a qualified physician can identify more angina patients than the RAQ, there are usually budget constraints for any public health research in a developing country, which could limit utilization of physicians and other additional expensive tools for such research. This study indicates that the RAQ can be used as an alternate but standard cost-effective tool for detecting CHD in epidemiological studies. In addition, utility of the RAQ is proven for prediction of prognosis, as indicated by a number of studies. A 20-year follow-up study in Scotland showed that people of 45-64 years with Rose positive angina had an increased risk of myocardial infarction and had an increased risk of mortality compared with the Rose negative patients. Another 26-year follow-up study among Norwegian men of 40-59 years also indicated that the RAQ angina was a strong predictor for CHD mortality in spite of normal ECG findings.

In terms of limitations, there could be some inconsistencies in the diagnoses of CHD by the cardiologists. However, as the cardiologists involved were highly qualified and experienced specialists at the tertiary hospitals, misclassification bias was likely to be low. Fatal CHD cases were not included in this study, because hospital death
registers in Bangladesh are not well developed. Therefore, findings of this study represent validation of the RAQ for non-fatal CHD cases only.

In summary, RAQ had moderate sensitivity but high specificity for detecting CHD compared with diagnoses by cardiologists among Bangladeshi adults. This is the first study from Bangladesh, reporting the utilization of the RAQ to detect CHD. This study points to the usefulness of the RAQ as a screening tool for further epidemiological studies in South Asian settings where specialists and equipments are often not available.
Appendix 1: Study questionnaire to diagnose coronary heart disease, based on the Rose Angina Questionnaire (RAQ)

<table>
<thead>
<tr>
<th>Questions</th>
<th>Answers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAQ possible myocardial infarction questionnaire</strong></td>
<td></td>
</tr>
<tr>
<td>1  Within the last one-year, have you ever had a severe pain across the front of your chest lasting for half an hour or more?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>If No, go to the 'angina of effort questionnaire'</td>
<td></td>
</tr>
<tr>
<td>If Yes, ask the following question:</td>
<td></td>
</tr>
<tr>
<td>2  Did the pain occur for the first time in the last year?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>If Yes to Q1 and Q2, diagnosed as 'incident case of possible myocardial infarction'.</td>
<td></td>
</tr>
<tr>
<td><strong>RAQ angina pectoris questionnaire</strong></td>
<td></td>
</tr>
<tr>
<td>1  Within the last one year, have you ever had any pain or discomfort in your chest?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>If No, within the last one year, have you ever had any pressure or heaviness in your chest?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>If No, diagnosed as 'not an incident case of angina pectoris'.</td>
<td></td>
</tr>
<tr>
<td>2  Did the pain/discomfort/pressure/heaviness in the chest occur for the first time in the last year?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>If No, diagnosed as 'not an incident case of angina pectoris'.</td>
<td></td>
</tr>
<tr>
<td>3  Did you get it when you walked uphill or hurry?</td>
<td>Yes/No/Never hurries nor walks uphill</td>
</tr>
<tr>
<td>4  Did you get it when you walked at an ordinary pace on the level?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>If Yes to either Q3 or Q4, proceed to the next question.</td>
<td></td>
</tr>
<tr>
<td>5  What did you do if you get it while you were walking?</td>
<td>Stops or slow down/Carry on</td>
</tr>
<tr>
<td>6  If you would stand still, what happened to it?</td>
<td>Relieved/Not relieved</td>
</tr>
<tr>
<td>7  How soon?</td>
<td>10 minutes or less/More than 10 minutes</td>
</tr>
<tr>
<td>8  Will you show me where it was?</td>
<td>Sternum/Left anterior chest/Left arm/Others</td>
</tr>
<tr>
<td>If Yes to Q1 and Q2, Q3 or Q4, 'stops or slow down' for Q5, 'relieved' for Q6, '10 minutes or less' for Q7, 'sternum' or 'left anterior chest and left arm' for Q8; diagnosed as 'incident case of angina pectoris'.</td>
<td></td>
</tr>
</tbody>
</table>

**Coronary heart disease diagnosis for this study**

If anyone was classified as 'incident case of possible myocardial infarction' or as 'incident case of angina pectoris', h/she was diagnosed as 'incident case of coronary heart disease' for this study.
Appendix 2: Bengali version of the Rose Angina Questionnaire used for this study

Rose Angina Questionnaire in Bengali
(extracted from the main study questionnaire)

1. যদি অধ্যায়ের মার্কিন আমাদের মানদনমূলক অবস্থা দেখাতে চাহিলাম, তাহলে কোনো গোপনীয় বিষয় অন্তর্ভুক্ত নির্দেশ কর।

[3 বাংলা ভাষায়]
[3 নং এলেট বনাম]

2. অধ্যায়ের মার্কিন আমাদের মানদনমূলক অবস্থা দেখাতে চাহিলাম, তাহলে কোনো গোপনীয় বিষয় অন্তর্ভুক্ত নির্দেশ কর।

[3 বাংলা ভাষায়]
[3 নং এলেট বনাম]

3. অধ্যায়ের মার্কিন আমাদের মানদনমূলক অবস্থা দেখাতে চাহিলাম, তাহলে কোনো গোপনীয় বিষয় অন্তর্ভুক্ত নির্দেশ কর।

[3 বাংলা ভাষায়]
[3 নং এলেট বনাম]

4. অধ্যায়ের মার্কিন আমাদের মানদনমূলক অবস্থা দেখাতে চাহিলাম, তাহলে কোনো গোপনীয় বিষয় অন্তর্ভুক্ত নির্দেশ কর।

[3 বাংলা ভাষায়]
[3 নং এলেট বনাম]

5. অধ্যায়ের মার্কিন আমাদের মানদনমূলক অবস্থা দেখাতে চাহিলাম, তাহলে কোনো গোপনীয় বিষয় অন্তর্ভুক্ত নির্দেশ কর।

[3 বাংলা ভাষায়]
[3 নং এলেট বনাম]

[4 বা 5 উইন্ডোর “হুলা”বলতে 6 নং এলেট বনাম; 4 ও 5 উইন্ডোর “হুলা”বলতে 8 নং এলেট বনাম]

6. অধ্যায়ের মার্কিন আমাদের মানদনমূলক অবস্থা দেখাতে চাহিলাম, তাহলে কোনো গোপনীয় বিষয় অন্তর্ভুক্ত নির্দেশ কর।

[8 বাংলা ভাষায়]
[8 নং এলেট বনাম]
(উপ্রেছ করন ..................................................)
খাবার না .................................................. ৭৭
লিঙ্গ .................................................. ৯৯

৬. (ক) আপনি যদি তখন দিনিয়ে থাকতেন, তাহলে আপনার এই গুচ্ছের ব্যায়াম/যোগীতাকে অন্তর্ভুক্ত করতে হবে?
সেরে থাকতে ........................................ ১
সাধারণ আনরতা ........................................ ২
[৮ দিনের খাদ্য]
খাবার না .................................................. ৭৭
লিঙ্গ .................................................. ৯৯

৬. (খ) কতক্ষণ পর আপনার এই গুচ্ছের ব্যায়াম/যোগীতাকে এক বার থেকে করতে?
১০ মিনিট বা এক কম সময় ................................ ১
২০ মিনিট এর বেশি সময় ................................ ২
খাবার না .................................................. ৭৭
লিঙ্গ .................................................. ৯৯

৭. আপনি কি আপনাকে প্রাক্তন গুচ্ছের ব্যায়াম/যোগীতা অর্জনে দিনিয়ে থাকছেন?
(সাধারণত এক দিন কাটার জন্য)
(এক প্রয়োজন মূল্যের উপর নির্ভর করে)

গুচ্ছের মাপাননে (উপর/নিচে) ..................... ১
গুচ্ছের সাধারণ বামের পর্যায় .................... ২
বাম নিচের দিকে ........................................ ৩
অন্য ক্ষেত্রে ............................................ ৪
খাবার না .................................................. ৭৭
লিঙ্গ .................................................. ৯৯

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রেকর্ড করে নিন ।

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CHAPTER 7

Additional information: Methods
Chapter outline

This chapter provides additional information about the methods used for this study, which was not included in the prior manuscript chapters due to journal constraints on length and content. I have chosen to include this information to enable the readers to understand the methods and data analyses in greater depth, health care context in Bangladesh, laboratory analysis for the SLT products, and quality control approach for this study. This chapter includes additional information regarding:

1. Selection of study sites
2. Selection of study participants
3. Study period
4. Study questionnaire
5. Selection and training of data collectors
6. Pilot study and finalising the questionnaire
7. Quality control
8. Data management
9. Laboratory analysis of SLT products
10. Data analysis
11. Ethical issues
7.1. Selection of study sites

As described in chapter 3, 4, 5 and 6, the following provides a more detailed description of the study sites. Two large and established tertiary care cardiac hospitals, the National Institute of Cardiovascular Diseases (NICVD) and the National Heart Foundation Hospital and Research Institute (NHFH&RI), situated in the capital city of Dhaka in Bangladesh, were selected for recruiting hospital cases and hospital controls. CHD cases were selected from the cardiac inpatient departments of the hospitals and hospital controls were selected from the cardiac outpatient departments of the same hospitals. The communities within Dhaka City Corporation (DCC), from where the cases visited to those two hospitals, were selected for recruiting community controls for this study.

7.1.1. Health care context of Bangladesh

Bangladesh, which has borders with India on three sides and the Bay of Bengal on the southern side, is one of the most densely populated countries of the world. With a population growth rate of 1.5%, Bangladeshi people have a life expectancy of 67 years at birth. Although there are primary, secondary and tertiary levels of health care system in Bangladesh, there is only one physician for approximately 2785 people. There are different non-government health care institutions besides public facilities to deliver services to the Bangladeshi people. The public hospitals provide free or subsidized treatment cost for the socially disadvantaged people. However, there is no national health insurance system in Bangladesh.

7.1.2. Hospitals

The National Institute of Cardiovascular Diseases (NICVD) is the largest tertiary care public cardiac hospital in Bangladesh, established in 1978 at Sher-E-Bangla
Nagar, Dhaka. Besides emergency, outpatient and inpatient departments (250 beds), the NICVD has modern facilities including a well-equipped coronary care unit (CCU), intensive care unit, catheter laboratory and operating theatres to manage all forms of cardiovascular diseases. The institute provides specialist training in cardiology and cardiothoracic surgery. It is the only national referral cardiac hospital in Bangladesh for any suspected cardiac case. Hundreds of patients from all social classes visit this hospital from all over Bangladesh each day. Unlike tertiary health care institutions in other developed countries like Australia, self referral to different outpatient department is possible.

The cardiac inpatient departments (IPDs) of the cardiovascular medicine unit and the post coronary care unit (PCCU) were selected for recruiting hospital cases of CHD. There are separate IPD for women and men (1 for women and 4 for men), and one PCCU to deal with the cardiovascular cases at the NICVD. The number of admitted patients in each of these departments is more than the allocated beds and patients often have to share floor space. On average, 550 patients are admitted to IPDs each day; 75 patients are admitted in each of the four male IPDs, 125 patients in the female IPD and 100 patients in the PCCU of the NICVD. Cardiac outpatient departments (OPDs) of cardiovascular medicine were selected for recruiting hospital controls for this study. There are six cardiac OPDs at the NICVD and on an average, 400 patients could be expected to visit each day, either self-referred or referred by a general physician (GP).

The National Heart Foundation Hospital and Research Institute (NHFH&RI) is a non-government, non-profit organization, established in 1978 to enhance the prevention and control of cardiovascular diseases. It is a 300-bed Government
funded hospital, located at Mirpur area-2, Dhaka. The hospital provides modern facilities including invasive and non-invasive investigations as well as general medical and surgical management of cardiovascular diseases. There are emergency departments, OPDs and IPDs in the hospital to deal with cardiovascular patients. Besides medical management of these patients, both closed and open heart surgery including coronary artery bypass surgery are conducted there\textsuperscript{203}. The hospital, managed by National Heart Foundation Hospital Trust, provides free service to approximately one-third of the socially disadvantaged patients admitted making treatment costs lower than other private hospitals in Bangladesh\textsuperscript{203}.

Similar to the NICVD, cardiac IPDs of the cardiovascular medicine unit and the PCCU of the NHFH&RI were selected for recruiting hospital cases of CHD. There are two male cardiac IPDs, one female cardiac IPD, one heart failure IPD, one post-catheter IPD, one male and one female PCCU to manage CHD patients in that hospital. All of these units were selected for this study. According to hospital policy, if all of the beds are occupied in these departments in a day, no further patients are admitted. During the period of study recruitment, approximately 110 patients were admitted in these units per day; 20 patients were admitted in each of the two male IPDs, 20 patients in the female IPD, 15 patients in the heart failure IPD, 20 patients in post-catheter IPD and 15 patients in the PCCU of the NHFH&RI. Cardiac OPDs and the hypertension clinic were selected for recruiting hospital controls. There were three cardiac OPDs running daily and one hypertension clinic running twice a week at the NHFH&RI. On an average, 60 patients visited each day to those three OPDs and 30 patients in two sessions of hypertension clinic in a week. Hypertensive patients visited the clinic for treatment
and follow-up. In addition, some patients visited the clinic to screen for hypertension. About two-thirds (64%) of the hospital controls were selected from the hypertension clinic of NHFH&RI, which was the main source of recruiting controls from that hospital.

7.1.3. Communities

Dhaka, the capital city of Bangladesh, is under the administrative management of Dhaka City Corporation (DCC). DCC encompasses an area of about 390 square kilometres with a population of six million \(^{204}\). The literacy rate of the population of DCC is about 63% and the average per capita annual income of US$ 550 \(^{204}\). The neighbourhood households of a hospital case from the same communities within DCC were selected for recruiting community controls.

7.1.4. Collaboration

The Institute of Epidemiology, Disease Control and Research (IEDCR), Government of the People’s Republic of Bangladesh was the collaborating agency for this project in Bangladesh. IEDCR, established in 1978 at Mohakhali in Dhaka, is the national institute for conducting disease surveillance and outbreak investigations in Bangladesh \(^{205}\). This organisation is involved in controlling disease of public health importance, training health care professionals and conducting public health research including clinical trials \(^{205}\). The Director of IEDCR was the local supervisor for the PhD candidate and provided administrative and academic support and mentoring during the field activities in Bangladesh.
7.2. Selection of study participants

7.2.1. Identifying CHD cases

There are three groups of patients who visit the two cardiac hospitals each day. One group of patient is characterised by having symptoms of moderate to severe chest pain and/or breathlessness are either referred by a GP or self-referred, and attend the emergency department of the hospitals. Following further investigations such as ECG and/or cardiac enzymes, these patients are diagnosed to have cardiac disease or not. Those diagnosed with cardiac disease are admitted to either CCU or cardiac IPDs, depending upon the severity of symptoms and signs. After being stabilised in the CCU, patients are shifted to PCCU and then to cardiac IPDs. The second group of patients attend the cardiac OPDs with symptoms of mild chest pain and/or breathlessness. Following further investigation, most of these individuals are managed medically with drug prescriptions whilst a small number are admitted to the cardiac IPDs for further management. The third group of patients who have established diagnoses of CHD make regular visit to the cardiac OPDs for ongoing management. In the cardiac IPDs, those patients underwent further necessary investigations like ECG, cardiac enzymes, ETT or coronary artery angiogram (CAG).

CHD cases were selected for this study from patients admitted to an IPD or PCCU and diagnosed as CHD by a hospital cardiologist (either for the first time or diagnosed for the first time within the last one year). For admitted patients, diagnoses of CHD and results of supporting investigations were ascertained from patients’ treatment file. Interviews were also conducted with patients regarding their understanding of the diagnoses. Careful consideration was given to select the appropriate cases and this was done solely by the PhD candidate, who is also a
Medical Graduate from Bangladesh. Diagnosis terms that were considered CHD in this study were CHD, ischemic heart disease, acute coronary syndrome, angina, unstable angina, chronic stable angina, efforts angina, acute myocardial infarction, myocardial infarction (MI), anterior MI, lateral MI, inferior MI and old MI. Any CHD patient having additional heart disease, like valvular heart disease, heart failure was also considered eligible for this study. The PhD candidate selected the eligible cases of CHD and the data collectors proceeded with the full interview process. Four data collectors worked together as a team to select hospital cases and the team visited each hospital twice a week by turn.

7.2.2. Identifying community controls

The residential areas from where the CHD cases reside were stratified according to different areas. The data collectors were divided into two groups of two interviewers. This was done to provide peer support including safety concern of the female data collectors. The PhD candidate accompanied one group every day to facilitate the selection of appropriate controls and ensuring adequacy of the interview process. Each group visited communities three times a week on alternate days. At first, the residential address of the CHD case was located, and then the interviewers approached the immediate neighbour to locate an eligible control for that case. The interviewers screened out residents of a household according to the screening criteria of age, smoking and heart disease status. Depending upon the availability of neighbourhood residents and willingness to participate in the study, eligible controls were matched by age (±5 years), sex and socio-economic status (stratified by monthly house-rent) to the corresponding case. If the respondents were never informed of having any heart disease by any health worker in their lifetime, they were considered eligible. If any respondent was
confused regarding his/her heart disease status, h/she was not considered eligible for this study. If the required criteria for a community control were unable to be matched in the same community of the corresponding case, the adjacent communities with similar pattern in terms of SES of the population were selected. Repeated (at the most three) attempts were taken to contact each eligible control, and to request him/her to participate in the study. If someone decided not to participate at the first contact, h/she was not contacted again.

7.2.3. Identifying hospital controls

Interviewers approached patients attending to the cardiac OPDs of two study hospitals following completion of their scheduled OPD consultation. Interviews were conducted in a private corner of the waiting room. At first, patients were screened out on the basis of age, smoking and heart disease status to find eligible study participants. Their case-notes were reviewed to determine the cardiologists’ diagnoses by the PhD candidate to find the eligible hospital controls. Diagnoses for these patients included hypertension (62%), non-specific chest pain (48%), and gastric hyper-acidity (13%). Some patients were not assigned a diagnosis, and symptoms of palpitation (10%) or breathlessness (8%) were given in the case-notes. Each of the selected controls was matched by age (±5 years) and sex with a corresponding case. Hospital controls were selected at the end of recruiting the target numbers of hospital cases and community controls. Two interviewers worked for that purpose, one in each hospital. The PhD candidate accompanied either of them every day, to help them in selecting appropriate hospital controls.
7.2.4. Interviewing cases and controls

Following the initial briefing of the research objectives and fulfilling the criteria to be included as either case or control for this study, written consent was taken from each study participant in presence of a witness prior to proceeding with the full interview schedule. If any of the selected participants did not wish to continue with the interviews, notes were taken down regarding the reasons for non-response. Information on age and gender of the non-respondents were also recorded in order to compare any difference between respondents and non-respondents later on. Those who agreed and proceeded with the full interview were provided with an information sheet explaining the research objectives and the contact information of the study coordinators. They were then interviewed using the study questionnaire. Because of the relatively low level of literacy in Bangladesh, all questions were read out to all study participants. At the end of each interview, data collectors were able to provide general health promotion messages regarding CHD or SLT use if requested by the participants.

7.2.5. Exclusion criteria

People aged less than 40 or above 75 years of age, current smokers, occasional smokers (even if smoked for a single occasion within last 10 years), ex-smokers (except those who quit >10 years ago), known diagnosed cases of CHD for more than a year for cases, any kind of known heart disease for either hospital or community controls, and severely ill individuals who were not able to participate in interviews, were excluded from the study.
7.3. Study period

The study was conducted during January-July 2010. Recruitment and training of the data collectors were done during the first and second week of January. Data collection for the pilot study was conducted during the third and fourth week of January. Data collection for the final study started from February 2010. Data from hospital cases and hospital controls were collected between the hours of 9:00 AM and 3:00 PM on official working days of a week. Interviewers collected data from communities seven days a week between the hours of 9:00 AM and 5:00 PM, except the public holidays. However, the time of the study did not have any likely impact on results of this study.

7.4. Study questionnaire

A structured questionnaire was used to collect all data for this study. At first, a screening questionnaire was used to select the eligible cases and controls for the study. Other questionnaires collected information regarding basic demographic characteristics, history of SLT use and perceptions regarding effects of SLT use on health. As described previously in chapter 3, 5 and 6, the RAQ was also used for all cases and controls to allow further categorization of participants in a standardized way.

7.4.1. Screening questionnaire

The screening questionnaire included information on age (being 40-75 years of age), residence (residing within DCC areas), smoking status (being never-smokers or ex-smokers who quit >10 years ago) and heart disease status (cases being diagnosed for the first time within the last one-year, controls not being known to have any cardiac disease).
Unlike developed countries, many people in Bangladesh may not know their date of births. For those who could not provide the date of birth, interviewers referred to a historical event (the liberation war in Bangladesh in 1971) and asked the respondents to give their age at the time of that event. If someone could not still answer this question, interviewers prompted married respondents to describe family events such as the age of their first child, duration between marriage and birth of first child and age during marriage; age of the respondent was calculated as closely as possible from this information. For unmarried respondents, interviewers prompted regarding age of the immediate older or younger sibling of the respondent to calculate his/her age. If there was any discrepancy between the calculated age and the participants’ response, the calculated age was used for this study. All ages were recorded in completed full years.

Interviewers asked the respondents where they lived. If the area of residence was within DCC areas, details of their address were recorded. For those who were visiting the DCC for a social visit or for healthcare treatment, but his/her original place to stay was outside DCC areas, h/she was not considered eligible for this study. If any respondent had recently moved to the DCC areas to live on a permanent basis, h/she was considered eligible. For those who travelled to other parts of his/her job, but was a permanent resident within DCC areas, h/she was considered eligible for this study. If any respondent worked in a particular area within DCC from morning till night, and went back home at night every day, his/her working area was considered as his/her residential area as the behaviour was likely to be influenced by the environment where the participants had spent most of their time.
Only people who had never smoked or ex-smokers, who quit more than ten years ago, were eligible for this study. If any respondent smoked occasionally (even a single puff within the last ten years), they were not considered eligible. Smoking included smoking any kind of tobacco products including cigarettes, bidis, hukkahs etc.

7.4.2. Socio-demographic questionnaire

A structured questionnaire, based on items used in prior studies of tobacco use in Bangladesh\textsuperscript{18,19} was used. Socio-demographic characteristics included age, gender, marriage, residence, education, occupation and housing. Age was calculated following the methods mentioned above and gender of the respondents was recorded. Interviewers asked participants about their marital status. If any respondent was married, h/she was further asked whether the couple lived together or not (in Bangladesh, couple may live apart mainly due to different work sites). Categories used included if respondents were single, married (living with spouse), married (spouse living other places), divorced, widowed and separated. Information on residential areas was collected in the way mentioned above.

The categories of education included illiterate, can sign names, literate, primary, secondary, higher secondary and above higher secondary. Literate was considered if anyone could read and/or write, primary education meant to complete class V, secondary to pass Secondary School Certificate (SSC) examination, higher secondary included passing of Higher Secondary Certificate (HSC) examination or any Diploma course, above higher secondary included any degree beyond higher secondary like Bachelors, Masters or other higher degrees,
others included any non-formal education (e.g. religious education like *madrashah* education/*hafez*).

All respondents were asked about their occupation. Occupation was later categorized to fewer items as service holder, business owner, housewife, retired, others and unemployed. Service holders included professionals such as doctors, engineers, lawyers etc., as well as paid and unpaid public or private workers. House ownership and monthly house-rent were recorded. If any respondent lived in his/her own house, approximate monthly rent of that house was estimated. The monthly house-rent that the respondents reported, with/without including the utilities bill, was recorded. If any respondent shared a room in a particular house, his/her monthly room-rent was considered to be the house-rent. Study participants were classified into three groups of socioeconomic status (SES) based on their monthly house-rent. Lower SES included people with house-rent below 5,000 Bangladesh Taka (BDT), middle SES included people with house-rent 5,000-10,000 BDT, and higher SES included people with house-rent above 10,000 BDT (1 Aus$ ≈ 65 BDT). These categories were made considering the average house-rent of middle SES people in DCC areas.

### 7.4.3. Questionnaire on risk factors for CHD

To ascertain the potential confounding effects on CHD for the main exposure variable (SLT use) in this study, several risk factors for CHD were included in the study questionnaire. The structured questionnaire included information on self-reported history of hypertension, diabetes, family history of heart diseases, level of physical activity, current use of hormonal drugs among female participants, exposure to indoor passive smoking, and occurrence of any psycho-social
stressful event within the last one year. Most of these selected risk factors had been evaluated in prior studies on tobacco use in Bangladesh \(^{18,19}\).

The presence or absence of a diagnosis of hypertension was ascertained. Diagnoses could have been by doctors or community health workers (Government or private), but not traditional healers like hakeem or kabiraj. Self-perception of hypertension was also not included. Similarly, interviewers asked whether respondents had diabetes or a family history of any form of heart disease among family members. Only parents and siblings (not spouse and children) were considered family members with respect to this question.

Respondents were asked to self-report their level of physical activity for at least 30 minutes in a week that made them huff and puff (made them sweat or breathe faster, or where they could talk but could not sing). This definition was chosen as used in other studies \(^{206,207}\). The respondents were facilitated with few examples of such activities, like brisk walking, jogging, running, heavy household works, beating clothes, heavy manual works etc. There could be multiple episodes of physical activity comprising at least 30 minutes in a week, but each episode must be for at least 10 minutes each. The levels of physical activity were then classified into three categories in this study, as mild (1-2 times/week), moderate (3-4 times/week) and vigorous (>5 times/week).

Female participants were asked whether they were current users of hormonal contraceptives (pills or injection), or any other hormonal drugs like hormone replacement therapy (oestrogen or progesterone). For example, other forms of hormonal drugs used such as thyroid supplement drugs, were not included.
Interviewers asked whether any household member smoked regularly inside the same room h/she lived in. Household members included family members, friends or colleagues with whom h/she stayed most of the time of a day. Collection of valid data on passive exposure to tobacco smoke at work was not considered feasible for this study, as there are still limited restrictions of smoking in most of the workplaces in Bangladesh specifically workplaces for middle and lower SES. Stressful life events within the last one year were recorded. The interviewers asked about such incidents that had caused mental agony, sorrow, unhappiness or anxiety. Examples included death of family members, divorce, separation, sudden job loss, unemployment, financial loss etc. Only events occurring within the past one year were included.

7.4.4. Questionnaire on SLT use

A comprehensive structured questionnaire regarding detailed history of SLT use was administered to all of the study participants. The questionnaire was based on prior studies on tobacco use in Bangladesh, from where we have identified the names of SLT products; frequency and duration questionnaire were also followed. The questionnaire included information on SLT use separately for current and past users.

First, current use of SLT products was established. It was clearly stated to each respondent that SLT did not include betel-leaf (paan) or areca-nut chewing. If any respondent was using any tobacco product with/without betel-leaf or areca-nut in the last one year, they were considered as current users of SLT products. Past SLT users were individuals who had quit SLT products for at least twelve months within the last one year. If any respondent responded negatively for both current
and past use, they were considered to be as never tobacco users (as all participants were non-smokers).

For individuals currently using SLT, the types of SLT used were recorded. The interviewers prompted the names of all SLT products mentioned in the questionnaire as *paan-masala, jarda, sada-pata, gul, khaini, snuff and others*. The names of these SLT products were included from literature review as mentioned before 18, 19, and the PhD candidate’s knowledge of local customs. All of the responses, including multiple responses for that question, were recorded. The frequency of each SLT products was recorded. The options were 4 or more times a day, 2-3 times a day, once a day, 2-3 times a week, once a week, once a month, less than once a month. During data analysis, these categories were re-coded into light use (less than once a day) and heavy use (at least once a day) for each SLT product. Duration of SLT use in terms of months (if less than a year) or years (counted as completed full year) was recorded. Duration was further re-categorised into two groups during data analysis, as short duration of use (duration <10 years) and long duration of use (duration >10 years).

If any respondent used any SLT products currently, they were not further asked regarding the past usage. Similar to the current usage, probing was done to explore even the occasional past usage among the respondents. Anyone who quit using SLT products within last one year, were included as current SLT users. The interviewers asked the quitters regarding the types of SLT products used in the past; the names of the SLT products were the same as noted above for current users. Multiple responses, if any, were recorded. Then the interviewers asked the quitters regarding the duration since stopped using SLT products. Duration in
terms of months (if less than a year) or years (counted as completed full year) was recorded. Later on, quit duration was further re-categorized into short-term quit (quit duration 2-10 years) and long-term quit (quit duration >10 years). Reasons for quitting SLT products were recorded. Options for quitting included advice from a doctor or a health worker, any health problem with specification of the problem, or other reasons with specification.

7.4.5. Questionnaire on perceptions of SLT use

A semi-structured questionnaire was used to explore the perceptions of the study population about the use of SLT products and perceived impacts on health. Questions on perceived harmful and beneficial effects of SLT use on health and the factors influencing initiation of SLT use were also used in prior previous perception studies in India \(^{59}\) and Pakistan \(^{91}\). Questions on weekly expenditure for SLT use and quitting practice were used in prior studies from Bangladesh \(^{17}\). However, the question on reasons for using SLT products by Bangladeshi population was used to understand the context of SLT use in Bangladesh. All the items of perception questionnaire have already been described in chapter 4.

7.4.6. Rose Angina Questionnaire (RAQ)

As mentioned in chapter 6, the RAQ included the full version/seven-items angina of effort questionnaire and the single diagnostic question of possible myocardial infarction questionnaire \(^{97}\). To provide a logical flow, the “possible myocardial infarction” items were asked first, followed by the “angina of effort” items. Each of the questionnaires was linked with the time period questionnaire (onset of symptoms for the first time within last one-year) to diagnose the incident cases. The RAQ included information regarding the characteristics of chest pain in terms
of duration, exertion, relief of the pain by rest and location of the chest pain. Therefore, patients meeting the criteria for a positive case in either “possible myocardial infarction” items or the “angina of effort” items, with the onset of symptoms for the first time within the last one-year, were considered as cases by RAQ in this study. CHD was defined as a single disease entity in this study including both angina and myocardial infarction.

According to the original version of the RAQ, the respondents were asked to report the occurrence of severe pain across the front of the chest lasting for 30 minutes or more. Those who responded positively for this question were asked whether symptoms occurred for the first time within the last one year according to the objective of finding incident cases. Those who answered positively were considered incident cases of possible myocardial infarction. The respondents categorized as incident cases of possible myocardial infarction, were not further interviewed with the “angina of effort” items. If any respondent answered positively to the initial question but the symptoms occurred for the first time more than a year ago, they were considered prevalent cases and were not interviewed further.

The study participants, who responded negatively to the initial question of the “possible myocardial infarction” items, were asked regarding pain, discomfort, pressure or heaviness in the chest. If they responded positively to any of these symptoms, they were interviewed with further question of the RAQ section. If any respondent responded negatively to all of the initial symptoms of both “possible myocardial infarction” items and “angina of effort” items, they were considered as controls and the rest of the RAQ was omitted. If they responded positively to any of the symptoms, they were asked whether those symptoms had occurred for the
first time within the last one year according to the objective of finding incident cases. If the response was yes, they were interviewed with the rest of the “angina of effort” items to allow diagnosing incident cases of angina of effort. If the response was no, they were considered to be prevalent cases and the rest of the RAQ was omitted.

Those who responded positively for the first time occurrence of any of the symptoms within last one year were further asked about the symptoms in terms of exertion (like walking uphill or hurry, or walking in ordinary pace). If the symptoms persisted with any of those exertions, they were asked further about the actions taken, whether the symptoms relieved by rest, duration took to relieve the symptoms and finally, the location of the chest symptoms. There was a chest diagram in the questionnaire which enabled the respondents in pointing out the locations of the symptoms. If the symptoms did not persist with any of those exertions, they were considered as controls and the rest of the RAQ was omitted.

Therefore, the respondents, who described the chest pain/ discomfort/ pressure/ heaviness limited on exertion, situated over the sternum or in the left chest and left arm, and relieved within 10 minutes by rest, with all of the symptoms onset for the first time within the last one year, were considered as incident cases of angina of effort in this study. We used a Bengali version of the RAQ, translation steps are described in chapter 6.

7.4.7. Translation of the questionnaire

The English version of the study questionnaire, developed in consultation with study supervisors and mentors, was initially translated into the local Bengali
language by the PhD candidate. Then two independent Bangladeshi translators undertook a forward-translation of the English version of the questionnaire into Bengali. Both translators were native Bengali speakers and had good command of written and spoken English; one of them was a medical graduate and the other was a non-medical professional. Both were kept blinded to the study aims and objectives. Finally, another individual, who is the researcher from the IEDCR, Dhaka, Bangladesh compared the three translated versions of the questionnaire. All of the versions were similar except few grammatical errors, which were not significant. The PhD candidate and this academic researcher finalised one Bengali questionnaire based upon these comparisons. The Bengali version of the questionnaire was back-translated into English by another two independent translators. Their language proficiency and profession was similar to the forward-translators; they were also kept blinded to the study aims and objectives. Then the PhD candidate and the same researcher from IEDCR reviewed the back-translated English questionnaire; any difference between the original version and the translated version of the English questionnaire was addressed. Differences included different synonyms and few grammatical errors. The Bengali questionnaire was approved by the Director of IEDCR, who was the local supervisor of the PhD candidate in Bangladesh; the English version was approved by the Australian supervisors.

7.5. Selection and training of data collectors

A vacancy notice for the recruitment of data collectors for this study was circulated among the personal network of the public health researchers in Bangladesh. Sixteen applications were received against four positions for data collectors. All were invited to attend for a written and an interview examination. A one hour
written and a ten-minute interview examination were held at IEDCR. Performance on the examination along with prior work experience was used to assess capability of the applicants to undertake the data collection for this study. The PhD candidate and the Director of IEDCR selected nine applicants for a training session. Nine candidates were selected instead of four, with the objective of keeping a panel of data collectors prepared for this study to provide back up during the data collection period.

The PhD candidate conducted three days of intensive training at IEDCR. The training participants were oriented with the research topic, data collection steps and the questionnaire on the first day. On the second day, they went to a field-site, other than the selected study sites for this study, for field-testing of the initial study questionnaire. The site was Dhaka Medical College Hospital, which is the largest Government tertiary care medical college hospital in Bangladesh. The data collectors interviewed patients from the OPDs of the hospital and each of them interviewed at least one patient with the existing questionnaire on that day. Experience of the field-survey was shared on the third day of the training session and the feedback was recorded to improve the questionnaire further. The training participants received further clarification regarding their concerns during data collection in the field. Each trainee performed a role-play with the study questionnaire separately and a panel of five researchers from IEDCR recommended four of them as data collectors for this study. Based upon their recommendation, the PhD candidate and the Director of IEDCR finally selected those four data collectors. At the end of the training session, each of the participants was awarded a certificate for attending the training session. One male and three female data collectors were finally selected. They were further oriented
with the data collection procedure in details and they received a detailed written interview guideline as a reference guide.

7.6. Pilot study and finalising the study questionnaire

A 2-week pilot study was conducted at the selected study sites, before initiation of the main study. This was to provide an opportunity to address challenges of selecting and interviewing cases and controls. It also helped to address the order of the items in the study questionnaire. The trained data collectors selected cases of CHD from two cardiac hospitals and the corresponding controls from the respective communities of DCC. Based upon the experience from the pilot study, items of questions were modified slightly. This was in terms of using alternate Bengali synonyms to clarify questions such as perceptions, and re-ordering few perception items in the questionnaire. The final version of the study questionnaire was reviewed and approved by all supervisors. Hard copies of questionnaire were used for data collection.

7.7. Quality control

The PhD candidate was responsible for the active supervision during the process of data collection, both from the cases and the controls. Selection of CHD cases according to the case definition was solely done by him and selection of most of the controls was done in his presence. Daily reporting and updating was ensured for the collected data. The local supervisor was consulted instantly, for any confusion raised during the selection or interview process at field-sites. The coordinators from both hospitals were also consulted according to the need of data collection.
Besides regular and constant supervision, 1% (4) of hospital cases, 2% (24) of community controls and 2% (6) of hospital controls were re-interviewed for the quality assurance of the collected data. The participants for re-interviews were selected randomly. The PhD candidate re-interviewed them by telephone within four weeks of data collection. If any participant did not have any contact telephone number or there was no response over the telephone for at least three sessions, the next participant was selected for that purpose. During the re-interview session, the responses were compared with the earlier response and any discrepancy was noted separately; no information regarding earlier response was shared with the participants. Only 4 of the 34 re-interviews (12%) had some minor discrepancy like frequency or duration of SLT use.

7.8. Data management

All completed questionnaires in hard copy format from the study sites were regularly collected by the PhD candidate and stored in folders at his personal storage. Following the completion of the data collection, all of the questionnaires were scanned for electronic storage and the hard copies were also retained. The hard copies were stored in the secured private dwelling of the PhD candidate in Bangladesh, as there was no suitable secure office available to store those either at the University of Adelaide or in any study hospital in Bangladesh. The PhD candidate stored all of the electronic data files on the personal, id-protected server of the University of Adelaide.

Data collected from the field-sites were entered into the electronic database of Statistical Package for the Social Sciences (SPSS) software by the PhD
candidate. The database was saved on the personal, id-protected, University of Adelaide server site of the PhD candidate. The database was converted to MSExcel and STATA later on for analysis of the collected data. Single-entry was given for each of the data entered into the database. The PhD candidate verified 10% (180) of the entered data randomly, by reviewing with the original data file. The questionnaires used in the field-sites were in Bengali; therefore, another Bangladeshi PhD candidate from the Discipline of Public Health kindly agreed to re-verify the dataset and she verified 2% (36) of the entered data randomly.

7.9. Laboratory analysis of SLT products

Besides conducting the case-control study and exploring the perceptions on SLT use, samples of mostly used SLT products were also analysed for the presence and content of nicotine. The following steps were followed for that purpose:

7.9.1. SLT market survey

At first, the PhD candidate selected one of the most popular wholesale markets of SLT products within DCC areas, by talking informally with the SLT users and fellow research colleagues in Bangladesh. The selected site was New Market Kacha-bazar in Dhaka. Various types of SLT products including betel-leaf are supplied to all over the DCC areas from there. The PhD candidate interviewed two sellers from two SLT shops separately and one sales-representative of one commercial SLT product company there. The objective was to identify the most commonly sold SLT products to the inhabitants of DCC areas. Informal interviews were also conducted with them regarding their perceptions of presence of nicotine in the available SLT products in the market. The names of mostly sold SLT products, obtained from the informal interviews, were noted down. Another
wholesale market from another area, Hatirpool Kacha-bazar, was purposefully selected for convenience of the PhD candidate, to compare the response regarding the names of SLT products received earlier. One seller of SLT products was interviewed there informally and the names of mostly sold SLT products mentioned by the seller were compared with those earlier names. In that way, three types of SLT products (five commercial samples), which were mostly sold in DCC areas, were ascertained.

The three types of SLT products ascertained from the market survey were then compared with the responses from the SLT users during the ongoing data collection. When the types of SLT products revealed from the market survey matched with the types mostly used by the study participants, the samples of those three SLT products (five commercial samples) were finally listed for laboratory analysis for nicotine.

7.9.2. Nicotine analysis of selected SLT products

The Institute of Food Science and Technology (IFST), an institute of Bangladesh Council of Scientific and Industrial Research (BCSIR), was selected for the analysis of nicotine content of the selected SLT products. BCSIR is a renowned Government scientific research organization in Bangladesh, established in 1973 at Dhanmondi in Dhaka, which conducts research on multidisciplinary areas like food science, human nutrition, food microbiology, plant science, biotechnology, tissue culture, pharmacology, environmental pollution, arsenic mitigation, biogas technology, fuel research, ceramic research, leather research and other analytical research. IFST is responsible for conducting different types of analytic research on food products and it is the designated institute for examining the quality of food.
products imported by various entrepreneurs in Bangladesh. The samples of SLT products were analysed for presence and content of nicotine, following ‘extraction, steam distillation and silicotungstic acid gravimetric method’ at IFST, an international standard method described elsewhere. Nicotine content was reported in percentage by weight (% by wt.) for each sample.

7.10. Data analysis

All statistical analyses were undertaken using SPSS version 17 and STATA version 10. Descriptive statistics were used to know the socio-demographic variables (age, sex, residence, marital status, education, occupation, housing), risk factors for CHD (hypertension, diabetes, family history of heart disease, physical activities, use of hormonal contraceptives for women, indoor smoking and acute stressful events), main exposure variable (prevalence, types, frequency and duration of SLT use) and categorization of CHD cases by the RAQ. For descriptive analysis of the collected data, various descriptive statistics like frequencies, measures of central tendency (mean, median, mode), measures of dispersion (standard deviation, skewness) were seen in tabular forms. Graphs were also used for that purpose. Most of the variables in the dataset were either nominal or ordinal. Age was the main scale variable for analysis in this study. Box whisker plot was used to show the symmetry of distribution of age among cases and controls. For the nominal and ordinal variables, bar graphs and pie-charts were used to describe the proportion, and comparison between cases and controls among the variables. Descriptive statistics were also used to explore the perceptions of SLT use on health among the study participants.
For inferential analysis of data, cases and controls were compared by cross-tabulation at first. We did chi-squared ($\chi^2$) test when the frequency in any of the cells was $\geq 5$ and Fisher’s exact test when the frequency was $<5$, to calculate $p$-values to assess whether observations significantly departed from what would be expected by chance ($p = <0.05$). Then we did univariate analysis by conditional logistic regression, and calculated matched odds ratios (ORs) with 95% confidence intervals (CIs) to determine the strength of association between SLT use and CHD. Afterwards, multivariate analysis was done using conditional logistic regression for adjusting potential confounding variables for CHD. Among all of the socio-demographic variables and risk factors for CHD, those were significant ($p<0.05$) along with other variables ($p<0.20$) at the initial analysis from $\chi^2$ test, were considered one by one for adjustment; finally, we selected those variables for adjustment, inclusion of which did not drop any observation in the multivariate analysis model. The adjusted ORs with 95% CIs finally determined the association between SLT use and CHD in this study. We analysed separately for non-smokers (all study population), never-smokers and ex-smokers population; also analysed separately for cases vs. community controls, cases vs. hospital controls, and finally, cases vs. both controls combined. For comparing hospital controls and community controls, similar univariate and multivariate analysis were done.

Regarding validation of the responses from the RAQ compared with cardiologists’ diagnosis, the indicators used were false positive, false negative, sensitivity, specificity, Likelihood Ratio Positive and Likelihood Ratio Negative.
7.11. Ethical issues

The protocol for this project was approved by The University of Adelaide Human Research Ethics Committee and the local ethics committee (Bangladesh Medical Research Council) in Bangladesh. Issues surrounding consent, confidentiality and privacy were considered as possible sources of ethical difficulty for this study.

7.11.1. Consent for the interviews

The interviewers narrated the consent form to each of the study-participants. Those who agreed to take part in the study provided their signatures in the prescribed informed consent form in presence of a witness. If any participant was not literate enough to provide a signature, verbal informed consent was obtained in those circumstances in the presence of a witness. The consent form clearly described purpose and methods of the study, confidentiality of the interviews, risks and benefits of participating in the study, individuals’ rights to participate voluntarily and to withdraw from the study at any time without any consequences. The interviewers also provided an information sheet regarding the study objectives and a complaint form with contact details of the study coordinators.

7.11.2. Confidentiality and privacy

Data collected from the study-sites were used for study purpose and only the PhD candidate was authorized to view the details information of a particular respondent. Privacy and confidentially were maintained regarding the collected information. No information that could identify any individual was used or published anywhere. Questionnaires in hard copy were stored in the private secure personal dwelling of the PhD candidate and the electronic copies were
stored on the personal, id-protected, the University of Adelaide server site of the PhD candidate.

7.11.3. Other issues

Questionnaires on non-communicable disease and tobacco use do not raise any special cultural sensitivity. To accommodate the illiteracy situation in rural areas of Bangladesh, data were collected using structured questionnaires rather than self-administered instruments. Training of the data collectors included data collection procedures for the study, general information regarding CHD and tobacco to disseminate health awareness message at the end of each interview, and instructions regarding referral to the nearby health facility of any individual with an acute physical condition encountered during data collection in the community-settings. Information gathered from one household was not shared with other households. Proxy respondents were not used either for cases or controls in this study.
CHAPTER 8

Additional information: Results
Chapter outline

This chapter provides further results, both descriptive and analytic, which were not included in the prior manuscript chapters due to journal constraints on length and content. This chapter includes information about:

1. Non-response: This information has been included because it is important to assess the generalizability of the study findings.
2. Dose-response relationship between SLT use and CHD: Re-categorisation of frequency and duration of each SLT use was undertaken to assess the potential dose-response relationship between SLT use and CHD.

8.1. Non-response

Overall non-response was 6% in this study (Table 17). Reasons for non-response included reluctance to participate in a 10-minute interview session, less motivation to participate in a public health research, and being busy with household activities during the data collection period. Respondents and non-respondents did not vary by mean age and gender distribution.

8.2. Dose-response relationship between SLT use and CHD

8.2.1. Frequency and duration of each SLT used

Among 447 current exclusive jarda consumers, 406 (90.8%) of them used jarda for at least once a day (heavy users). Similar distribution was observed within each group of cases, community controls or hospital controls. Heavy use of jarda was more common among community controls compared to cases and to hospital
controls. Similarly, among 43 exclusive sada-pata consumers, 42 (97.7%) of them were heavy users. Distribution of frequency of sada-pata use was similar among cases, community controls and hospital controls. Again, among 48 exclusive gul users, 45 (93.8%) of them were heavy users. Heavy use of gul was slightly more common among cases than that of community controls or of hospital controls (Table 18).

Duration of jarda use ranged from 1 month to 55 years, with mean duration of 16 years. More than half of the exclusive jarda consumers (58.4%) used jarda for more than ten years (long duration users). Long duration of jarda use was slightly more common among hospital controls and community controls compared to cases. Duration of sada-pata use ranged from 3 years to 60 years, with mean duration of 28 years. The majority of the exclusive sada-pata users (81.4%) were long duration users. Distribution of duration of sada-pata use was similar among cases, community controls and hospital controls. Duration of gul use ranged from 6 months to 45 years, with mean duration of 17 years. More than half of the exclusive gul users (58.3%) used gul for long duration. Distribution of duration of gul use was similar among cases, community controls and hospital controls (Table 18).

When cumulative exposure of each SLT product was considered by combining frequency and duration of use, the group of ‘heavy use-long duration’ users was more common for each individual SLT product. There was no difference of cases, community controls and hospital controls in different groups of cumulative exposure for jarda, sada-pata or gul use (Table 19, 20, 21).
8.2.2. Dose-response relationship between SLT use and CHD

Table 19 shows that when community control data were analysed, ‘heavy use-long duration’ *gul* use was significantly associated with an increased risk of CHD among total study participants (adjusted OR 4.36, 95% CI 1.05-18.2). Alternately, heavy use-long duration *jarda* use was significantly associated with a decreased risk of CHD among never smokers (adjusted OR 0.30, 95% CI 0.13-0.68). When we analysed hospital control data, there was no statistically significant dose-response relationship between SLT use and CHD, when total participants were considered, or when we stratified our analyses according to smoking status (Table 20). When we combined both controls together for our analyses, ‘heavy use-long duration’ *gul* use was significantly associated with an increased risk of CHD among total study participants (adjusted OR 3.76, 95% CI 1.23-1.15). In contrast, heavy use-long duration *jarda* use was significantly associated with a decreased risk of CHD among never smokers (adjusted OR 0.30, 95% CI 0.14-0.67) (Table 21).

However, as mentioned earlier in chapter 3, that there may have been a problem with lack of power to make stratified analyses with each SLT product to identify the association with CHD or to identify the dose-response relationship, as there were very few users of each SLT product in this study.
Table 17: Selection of the study participants

<table>
<thead>
<tr>
<th>Category</th>
<th>Site</th>
<th>n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible study population</td>
<td></td>
<td></td>
<td>1920</td>
</tr>
<tr>
<td>Cases Hospitals</td>
<td></td>
<td>311</td>
<td></td>
</tr>
<tr>
<td>Controls Hospitals</td>
<td></td>
<td>316</td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td></td>
<td>1293</td>
<td></td>
</tr>
<tr>
<td>Non-response</td>
<td></td>
<td></td>
<td>108</td>
</tr>
<tr>
<td>Cases Hospitals</td>
<td></td>
<td>9 (3)</td>
<td></td>
</tr>
<tr>
<td>Controls Hospitals</td>
<td></td>
<td>14 (4)</td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td></td>
<td>85 (7)</td>
<td></td>
</tr>
<tr>
<td>Total study participants</td>
<td></td>
<td></td>
<td>1812</td>
</tr>
<tr>
<td>Cases Hospitals NICVD</td>
<td></td>
<td>209 (69)</td>
<td></td>
</tr>
<tr>
<td>Cases Hospitals NHFH&amp;RI</td>
<td></td>
<td>93 (31)</td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td></td>
<td>1208 (100)</td>
<td></td>
</tr>
<tr>
<td>Controls Hospitals NICVD</td>
<td></td>
<td>108 (36)</td>
<td></td>
</tr>
<tr>
<td>Controls Hospitals NHFH&amp;RI</td>
<td></td>
<td>194 (64)</td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td></td>
<td>1208 (100)</td>
<td></td>
</tr>
</tbody>
</table>
Table 18: Frequency and duration of each SLT product used by the study participants (exclusive users)

<table>
<thead>
<tr>
<th></th>
<th>Jarda (0.96% nicotine) use</th>
<th>Sada-pata (1.97% nicotine) use</th>
<th>Gul (5.48% nicotine) use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases, n(%)</td>
<td>Community Controls, n(%)</td>
<td>Hospital controls, n(%)</td>
</tr>
<tr>
<td>Total study participants (non-smokers)</td>
<td>302</td>
<td>1208</td>
<td>302</td>
</tr>
<tr>
<td>Frequency of use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than once a month</td>
<td>3 (1.0)</td>
<td>6 (0.5)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Once a month</td>
<td>2 (0.7)</td>
<td>4 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Once a week</td>
<td>2 (0.7)</td>
<td>3</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>2-3 times per week</td>
<td>3 (1.0)</td>
<td>10</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Once a day</td>
<td>4 (1.3)</td>
<td>8 (0.7)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>2-3 times per day</td>
<td>11 (3.6)</td>
<td>39</td>
<td>13 (4.3)</td>
</tr>
<tr>
<td>4 or more times per day</td>
<td>37 (12.3)</td>
<td>244 (20.2)</td>
<td>47 (15.6)</td>
</tr>
<tr>
<td>Frequency of use (recoded)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light use (less than once a day)</td>
<td>10 (3.3)</td>
<td>23 (1.9)</td>
<td>8 (2.6)</td>
</tr>
<tr>
<td>Heavy use (at least once a day)</td>
<td>52 (17.2)</td>
<td>291 (24.1)</td>
<td>63 (20.9)</td>
</tr>
<tr>
<td>Duration of use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range Mean (SD) in years</td>
<td>0.1-55.0</td>
<td>16.3 (12.2)</td>
<td>3.0-60.0</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>1 (0.3)</td>
<td>9 (0.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1-5 years</td>
<td>13 (4.3)</td>
<td>71 (5.9)</td>
<td>11 (3.6)</td>
</tr>
<tr>
<td>6-10 years</td>
<td>11 (3.6)</td>
<td>56 (4.6)</td>
<td>14 (4.6)</td>
</tr>
<tr>
<td>11-15 years</td>
<td>6 (2.0)</td>
<td>48 (4.0)</td>
<td>11 (3.6)</td>
</tr>
<tr>
<td>16-20 years</td>
<td>10 (3.3)</td>
<td>46 (3.8)</td>
<td>11 (3.6)</td>
</tr>
<tr>
<td>21-25 years</td>
<td>2 (0.7)</td>
<td>20 (1.7)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>26-30 years</td>
<td>7 (2.3)</td>
<td>27 (2.2)</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td>31-35 years</td>
<td>1 (0.3)</td>
<td>12 (1.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Duration of use (recoded)</td>
<td>Short duration (&lt;10 years)</td>
<td>Long duration (&gt;10 years)</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------</td>
<td>---------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (2.0)</td>
<td>37 (12.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18 (1.5)</td>
<td>178 (14.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (1.7)</td>
<td>46 (15.2)</td>
<td></td>
</tr>
<tr>
<td>36-40 years</td>
<td>1 (0.3)</td>
<td>4 (1.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 (0.6)</td>
<td>25 (2.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (0.3)</td>
<td>6 (2.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (0.3)</td>
<td>10 (3.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (0.3)</td>
<td>15 (1.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 (0)</td>
<td>3 (1.0)</td>
<td></td>
</tr>
<tr>
<td>41-45 years</td>
<td>2 (0.7)</td>
<td>3 (1.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (0.2)</td>
<td>13 (1.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (1.3)</td>
<td>3 (1.0)</td>
<td></td>
</tr>
<tr>
<td>46-50 years</td>
<td>2 (0.7)</td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (0.3)</td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (0.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>51-55 years</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (0.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>56-60 years</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
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<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>
Table 19: Univariate and multivariate matched analysis showing the association between cumulative exposure (frequency and duration combined) of each smokeless tobacco (SLT) and coronary heart disease (cases vs. community controls)

<table>
<thead>
<tr>
<th></th>
<th>Hospital Cases, n(%)</th>
<th>Community Controls, n(%)</th>
<th>OR</th>
<th>95% CI</th>
<th>Adj. OR§</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never users of any tobacco (Reference)</td>
<td></td>
<td></td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smokers (total study participants)</td>
<td>302</td>
<td>1208</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative exposure of jarda (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light use-Long duration</td>
<td>3 (1.0)</td>
<td>8 (0.7)</td>
<td>0.62</td>
<td>0.07-5.38</td>
<td>0.36</td>
<td>0.04-3.26</td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>20 (6.6)</td>
<td>122 (10.1)</td>
<td>0.49</td>
<td>0.28-0.88</td>
<td>0.65</td>
<td>0.35-1.21</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>35 (11.6)</td>
<td>170 (14.1)</td>
<td>0.61</td>
<td>0.38-1.00</td>
<td>0.64</td>
<td>0.37-1.08</td>
</tr>
<tr>
<td>Cumulative exposure of sada-pata (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>2 (0.7)</td>
<td>3 (0.2)</td>
<td>4.38</td>
<td>0.37-51.3</td>
<td>5.09</td>
<td>0.27-94.4</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>4 (1.3)</td>
<td>25 (2.1)</td>
<td>0.5</td>
<td>0.14-1.81</td>
<td>0.72</td>
<td>0.17-3.01</td>
</tr>
<tr>
<td>Cumulative exposure of gul (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>4 (1.3)</td>
<td>11 (0.9)</td>
<td>1.62</td>
<td>0.45-5.86</td>
<td>1.99</td>
<td>0.48-8.28</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>10 (3.3)</td>
<td>14 (1.2)</td>
<td>3.78</td>
<td>1.17-12.3</td>
<td>4.36</td>
<td>1.05-18.2</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>203</td>
<td>864</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative exposure of jarda (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light use-Long duration</td>
<td>3 (1.5)</td>
<td>3 (0.3)</td>
<td>1.64</td>
<td>0.10-26.6</td>
<td>1.74</td>
<td>0.09-32.2</td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>12 (5.9)</td>
<td>81 (9.4)</td>
<td>0.43</td>
<td>0.21-0.89</td>
<td>0.61</td>
<td>0.28-1.32</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>13 (6.4)</td>
<td>109 (12.6)</td>
<td>0.32</td>
<td>0.15-0.68</td>
<td>0.30</td>
<td>0.13-0.68</td>
</tr>
<tr>
<td>Cumulative exposure of sada-pata (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>2 (1.0)</td>
<td>3 (0.3)</td>
<td>3.77</td>
<td>0.32-43.8</td>
<td>4.14</td>
<td>0.16-108</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>2 (1.0)</td>
<td>18 (2.1)</td>
<td>0.18</td>
<td>0.02-1.46</td>
<td>0.27</td>
<td>0.03-2.68</td>
</tr>
<tr>
<td>Cumulative exposure of gul (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>3 (1.5)</td>
<td>6 (0.7)</td>
<td>1.33</td>
<td>0.28-6.34</td>
<td>1.53</td>
<td>0.23-10.1</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>3 (1.5)</td>
<td>10 (1.2)</td>
<td>1.68</td>
<td>0.22-12.9</td>
<td>3</td>
<td>0.35-26.1</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>99</td>
<td>344</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative exposure of jarda (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>8 (8.1)</td>
<td>41 (11.9)</td>
<td>0.93</td>
<td>0.32-2.72</td>
<td>1.62</td>
<td>0.45-5.84</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>22 (22.2)</td>
<td>61 (17.7)</td>
<td>2.16</td>
<td>0.84-5.56</td>
<td>1.93</td>
<td>0.63-5.91</td>
</tr>
<tr>
<td>Cumulative exposure of sada-pata (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>2 (2.0)</td>
<td>7 (2.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative exposure of gul (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>1 (1.0)</td>
<td>5 (1.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>7 (7.1)</td>
<td>4 (1.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The variables those were significant (p<0.20) during initial univariate analysis, were selected as confounders and adjusted during multivariate analysis. §Adjusted for: age, hypertension, diabetes and acute psycho-social stress; matched for: age, sex, residential areas and monthly house rent.
Table 20: Univariate and multivariate matched analysis showing the association between cumulative exposure (frequency and duration combined) of each smokeless tobacco (SLT) and coronary heart disease (cases vs. hospital controls)

<table>
<thead>
<tr>
<th>Hospital Cases</th>
<th>OR 95% CI</th>
<th>Adj. OR* 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never users of any tobacco (Reference)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-smokers (total study participants)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative exposure of <em>jarda</em> (freq-dur combined)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light use-Long duration</td>
<td>3 (1.0)</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>20 (6.6)</td>
<td>24 (7.9)</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>35 (11.6)</td>
<td>41 (13.6)</td>
</tr>
<tr>
<td>Cumulative exposure of <em>sada-pata</em> (freq-dur combined)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>2 (0.7)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>4 (1.3)</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td>Cumulative exposure of <em>gul</em> (freq-dur combined)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>4 (1.3)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>10 (3.3)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Never-smokers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative exposure of <em>jarda</em> (freq-dur combined)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light use-Long duration</td>
<td>1 (0.3)</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>10 (3.3)</td>
<td>17 (7.6)</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>9 (3.0)</td>
<td>28 (12.4)</td>
</tr>
<tr>
<td>Cumulative exposure of <em>sada-pata</em> (freq-dur combined)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>2 (0.7)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>2 (0.7)</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td>Cumulative exposure of <em>gul</em> (freq-dur combined)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>3 (1.0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>3 (1.0)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative exposure of <em>jarda</em> (freq-dur combined)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>6 (2.0)</td>
<td>7 (9.1)</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>17 (5.6)</td>
<td>13 (16.9)</td>
</tr>
<tr>
<td>Cumulative exposure of <em>sada-pata</em> (freq-dur combined)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>2 (0.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cumulative exposure of <em>gul</em> (freq-dur combined)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>1 (0.3)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>7 (2.3)</td>
<td>1 (1.3)</td>
</tr>
</tbody>
</table>

The variables those were significant (p<0.20) during initial univariate analysis, were selected as confounders and adjusted during multivariate analysis.

* Adjusted for: age, marital status, hypertension, diabetes, indoor smoking exposure and acute psycho-social stress; matched for: age and sex.
Table 21: Univariate and multivariate matched analysis showing the association between cumulative exposure (frequency and duration combined) of each smokeless tobacco (SLT) and coronary heart disease (cases vs. both controls)

<table>
<thead>
<tr>
<th></th>
<th>Hospital Cases, n(%)</th>
<th>Both Controls, n(%)</th>
<th>OR</th>
<th>95% CI</th>
<th>Adj. OR¶</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never users of any tobacco (Reference)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smokers (total study participants)</td>
<td>302</td>
<td>1510</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative exposure of jarda (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light use-Long duration</td>
<td>1 (0.3)</td>
<td>11 (0.7)</td>
<td>0.41</td>
<td>0.05-3.23</td>
<td>0.30</td>
<td>0.04-2.53</td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>16 (5.3)</td>
<td>142 (9.4)</td>
<td>0.55</td>
<td>0.31-0.96</td>
<td>0.69</td>
<td>0.38-1.24</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>26 (8.6)</td>
<td>204 (13.5)</td>
<td>0.62</td>
<td>0.39-1.01</td>
<td>0.68</td>
<td>0.41-1.12</td>
</tr>
<tr>
<td>Cumulative exposure of sada-pata (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>2 (0.7)</td>
<td>5 (0.5)</td>
<td>1.69</td>
<td>0.26-10.8</td>
<td>2.07</td>
<td>0.30-14.2</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>4 (1.3)</td>
<td>31 (2.1)</td>
<td>0.65</td>
<td>0.20-2.09</td>
<td>0.98</td>
<td>0.28-3.45</td>
</tr>
<tr>
<td>Cumulative exposure of gul (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>4 (1.3)</td>
<td>14 (0.9)</td>
<td>1.83</td>
<td>0.53-6.37</td>
<td>2.23</td>
<td>0.56-8.79</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>10 (3.3)</td>
<td>17 (1.1)</td>
<td>3.41</td>
<td>1.26-9.28</td>
<td>3.76</td>
<td>1.23-11.5</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>203</td>
<td>1089</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative exposure of jarda (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light use-Long duration</td>
<td>1 (0.5)</td>
<td>5 (0.5)</td>
<td>0.58</td>
<td>0.07-5.10</td>
<td>0.52</td>
<td>0.05-5.51</td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>10 (4.9)</td>
<td>96 (8.8)</td>
<td>0.48</td>
<td>0.23-0.97</td>
<td>0.64</td>
<td>0.30-1.35</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>9 (4.4)</td>
<td>133 (12.2)</td>
<td>0.31</td>
<td>0.15-0.64</td>
<td>0.30</td>
<td>0.14-0.67</td>
</tr>
<tr>
<td>Cumulative exposure of sada-pata (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>2 (1.0)</td>
<td>5 (0.5)</td>
<td>1.57</td>
<td>0.25-9.96</td>
<td>2.07</td>
<td>0.29-14.7</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>2 (1.0)</td>
<td>24 (2.2)</td>
<td>0.35</td>
<td>0.07-1.70</td>
<td>0.59</td>
<td>0.11-3.29</td>
</tr>
<tr>
<td>Cumulative exposure of gul (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>3 (1.5)</td>
<td>7 (0.6)</td>
<td>1.47</td>
<td>0.33-6.45</td>
<td>1.78</td>
<td>0.31-10.2</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>3 (1.5)</td>
<td>12 (1.1)</td>
<td>1.72</td>
<td>0.28-10.5</td>
<td>2.3</td>
<td>0.34-15.4</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>99</td>
<td>421</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative exposure of jarda (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>6 (6.1)</td>
<td>46 (10.9)</td>
<td>1</td>
<td>0.36-2.82</td>
<td>1.37</td>
<td>0.42-4.47</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>17 (17.2)</td>
<td>71 (16.9)</td>
<td>2.21</td>
<td>0.89-5.48</td>
<td>1.92</td>
<td>0.72-5.13</td>
</tr>
<tr>
<td>Cumulative exposure of sada-pata (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>2 (2.0)</td>
<td>7 (1.7)</td>
<td>Undef</td>
<td>Undef</td>
<td>Undef</td>
<td>Undef</td>
</tr>
<tr>
<td>Cumulative exposure of gul (freq-dur combined)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy use-Short duration</td>
<td>1 (1.0)</td>
<td>7 (1.7)</td>
<td>Undef</td>
<td>Undef</td>
<td>Undef</td>
<td>Undef</td>
</tr>
<tr>
<td>Heavy use-Long duration</td>
<td>7 (7.1)</td>
<td>5 (1.2)</td>
<td>Undef</td>
<td>Undef</td>
<td>Undef</td>
<td>Undef</td>
</tr>
</tbody>
</table>

The variables those were significant (p<0.20) during initial univariate analysis, were selected as confounders and adjusted during multivariate analysis.

¶ Adjusted for: age, hypertension, diabetes and acute psycho-social stress; matched for: age, sex, residential areas and monthly house rent.
CHAPTER 9

Conclusions
Chapter outline

This chapter summarizes the entire study findings along with the strengths and limitations of this research. The implications of these findings in terms of public health and in particular tobacco control policy in Bangladesh are discussed. This chapter includes the following information:

1. Summary of the study findings
2. Strengths of the study
3. Limitations of the study
4. Implications and recommendations

9.1. Summary of the study findings

This thesis has explored whether there is an association between the use of different SLT products and CHD among non-smoking adults in Bangladesh. To recapitulate, a systematic literature review (chapter 2) was conducted to provide the rationale for conducting this study. The results of the case-control study exploring the association between SLT use and CHD among the Bangladeshi population were presented in chapter 3. Chapter 4 described the perceptions of using SLT products by Bangladeshi people. Based on the results of the case-control study, chapter 5 explored the theoretical and practical aspects of selecting control subjects in a case-control study. Similarly, based on the results of the case-control study, chapter 6 provided information about the validation of the RAQ compared with cardiologist diagnosis to detect CHD.

The main findings of this study can be summarized as follows:
Is there any association between SLT use and CHD among non-smoking adults in Bangladesh?

This study did not find any increased risk of CHD with use of SLT products in general among non-smoking Bangladeshi adults. Risk of CHD did not increase with current use, past use, use of individual types (except *gul*), frequency, and duration of SLT use. Using community controls, hospital controls, both controls combined, and using the RAQ re-classification did not change the study findings.

What are the perceptions of Bangladeshi adults about the health effects of SLT use?

Addiction and lifestyle habit were the main perceived reasons for using SLT products by Bangladeshi adults. The level of awareness regarding harmful effects of SLT use on health was relatively high among the participants in this study. SLT use was perceived to be associated with heart disease, cancer, tuberculosis, lung disease and hypertension, although SLT users were less likely to believe this association compared to SLT non-users. The majority of participants did not mention any benefit, but SLT users considered SLT could be a remedy for toothache. Advice from family members influenced the SLT users to initiate using SLT products, whereas advice from doctors was the common motivating factor to quit.

Does using hospital controls or community controls in a case-control study in Bangladesh give different results?

Compared to community controls, hospital controls were more educated, had higher rates of hypertension, reported more positive family history of heart diseases, and performed less physical activity. Current use of SLT was higher
amongst community controls compared to hospital controls, although this difference was not statistically significant. Current use of SLT was not associated with an increased risk of CHD when data from community controls were used, nor when data from hospital controls were used.

*What is the utility of the RAQ for detecting CHD among Bangladeshi adults?*

The RAQ had moderate sensitivity and high specificity for detecting CHD compared with diagnoses made by cardiologists among Bangladeshi adults. There was no difference on sensitivity or specificity when subgroup analyses were conducted by age and gender. However, the RAQ showed higher sensitivity among people of lower SES compared to those of higher SES.

*Additional findings*

This study was also able to document the presence and content of nicotine in some of the most commonly used SLT products in Bangladesh. Interestingly, *paan-masala*, one of the most commonly used SLT products, did not contain any nicotine. However, this finding is likely to only apply to Bangladeshi *paan-masala* as other countries may include nicotine in their products. *Jarda* contained 0.96% nicotine and *gul* contained 5.48% nicotine.

**9.2. Strengths of the study**

The study design of this project addressed many of the limitations of earlier studies exploring the association between SLT use and CHD. In addition, the study was also able to provide insight into some important methodological constraints of epidemiological studies.
Exclusion of smokers from the study population controlled the strong confounding effects of smoking on CHD at the design stage of this study. Initially because we considered it would be difficult to obtain enough subjects in the study time frame, ex-smokers (who quit at least 10 years ago) were also included. In retrospect, it may have been preferable (and probably possible) to only recruit never-smokers. Including people of 40-75 years old in this study compared to the earlier Bangladeshi case-control study allowed an assessment of the association between SLT use and CHD among a broader range of adults in Bangladesh. This is important because this age group is at the highest risk of developing CHD in South Asia. Because SLT products are used equally by both men and women in Bangladesh with CHD mortality differing between men and women, it is important to evaluate the risk of CHD among both genders. The study findings have greater generalizability compared to some of the prior Western studies (particularly those from Sweden, where only men were included).

The earlier study from Bangladesh had a relatively small sample size, which increased the risk of type II error. The current study had an adequate sample size to have 80% power to detect a 5% difference in CHD between cases and controls. Including incident cases of CHD instead of prevalent cases minimises the chance of missing the true exposure history of SLT use in this study, as discussed in chapter 1. Furthermore, including both hospital controls and community controls gave the opportunity to assess possible selection bias inherent in selecting controls for a case-control study (discussed in chapter 5).

Betel-quid or areca-nut was not included as SLT products in this study as they had been in other prior studies. These products generally do not contain nicotine,
but may be associated with CHD. Instead, SLT products for this study were selected based on nicotine content analysis of the local SLT products. This allows greater confidence in attributing nicotine to the development of CHD and not some other ingredient.

Cases and controls were interviewed using the same questionnaire by the same interviewers, who were fully supervised. Data collectors were carefully selected and were comprehensively trained by the PhD candidate. Feedback from the pilot study improved the quality of the study questionnaire. The study questionnaire along with the RAQ was translated systematically, as discussed earlier. Selection criteria for the study participants were strictly adhered to. Any potential participant who had smoked for a single puff of tobacco within the last ten years was not considered eligible for this study. Diagnosis of CHD for cases and non-CHD for hospital controls was ascertained by hospital cardiologists. In most instances selection of cases and controls from the field-sites was done in the presence of the PhD candidate. Re-interviewing a small percentage of both cases and controls did not reveal any discrepancy in the collected data.

This is the first large scale study not only from Bangladesh but also from the South Asian region that focuses on the association between SLT use and CHD among non-smoking adults, compares the use of hospital controls and community controls in a case-control study, and validates the accuracy of the RAQ to detect CHD compared with cardiologists’ diagnosis. This is the first study from Bangladesh that has reported on perceptions of local people about the health effects of SLT use, and nicotine content in most commonly used SLT products in Bangladesh.
9.3. Limitations of the study

This study has a number of limitations, which may have influenced the study findings.

First, the study was not able to standardise the diagnosis of CHD in a hospital setting. Cardiologists diagnosed CHD cases based on clinical judgment, which included a combination of classical symptoms with positive results from electrocardiogram, cardiac enzymes, exercise tolerance test, or coronary artery angiogram. From a practical perspective, the same diagnostic tool could not be used for each patient, because of cardiologists’ preference and the ability of the patient to pay the diagnostic fees. Therefore, it is likely that there were inconsistencies in the diagnosis of CHD among cases and hospital controls by cardiologists. However, because the cardiologists involved were qualified and experienced specialists working in tertiary hospitals, misclassification bias was likely to be minimal. In addition, data were analysed according to the RAQ, allowing the classification of outcome to be the same between cases and controls.

Self-reported diagnoses of non-CHD among the community controls were not verified by a qualified physician due to budget constraints in this study. This means that undiagnosed CHD cases could have been included in the community control group (explained in chapter 5 in detail). Within Bangladesh, it is highly likely that CHD cases could go undiagnosed in the community, as people only seek medical care when symptoms become unbearable. On the other hand, there is little stigma attached to CHD and thus self-reporting of symptoms should hopefully be high. In addition, as noted above, the RAQ was used to reclassify this
community control group based on pain perceptions, and the results of association between SLT use and CHD did not change by this re-classification.

Biochemical or serological test to compare the results between cases and controls regarding the effects of SLT use on CHD could not be done. However, self-reported histories of other risk factors for CHD were collected, and compared between cases and controls in this study. CHD patients could not be sub-classified as myocardial infarction or angina pectoris, because in many cases this level of detail was not consistently available in the case-notes of CHD patients. In addition, one-third of the selected CHD cases were classified using the general term CHD by cardiologists. Fatal CHD cases were not included in this study, because the hospital death register in Bangladesh is not well maintained in comparison to developed countries. Moreover, collection of SLT exposure data from the family members of deceased individuals is potentially not as valid as collecting data directly from patients. Therefore, findings of this study represent non-fatal CHD only.

Because of budget and time limitations, only one hospital control was obtained for each CHD case. This has resulted in reduced statistical power for the analyses using only hospital controls. However this does not detract from the main focus of this research using community controls to explore the association between SLT use and CHD. Height and weight measurements were not collected because it was not considered socially acceptable or practical to collect data in urban settings of Bangladesh as mentioned in chapter 3. BMI is acknowledged to be an important confounder and in retrospect the extra effort to obtain this could have been justified. However, as we did not find an increased risk of CHD with SLT use, it is
unlikely that not considering BMI as a potential confounder had an impact on the non-association results in this study.

We had very few samples of SLT products to test for nicotine concentration in this study. Whilst this information was somewhat useful in helping us interpret the main study findings, nicotine concentration may vary depending on manufacturers. Therefore, laboratory results should be interpreted with caution.

The findings regarding the association between SLT use and CHD may not be generalisable to a rural population of Bangladesh. This is important because the prevalence of SLT use is higher in rural areas\(^\text{16}\). Perceptions of SLT use also may differ in rural areas of Bangladesh due to different socio-demographics and levels of awareness. In addition, due to different constituents of SLT products in other parts of subcontinent such as India and Pakistan, the findings of this study may not apply to other South Asian countries. However, findings of control choice and utility of the RAQ are generalisable to any research-poor setting of South Asia or to other developing countries.

### 9.4. Implications and recommendations

Evaluating the health effects of SLT products in Bangladesh is important as SLT use is integrated within the culture of this country. Exploring the association between SLT use and CHD from Bangladesh adds to the epidemiological evidence from South Asia, where such studies are limited. Findings on the perceptions of SLT use are important to consider for tobacco control activities in Bangladesh as well as in other parts of the subcontinent. Epidemiological issues
such as selection of controls and the use of the RAQ are particularly important within a developing country context.

Findings from this research are relevant to health promotion activities in Bangladesh. Despite the fact that the current study did not find an association between Bangladeshi SLT products and CHD in general, *gul* which contains the highest nicotine concentration was significantly associated with CHD. In addition, SLT use is not harmless. There is consistent association between SLT use and oral/dental diseases and various cancers and tobacco control activities should focus on these specific SLT-related diseases. Whilst awareness regarding the harmful effects of SLT use in general was relatively high amongst participants in this study, specific disease-related awareness was not strong particularly amongst the SLT users. The literature suggests that the perceived benefits of smoking are high among smokers and this is one of the reasons that smoking cessation is difficult for some individuals. However, the perceived benefits of SLT use were not particularly high among the SLT users in this study. This suggests that if awareness among Bangladeshi adults to the harmful effects of SLT use can be increased, this may outweigh perceptions of benefit.

To create a supportive environment, health promotion activities should alert people to the influence of families and friends in introducing individuals to SLT products. Also, family members have an important role to play in supporting individuals with SLT use cessation. Existing community networks and the trained workforce used for other public health promotion initiatives such as immunisation, water and sanitation, tuberculosis and family planning could be mobilised to provide information and support for quitting SLT products in Bangladesh.
Supporting primary care services to screen for SLT use and provide counselling for individuals to aid quitting may be helpful. Our study found that advice from doctors was considered an important influencing factor for quitting SLT products. Hence, it will be important to educate physicians, particularly those in primary care settings, about the harmful effects of SLT products in addition to smoking.

In terms of public health policy, the issue of tobacco cultivation needs to be addressed in developing countries if substantial reductions in SLT use are to be realised. Whilst a significant number of farmers are involved in tobacco farming in order to make a relatively higher profit compared to rice cultivation, research has suggested that tobacco farming is not reducing poverty among these farmers. The Government of Bangladesh has already banned loans for tobacco farming for farmers in 2010. The Government and the non-government organizations are helping tobacco farmers convert from tobacco to rice cultivation by providing seeds and other technical assistance.

In line with the WHO Framework Convention on Tobacco Control (FCTC), the Government of Bangladesh formulated and enacted tobacco control laws in 2005. The new legislation includes a partial ban on smoking in selected public places and public transport, almost a total ban on advertisement of tobacco products, and incorporation of health warning messages in the text included on tobacco packs. The Government has also formed a National Tobacco Control Cell (NTCC) to coordinate tobacco control initiatives in the country; taskforce committees have also been formed at national, district and sub-district levels to oversee enforcement of the law at field level. The Government is considering price and tobacco taxation policies to reduce demand for tobacco products.
However, the issue of using SLT products has not yet gained substantial recognition in tobacco control activities in Bangladesh. Although there is no commercial promotion of SLT products in Bangladesh, these products are commonly sold with cigarettes by street hawkers. Selling of SLT products will be difficult to control as street hawkers are very common in all parts of Bangladesh and the use of betel leaf with/without SLT products are embedded in the cultural norms. Hence, there is a need to increase community knowledge and concern about the harmful health effects of SLT use in Bangladesh.

Another useful approach may be to introduce monitoring and regulation of nicotine concentrations in Bangladeshi SLT products. There is very little published information regarding the nicotine content and constituents of commercial SLT products in Bangladesh and this information would be very important in terms of planning further tobacco control activities. Future studies of the association between health outcomes and SLT products should include such analyses.

The finding that there was no association between SLT use and CHD in this study (other than for gul) seems to support the use of SLT as a harm reduction agent for smokers. As described in chapter 1, some countries such as Sweden have supported the use of SLT in this way. However, as there is consistent evidence of a strong association between SLT use and cancers, SLT use cannot be portrayed as a safe alternative. Given the fact that the burden of tobacco-related illnesses are more among people of lower SES and there are limited resources for health promotion activities in developing countries, policies supporting non-use of any form of tobacco are justified. Because SLT use is not harmless, the
strategic focus should be upon controlling both forms of tobacco use in Bangladesh.

Because SLT products differ between countries, further studies from other parts of the subcontinent such as India and Pakistan with different types of SLT products would add further epidemiological evidence regarding the association between SLT use and CHD in South Asia. In addition, recruiting participants from rural settings of Bangladesh in future studies would be useful.

Considering the budget constraints for public health research in resource-scarce settings like South Asia, researchers may wish to consider selecting hospital controls for a case-control study. However, our study has shown that this should only be done if potential confounders are carefully considered and adjusted for. This study has produced a Bengali version of the RAQ which appears to have high specificity. However, further exploration of the questionnaire’s validity and reliability in Bangladesh would support its future use. The RAQ is a very useful tool to detect CHD in large scale epidemiological surveys. In addition, the RAQ could be used in primary health care settings to screen for CHD among high risk individuals when other more sophisticated tests (such as exercise stress testing) are not available.

In conclusion, this thesis provides epidemiological evidence about the possible association between SLT use and CHD from a South Asian perspective. Contextualising the perceptions of SLT use provides helpful information for planning future tobacco control activities in Bangladesh. In addition, this thesis has highlighted the difficulties associated with selection of controls and thus provides
practical information for other researchers designing case-control studies in resource poor countries. Validating the RAQ with cardiologists’ diagnoses may assist future researchers use this tool to detect CHD in epidemiological surveys in South Asian countries.


http://www.bat.com/group/sites/uk__3mnfen.nsf/vwPagesWebLive/DO6CPCXZ?open
document&SKN=2&TMP=1.


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200. Bodegard J, Eriksson G, Bjornholt JV, Thelle D, Eriksson J. Possible angina detected by the WHO angina questionnaire in apparently healthy men with a


213. Heffner JL, Mingione C, Blom TJ, Anthenelli RM. Smoking history, nicotine dependence, and changes in craving and mood during short-term smoking


Appendix I: Study questionnaire in English

INFORMATION SHEET FOR THE RESEARCH PARTICIPANTS
(To be translated and printed in Bengali)

Introduction
The research on “Smokeless tobacco and coronary heart disease: risks among non-smokers in Bangladesh” is being conducted for a Bangladeshi PhD student, Dr. Muhammad Aziz Rahman, from The University of Adelaide, Australia, as a part of his study.

Purpose of the study
The purpose of this study is to ascertain the relationship of smokeless tobacco with coronary heart disease and to explore the perceptions of use of smokeless tobacco on health in Bangladesh. Information gathered from you will help the society to learn more about the coronary heart disease and smokeless tobacco in the Bangladesh context.

Methods
I will ask you some questions regarding you and about some factors related to heart diseases and use of tobacco. It won’t take more than 10 minutes.

Benefits
You will not get any benefits for your participation in this study. However, this research is conducted in close collaboration with the government health department and we are confident that this information that we collect from the hospital and the community will be used to develop policy and programs for health awareness, education, and improvement of cardiac care at the government health centers and hospitals.

Risks
There are no risks involved in this study since the data collected from you will be used for our research purpose only. Privacy and confidentiality regarding the interviews and data collected from the respondents will be maintained.

Confidentiality
All the information you give will be kept secured and be used for our research purpose only. No one will have access to them except the concerned researchers involved in this study. Your name or any information related to your identity will not be included in the report.

Right to participate or withdraw
You have every right not to participate in the study and discontinue the interview at any point. You may choose to answer any questions if you don’t want to. You will not be penalized if you choose not to participate.

Any query or complaints
If you have any query or complaint about the study or your right as a participant, you may ask me now or, you can contact with the coordinator of the study. I will provide you an individual Complaint Form with the contact details of the study coordinator.

Eligibility to participate
The person should be 40 or more years, never smoked, or if smoked in the past have stopped smoking ten years ago, not suffering from any heart disease for more than a year, and living in areas within Dhaka City Corporation.
COMPLAINT FORM
FOR THE RESEARCH PARTICIPANTS
(To be translated and printed in Bangali)

The Human Research Ethics Committee in Australia and Bangladesh are obliged to monitor approved research projects. In conjunction with other forms of monitoring it is necessary to provide an independent and confidential reporting mechanism to assure quality assurance of the institutional ethics committee system. This is done by providing research participants with an additional avenue for raising concerns regarding the conduct of any research in which they are involved.

The following study has been reviewed and approved by the University of Adelaide Human Research Ethics Committee and the Bangladesh Medical and Research Council (BMRC):

Project title: 
Smokeless tobacco and coronary heart disease: risks among non-smokers in Bangladesh

1. If you have questions or problems associated with the practical aspects of your participation in the project, or wish to raise a concern or complaint about the project, then you should consult the project co-ordinator:

   Name: Dr. Muhammad Aziz Rahman
   Telephone: +88-01715476880 (Mobile)

2. If you wish to discuss with an independent person matters related to
   - making a complaint, or
   - raising concerns on the conduct of the project, or
   - the University policy on research involving human participants, or
   - your rights as a participant

   You should contact:
   Professor Mahmudur Rahman
   Director
   Institute of epidemiology, Disease Control and Research (IEDCR),
   Mohakhali, Dhaka-1212, Bangladesh.
   Tel: +88-02-9896796, 9896691 (Office).
CONSENT FORM
FOR THE RESEARCH PARTICIPANTS
(To be translated and printed in Bengali

1. I, .............................................................................................. (please print name)
   consent to take part in the research project entitled:
   Smokeless tobacco and coronary heart disease: risks among non-smokers in Bangladesh

2. I acknowledge that I have read the attached Information Sheet entitled:
   Information Sheet for the Research Participants

3. I have had the project, so far as it affects me, fully explained to my satisfaction by the research worker. My consent is given freely.

4. Although I understand that the purpose of this research project is to improve the quality of medical care, it has also been explained that my involvement may not be of any benefit to me.

5. I have been given the opportunity to have a member of my family or a friend present while the project was explained to me.

6. I have been informed that, while information gained during the study may be published, I will not be identified and my personal results will not be divulged.

7. I understand that I am free to withdraw from the project at any time and that this will not affect medical advice in the management of my health, now or in the future.

8. I am aware that I should retain a copy of this Consent Form, when completed, the attached Information Sheet and the complaint form.

   ...........................................................................................................................
   (Signature) ............................................................................................................
   (Date)

WITNESS:

The details and nature of the research has been explained to ........................................
(name of subject)

In my opinion she/he understood the explanation.

Status in Project: ...............................................................

Name: .......................................................................................

...........................................................................................................................
   (Signature) ............................................................................................................
   (Date)
# Study Questionnaire for the Project

**Interviewer's Name**
________________________

**Interviewer's Signature**
________________________

**Date of Interview**
__/__/____ (Day/Month/Year)

**Survey Code Number**
[ ] [ ] [ ] [ ]

**Survey Site**

- NICVD [ ]
- NHFH&RI [ ]
- Community [ ]

**Category of the Participant**

- **CASE** [ ]
- **CONTROL** [ ] 1/2/3/4 for CASE No _________

**For CASE**

- **Date of Admission** ........................................ Ward ....................................... Bed ..............
- **Clinical Symptoms** ..........................................................
- **ECG** ...............................................................
- **CK-MB** ............................................................
- **Troponin-I** ..........................................................
- **Angiogram** ..........................................................
- **Others** ..................................................................

---

*Page 4*
(Screening Questionnaire)

1. Where do you live?
   Address ....................................................................................................................
   District .....................................................................................................................
   Contact telephone no ............................................................................................
   Within Dhaka City Corporation .......... 1 [proceed to the next question]
   Outside Dhaka City Corporation ......2 [end of interview]
   NR .............................................................. 99

2. How old are you? (Age in years)
   ........................................ Years  [if <40 years, end of interview]
   DK ............................................. 88
   NR ............................................. 99

3. Do you currently smoke any form of tobacco products?
   Yes ........................................... 1 [end of interview]
   No ............................................. 0 [proceed to the next question]
   NR ............................................. 99

3a. In the past, did you smoke any form of tobacco products?
   Yes ........................................... 1 [proceed to the next question]
   No ............................................. 0 [skip to Q4]
   INAP ........................................ 77
   NR ............................................. 99

3b. When did you stop smoking?
   <10 years ago ..................... 1 [end of interview]
   >10 years ago ................. 2 [proceed to the next question]
   INAP ........................................ 77
   NR ............................................. 99

4. Have you ever been told by a doctor or a health-worker that you have heart disease?
   Yes ........................................... 1 [For CASES, proceed to the next question. For CONTROLS, end of interview]
   No ............................................. 0 [proceed to the full interview session]
   NR ............................................. 99

4a. Was the heart disease diagnosed for the first time within the last one-year?
   Yes ........................................... 1 [proceed to the full interview session]
   No ............................................. 0 [end of interview]
   INAP ........................................ 77
   NR ............................................. 99
(Full Interview Session)

Now, I will ask some general information about you.

1. INTERVIEWER: Code gender of the respondents
   - Male .................................... 1
   - Female .................................. 2
   - Others ................................... 3

2. What is your marital status?
   - Single ...................................... 1
   - Married (and living with spouse) ............. 2
   - Married (and spouse working overseas) .......... 3
   - Divorced .................................... 4
   - Widowed ..................................... 5
   - Separated ................................... 6
   - NR ........................................... 99

3. What is your highest level of education?
   - Illiterate .................................... 0
   - Can sign names ................................ 1
   - Literate ..................................... 2
   - Primary ..................................... 3
   - Secondary ................................... 4
   - Higher secondary ............................. 5
   - Above higher secondary ......................... 6
   - NR ........................................... 99

4. What is your primary occupation? [If more than one, specify the primary one]
   ................................................................. 99

5. Do you own the house you are living in?
   - Yes .......................................... 1
   - No ........................................... 0
   - NR ........................................... 99

5a. What is your monthly house-rent? [If living in own house: what would be the house-rent of that house, if you rent it?]
   - $\leq 5,000$ BDT .................................... 1
   - $5,000 - 10,000$ BDT ................................. 2
   - $>10,000$ BDT ..................................... 3
   - DK ................................................ 88
   - NR ........................................... 99
Now, I am going to ask you some questions regarding your health. The following questions only relate to the last one year.

6. Within the last one-year, have you ever had a severe pain across the front of your chest lasting for half an hour or more?
   Yes ........................................ 1  [skip to Q8]
   No ........................................ 0
   NR ........................................... 99

7. Within the last one-year, have you ever had any pain or discomfort in your chest?
   Yes ........................................ 1  [skip to Q8]
   No ........................................ 0
   INAP ........................................ 77
   NR ........................................... 99

7a. Within the last one year, have you ever had any pressure or heaviness in your chest?
   Yes ........................................ 1
   No ........................................ 0  [skip to Q13]
   INAP ........................................ 77
   NR ........................................... 99

8. Did the pain/discomfort/pressure/heaviness in the chest occur for the first time in the last year?
   Yes ........................................ 1  [skip to Q13, if yes to Q6 and Q8]
   No ........................................ 0  [skip to Q13]
   INAP ........................................ 77
   NR ........................................... 99

9. Did you get the pain/discomfort/pressure/heaviness in the chest when you walked uphill or hurried?
   Yes ........................................... 1
   No ........................................... 0
   Never hurries nor walks uphill ............. 2
   INAP ........................................ 77
   NR ........................................... 99

10. Did you get the pain/discomfort/pressure/heaviness in the chest when you walked at an ordinary pace on the level?
    Yes ........................................ 1
    No ........................................ 0
    INAP ........................................ 77
    NR ........................................... 99

[Skip to Q12, if 'no' in both Q9 and Q10]
11. What did you do when you got the pain/discomfort/pressure/heaviness in the chest while you were walking?
   Stopped or slowed down ..................... 1
   Carried on .................................. 2 [skip to Q12]
   Others ...................................... 3 [skip to Q12]
   (Specify ....................................)
   INAP ........................................ 77
   NR ............................................. 99

11a. If you were standing still, what happened to the pain/discomfort/pressure/heaviness in the chest?
   Relieved ..................................... 1
   Not relieved ................................. 2 [skip to Q12]
   INAP ........................................ 77
   NR ............................................. 99

11b. How soon was the pain/discomfort/pressure/heaviness in the chest relieved?
   Within 10 minutes or less ............... 1
   More than 10 minutes .................... 2
   INAP ........................................ 77
   NR ............................................. 99

12. Could you please point to where the pain/discomfort/pressure/heaviness in your chest was? [Interviewer: note down the location and tick all that apply]

   Stennum (upper or middle or lower) .... 1
   Left anterior chest ......................... 2
   Left arm .................................... 3
   Other sites .................................. 4
   INAP ........................................ 77
   NR ............................................. 99
Now, I am going to ask you some questions regarding tobacco usage.

13. Do you currently use any form of smokeless tobacco products (e.g. paan-masala, jarda, sada-pata, gul etc.)?
   Yes ........................................ 1
   No ......................................... 0  [skip to Q14]
   NR ........................................... 99

13a. Which of the following do you use?

[Interviewer: prompt each of the following options and tick all those apply]

<table>
<thead>
<tr>
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<th>Yes</th>
<th>No</th>
<th>INAP</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1</td>
<td>0</td>
<td>77</td>
<td>99</td>
</tr>
<tr>
<td>Jarda</td>
<td>1</td>
<td>0</td>
<td>77</td>
<td>99</td>
</tr>
<tr>
<td>Sada-pata</td>
<td>1</td>
<td>0</td>
<td>77</td>
<td>99</td>
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<tr>
<td>Gul</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Khaini</td>
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<td>0</td>
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<td>Snuff</td>
<td>1</td>
<td>0</td>
<td>77</td>
<td>99</td>
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<tr>
<td>Others</td>
<td>1</td>
<td>0</td>
<td>77</td>
<td>99</td>
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</tbody>
</table>

(Specify ________________________________)

13b. How often do you use these smokeless tobacco products?

[Interviewer: prompt the following options, if the respondent can’t answer]

4 or more times per day .................. 1
2-3 times per day .......................... 2
Once a day ................................. 3
2-3 times per week ......................... 4
Once a week .................................. 5
Once a month ................................ 6
Less than once a month .................... 7
INAP .................................. 77
NR ........................................ 99

13c. For how long have you been using smokeless tobacco products?

.......... Months (if <12 months) .......... Years
INAP .................................. 77
NR ........................................ 99

14. Have you used any form of smokeless tobacco products (e.g. paan-masala, jarda, sada-pata, gul etc.) in the past?

Yes ........................................ 1
No ......................................... 0  [skip to Q15]
INAP .................................. 77
NR ........................................ 99
14a. Which of the following did you use?  
[Interviewer: prompt each of the following options and tick all those apply]

<table>
<thead>
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<th>Types</th>
<th>Yes</th>
<th>No</th>
<th>INAP</th>
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<td>0</td>
<td>77</td>
<td>99</td>
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<tr>
<td>Jarda</td>
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<td>Sada-pata</td>
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<td>Gul</td>
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<td>Khaini</td>
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<td>0</td>
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<td>99</td>
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<tr>
<td>Snuff</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Others</td>
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<td>77</td>
<td>99</td>
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<td>(Specify)</td>
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14b. What is the duration since you stopped using these smokeless tobacco products?  

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<thead>
<tr>
<th></th>
<th>years</th>
<th>INAP</th>
<th>NR</th>
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<td>77</td>
<td>99</td>
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</table>

14c. Why did you stop using these smokeless tobacco products? (Tick all that apply)

- Advice from doctor or health-worker ........................................ 1
- Because of a health problem.................................................... 2
- (Specify ..................................................................................)
- Others ....................................................................................... 3
- (Specify ..................................................................................)
- INAP ......................................................................................... 77
- NR ........................................................................................... 99

Now, I am going to ask you some questions regarding other factors related to your health.

15. Have you ever been told by a doctor or a health-worker that you have raised blood-pressure or hypertension?

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<thead>
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<th>Yes</th>
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<th>NR</th>
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<td>1</td>
<td>0</td>
<td>99</td>
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</table>

16. Have you ever been told by a doctor or a health-worker that you have raised blood-glucose or diabetes?

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<th></th>
<th>Yes</th>
<th>No</th>
<th>NR</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>1</td>
<td>0</td>
<td>99</td>
</tr>
</tbody>
</table>
17. Have any members of your immediate family (father, mother, brothers, sisters) suffered from heart disease?
   Yes .................................. 1
   No .................................. 0
   DK .................................. 88
   NR .................................. 99

18. How many times a week do you usually undertake moderate to vigorous physical activity for at least 30 minutes, which will make you huff and puff (where you can still talk but can’t sing)?
   None .................................. 0
   1-2 times/week ........................... 1
   3-4 times/week ........................... 2
   ≥5 times/week ........................... 3
   NR .................................. 99

19. For FEMALE PARTICIPANTS, are you currently using any hormonal methods of contraception (pills, injection) or any other hormonal tablets (hormone replacement therapy)?
   Yes .................................. 1
   No .................................. 0
   INAP .................................. 77
   NR .................................. 99

20. Does anyone smoke inside the same room, where you live?
   Yes .................................. 1
   No .................................. 0
   NR .................................. 99

21. Was there any significant stressful event in your family in last one-year? [e.g. death of family members, separation, divorce, unemployment, job loss, financial loss etc.]
   Yes .................................. 1
   No .................................. 0
   NR .................................. 99
Now, I am going to ask you some questions regarding your tobacco usage.

22. What do you think are the reasons people use smokeless tobacco products (e.g. paan-masala, jarda, sada-pata, gul etc.) in Bangladesh?
   Specify .................................................................
   INAP ...................................................................... 77
   NR ........................................................................ 99

23. What do you think regarding smokeless tobacco products, are they beneficial or harmful to health?
   Harmful ................................................. 1
   Beneficial ........................................... 0
   DK .......................................................... 88
   NR ......................................................... 99

23a. Specifically, are you aware of any diseases associated with use of smokeless tobacco products?
   Specify .................................................................
   INAP ...................................................................... 77
   DK ............................................................... 88
   NR ........................................................................ 99

23b. What do you consider to be the other negative aspects of using smokeless tobacco products?
   Specify .................................................................
   DK ............................................................... 88
   NR ........................................................................ 99

24. What do you consider to be the benefits of using smokeless tobacco?
   Specify .................................................................
   DK ............................................................... 88
   NR ........................................................................ 99

25. Only for present/past smokeless tobacco users: Please, tell us how you began using smokeless tobacco at first in your life?
   Specify .................................................................
   INAP ...................................................................... 77
   NR ........................................................................ 99

26. Only for present smokeless tobacco users: Have you previously tried to quit or give up using smokeless tobacco products?
   Yes ......................................................... 1
   (Specify the reason ................................................................)
   No ......................................................... 0
27. Only for present smokeless tobacco users: What amount do you usually spend a week purchasing smokeless tobacco products?

INAP ......................... 77
NR .......................... 99

Thank you very much for your time and assistance.
Appendix II: Study questionnaire in Bengali
সরকারী অন্তরালের কর্মীদের জন্য অভিযোগপত্র

Australia এবং বাংলাদেশের গবেষণা কমিটি এই অন্তরালির গবেষণার কার্যান্তর করেছে। আমাদের কার্যান্তর পর্যায়ে একটি সম্পূর্ণ ও হালকার পর্যায় মাননীয়তা গবেষণা নিশ্চিত করতে হবে। এ পর্যায় গবেষণার অন্তরালকর্তাদের জন্য একটি অতিরিক্ত উপাদান যাতে গবেষণার পর্যায়ের সময় তারা প্রস্তুতি করতে পারবে।

নিয়ে গবেষণার Australia এবং বাংলাদেশের গবেষণা কমিটি যারা অন্তরালির হয়েছে।

"মুম্বাই মহানগর ও কুকুরোগ : বাংলাদেশে অন্তরালকর্তাদের জন্য প্রোগেটি"

০১. এই গবেষণায় অন্তরালে হিনি, আপনার কোনো প্রশ্ন বা প্রশ্নের ধারণা, এমনকি অল্প কোনো অভিপ্রেতি করতে চান তাহে আপনি নিজের গবেষণা সমাবেশকর্তার সাথে কেঁগে হাজার করতে পারবেন।

নাম : সুমন আজিজ রহমান

ফোন : ০১৭১৫-০৭৩৬৪০ (সেন্টারাল)

০২. হিনি, আপনি নিজের কোনো বিষয়ে ব্যাখ্যাধীনতার আলোচনা করতে চান, যেমন -

- কোনো বিষয়কে অভিজ্ঞতা করতে, আলোচনা করতে, আলোচনা করতে, আলোচনা করতে, আলোচনা করতে, আলোচনা করতে, আলোচনা করতে, আলোচনা করতে, আলোচনা করতে, আলোচনা করতে

তাহলে লেখালেখি করন।

অধ্যাপক মহদুয়ার হামান, পিএইচডি

পরিচালক

বোয়াল্ডো, বোয়াল্ডো ইনস্টিটিউট (এইচআরডিএম) ও বাংলাদেশ মাদানিনা ইন্সটিটিউট (এইচআরডিএম),
গবেষণাকর্তা বাংলাদেশ সরকার, বাংলাদেশ।

ফোন : ১৮২৮৫৬৯৬, ১৮২৮৫৬৯৬ (সেন্টারাল)

283
Survey site
NICVD □ NHFH&RI □ Community □

Category of the participant
CASE □

CONTROL □ 1/2/3/4 for CASE No ______

For CASE
Date of admission ........................................ Ward ................................ Bed ..................
Clinical symptoms .................................................................
ECG ......................................................................................
CK-MB ..............................................................................
Troponin-I ...........................................................................
Angiogram ...........................................................................
Others ..................................................................................

গবেষণায় অংশগ্রহণকারীদের জন্য অনুদানসমর্পণ

গবেষণায় অংশগ্রহনকারী:

০১. নাম: ......................................................................................................................... (পূর্ন নাম) নিয়ন্ত্র

গবেষণায় অংশগ্রহনের জন্য সমর্পিত প্রস্তাব কাঠামো:

“পুনর্নির্দেশ কারোক্রমের স্বাধীনতা ও সুষ্ঠুতার জন্য চাহিদা”

০২. নাম “পুনর্নির্দেশ কারোক্রমকারীদের জন্য চাহিদা” প্রকাশ করা।

০৩. গবেষণার সমস্ত অভিজ্ঞতা ও সম্পদ অর্থনীতির জন্য ব্যবহার করা হয়েছে।

০৪. যদিও এই গবেষণার উদ্দেশ্য হয়েছিল নিরস্তর কারোক্রমের প্রতিষ্ঠান সম্পর্কে সুষ্ঠুতার জন্য চাহিদা, এই গবেষণার অংশগ্রহনের জন্য অনুমোধ্যে হয়েছে।

০৫. সমস্ত অভিজ্ঞতা ও সম্পদ অন্তর্ভুক্ত হয়েছে, যেহেতু এই গবেষণায় অংশগ্রহনের জন্য অনুমোধ্যে হয়েছে।

০৬. অমার সহযোগিতার জন্য ব্যবহার করা হয়েছে।

০৭. প্রথমে জানানো হয়েছে যে, গবেষণায় অংশগ্রহনের জন্য অনুমোধ্যে হয়েছে।

০৮. কর্মরত প্রথমে জানানো হয়, যে এই গবেষণায় অংশগ্রহনের জন্য চাহিদা জানানো হয়।

আগমের নাম: ..................................................................................................................

সাক্ষী ৪:

এই গবেষণার সম্পর্কে: .......................................................................................... (পূর্ন নাম) কে, বিশ্ববিদ্যালয়ের ব্যবস্থাপক কোর্স নির্মাণ করা হয়।

প্রতিপাদন: ..................................................................................................................

সাক্ষীর নাম: .............................................................................................................

খাত্রী: .......................................................................................................................
Screening Questionnaire

1. ¿Apoptin kheyaar dhacono?
   
   1. [Parakjita Prelo yhan]  
   2. [Lagrajekar Samhash]
   3. Nickar

2. Apnain yaro karo (yhan yaro elo yuipho yekho)
   
   [0-40 yaro hlo lekharakar samhash]
   1. Qaror
   2. Nickar

3. ¿Apoptin kiko yarlo, olyekar yaro lahar yari parpath yumpano karo?
   
   1. [Lagrajekar Samhash]
   0 [Parakjita Prelo yhan]
   3. Nickar

4. ¿Apnotin kiko yarlo, olyekar yaro lahar yari parpath yumpano karo?
   
   1. [Lagrajekar Samhash]
   0 [Parakjita Prelo yhan]

5. ¿Apnotin kiko yarlo, yarlo yalo yarlo, yarlo yarlo karo?
   
   1. Nickar

6. Apnain kiko yarlo, yarlo yarlo, yarlo yarlo karo?
   
   1. Nickar

7. ¿Apnotin kiko yarlo, yarlo yarlo karo?
   
   1. Nickar

8. Apnain kiko yarlo, yarlo yarlo, yarlo yarlo karo?
   
   1. Nickar

9. ¿Apnotin kiko yarlo, yarlo yarlo, yarlo yarlo karo?
   
   1. Nickar

10. ¿Apnotin kiko yarlo, yarlo yarlo, yarlo yarlo karo?
    
    1. Nickar

11. ¿Apnotin kiko yarlo, yarlo yarlo, yarlo yarlo karo?
    
    1. Nickar
4. (ক) আপনার হাতের সাধারণ টিকি দিতে ০১ বছরের মধ্যেই সম্পন্ন হয়ো না।

<table>
<thead>
<tr>
<th>হ্যা</th>
<th>১</th>
</tr>
</thead>
<tbody>
<tr>
<td>না</td>
<td>০</td>
</tr>
<tr>
<td>বহুল নয়</td>
<td>৭৭</td>
</tr>
<tr>
<td>নির্বাচন</td>
<td>৯৯</td>
</tr>
</tbody>
</table>

**সম্পূর্ণ সাক্ষাতকার**

এখানে আমি আপনার সাথে কিছু সাধারণ তথ্য চিহ্নিত করতে চাই।

1. সাক্ষাতকারের প্রথমতায় আপনার অবকাশিকির লিখিত উপস্থাপন করুন।
   | ১ |
   | ২ |
   | ৩ |

2. আপনার বৈশিষ্ট্যগত অবস্থা কি?
   | ১ |
   | ২ |
   | ৩ |
   | ৪ |
   | ৫ |
   | ৬ |
   | ৮ |

3. আপনার সর্বনিকট বিভাগের মোটামুটি কিছু?
   | ০ |
   | ১ |
   | ২ |
   | ৩ |
   | ৪ |
   | ৫ |
   | ৬ |
   | ৯ |

4. আপনার প্রথম পেশার কি?
   | উপস্থাপন |
নিজের সমস্ত দেওয়ানা দেখুন, কে আপনার দিবসের জীবন?

হাঁ .................................................. ১

না .................................................. ০

নির্দিষ্ট ........................................... ১৯

পরামর্শ

(ফ) আপনার সমস্ত দেওয়ান কোথায় থাকে?

(দিনের মাত্র) থাকান, আপনি কাজ নিলে আমাদের কাজ করার ঘটনা হবে?

< ৫,০০০ টাকা ........................................ ১

৫,০০০-১০,০০০ টাকা .................................. ২

> ১০,০০০ টাকা ......................................... ৩

না .................................................. ৮

নির্দিষ্ট ........................................... ১৯

এক্ষেত্রে আপনি আপনার পাত্রতা অনুসারে কিভাবে প্রতিকার চাহিদা? প্রশ্নগুলো ৩০ বছরের মধ্যে স্থিতিস্থল।

৬. গত ৩০ বছরের মধ্যে আপনি কি কোনো আপনার লোকের সন্তান হয়নি কেননা যারা যে যার আগে তাঁর সময় হাতে পড়া হয় নি?

হাঁ .................................................. ১ [৮ ঘন্টা যাত্রা]

না .................................................. ০

নির্দিষ্ট ........................................... ১৯

৭. গত ৩০ বছরের মধ্যে আপনি কি কোনো আপনার লোকের সন্তানের মা বা মহিলা দেবি হয়নি?

হাঁ .................................................. ১ [৮ ঘন্টা যাত্রা]

না .................................................. ০

নির্দিষ্ট ........................................... ১৯

৮. (ফ) গত ৩০ বছরের মধ্যে আপনি কি আপনার লোকের সন্তানের জীবন বা তাঁর বোধ করেছিলেন?

হাঁ .................................................. ১ [১৩ ঘন্টা যাত্রা]

না .................................................. ০ [৬০ ঘন্টা যাত্রা]

নির্দিষ্ট ........................................... ১৯

আপনি কি গত ৩০ বছরের মধ্যে এই ব্যবস্থার সমক্ষে এই লোকের জীবন/আর্থিক/সাঝা/সম্পদ বোধ করেছিলেন?

হাঁ .................................................. ১ [৬০৮ ঘন্টা যাত্রা "হাঁ" হলে ১৩ ঘন্টা যাত্রা]


[10 সং প্রশ্ন সমাধান]

$\delta$ ..................................................... ০
কলিকা নার ............................................ ০

৯. আপনি যখন সিঁড়ি দেখে উপরের উক্তকেন্দ্র যা কাজের ব্যবস্থাপনা রুক্ষেব, তখন কি এই রুক্ষের সাধা/অর্থনীতি/শাসন বোধ করতেন?

$\text{হা} .................................................... ১$
$\text{না} ..................................................... ০
কর্মকর্তা সিঁড়ি দেখে উপরের উক্তকেন্দ্র যা কাজের ব্যবস্থাপনা রুক্ষেব যা ................................ ২
এরোজাব না ............................................... ০
লিখিত ...................................................... ১৯

১০. আপনি যখন সকল জায়গায় সাধারিককেন্দ্রে উক্তকেন্দ্র, তখন কি এই রুক্ষের সাধা/অর্থনীতি/শাসন বোধ করতেন?

$\text{হা} .................................................... ১$
$\text{না} ..................................................... ০
এরোজাব না ............................................... ০
লিখিত ...................................................... ১৯

[২ রা ১০ উক্ত, হার হলো ১১ সং প্রশ্ন সমাধান, ৩ রা ১০ উক্ত, না হলো ১২ সং প্রশ্ন সমাধান]

১১. আপনি ইতিসমান সময় এই রুক্ষের বাধা/অর্থনীতি/শাসন বোধ করতে পারিলে কি করতেন?

$\text{সুন্দর} যা যেমন রুক্ষেন .................................. ১$
উক্তকেন্দ্র ধানময় ........................................ ২
$(
(উক্তকেন্দ্র ধানময়) ........................................
এরোজাব না ............................................... ০
লিখিত ...................................................... ১৯

১২. (৫) আপনি বদল তখন সিঁড়িতে থাকতেন, তাহলে আপনার এই রুক্ষের সাধা/অর্থনীতি/শাসন কি হত?

$\text{হেতু দেখা} ............................................ ১$
$\text{সাধা না} ............................................... ০
এরোজাব না ............................................... ২
লিখিত ...................................................... ১৯

১৩. (৫) ক্ষত্রে পর আপনার এই রুক্ষের বাধা/অর্থনীতি/শাসন কি দেখা হত?

$\text{১০} \text{সুন্দর বাধা} ........................................ ১$
$\text{১০} \text{সুন্দর বাধা} ........................................ ২$
এরোজাব না ............................................... ০
টথ্য সংগ্রহ বা বিশ্বাস গ্রহণ করার জন্য নিম্নলিখিত প্রশ্নগুলি নিবেদিত করা হয়েছে:

12. আপনি কি আমাকে আপনার স্বাস্থ্য সম্বন্ধে আপনার মতামত বা অন্য কোনো বিষয় উল্লেখ করতে চান?
(সম্প্রতি এই প্রশ্নগুলি উল্লেখ করা হলো, এই প্রশ্নগুলি এক্সলিচিত উত্তর হচ্ছে পাওয়া যায়)

- স্বাস্থ্য মন্ত্রণালয় (যুগল মন্ত্রণালয়) ........................................ 1
- স্বাস্থ্য সমন্বয় ব্যবস্থা ........................................ 2
- আয়োজন রোগমূলক ........................................... 3
- আয়োজন রোগমূলক ........................................... 4
- খাদ্যসূচনা নয় ........................................... 77
- নির্দেশ ...................................................... 19

এখন আপনি আপনাকে স্বাস্থ্য সম্বন্ধে দিকে প্রশ্ন করতে চান না কিছু ।

13. আপনি কি বর্তমানে কোনো ধরনের চর্চা পরিস্থিতিতে আপনাকে করা হচ্ছে (যেমন: চিকিৎসা, বিদ্যমান সেবা প্রদান ইত্যাদি) করা হচ্ছে?
- হ্যা ...................................................... 1
- না ...................................................... 0 [14 সং এন্ড সেন]
- নির্দেশ ................................................... 19

13.(3) নিচের কোনটি আপনি ব্যবহার করেন?
(সাধারণত এই প্রশ্নগুলি 1 সমগ্র উল্লেখ করা, এই প্রশ্নগুলি এক্সলিচিত উত্তর হচ্ছে পাওয়া যায়)

- ধরন হ্যা না এবং যা নির্দেশ
- পানি,মস্তিষ্ক ........................................... 1 0 77 19
- জ্বালা ........................................... 3 0 77 19
- সামা পাত্র ........................................... 1 0 77 19
- উল্লেখ ........................................... 1 0 77 19
- স্বাস্থ্য ........................................... 1 0 77 19
- নাল্লা ........................................... 1 0 77 19
- অন্যান্য ........................................... 1 0 77 19
(উল্লেখ করা: .........................................................................................)
১৩. (প) আপনি কত মানসা এই যুগপত্তনকৃত জাতকে ব্যবহার করেন?

(সাধারণের প্রেরণকারী ৪ উত্তর দেন না গর্ভস্থ সবগুলো উত্তর উপরের করন)

<table>
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<tr>
<th>উত্তর</th>
<th>প্রতিবেদন</th>
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<tr>
<td>১</td>
<td>২-৩ বার</td>
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<td>২</td>
<td>১ বার</td>
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<td>৩</td>
<td>১ বার</td>
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<td>২-৩ বার</td>
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<td>৬</td>
<td>১ বার</td>
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<tr>
<td>৭</td>
<td>১ বার</td>
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</tbody>
</table>

নিয়ম: ১৯

১৫. (প) কতদিন ধরে আপনি এই যুগপত্তনকৃত জাতকে ব্যবহার করেন?

লাল মাল বজায় রাখুন: ১২

নিয়ম: ৯৯

[প্রশ্নের সম্পর্কে দ্বিতীয় অনুচ্ছেদ ১৩ নং প্রশ্নের উত্তর দিলে ১৫ নং প্রশ্ন দাখান]

১৪. আপনি কি মানসা এই যুগপত্তনকৃত জাতকে (লাল মাল, বাড়ি, মানসা পাতা) ব্যবহার করেন?

<table>
<thead>
<tr>
<th>হ্যা</th>
<th>না</th>
<th>[১৫ নং প্রশ্ন দাখান]</th>
</tr>
</thead>
<tbody>
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<td>১</td>
<td>০</td>
<td></td>
</tr>
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</table>

নিয়ম: ৯৯

১৬. (প) কোনটি আপনি ব্যবহার করেন?

(সাধারনের প্রেরণকারী ৫ সবগুলো উত্তর উপরের করন, এই প্রশ্নের একবিংশতিতম উত্তর হতে পারে)

<table>
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<tr>
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<td>০</td>
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</table>

নিয়ম: ৯৯

প্রকাশিত দিন: ২৯১
(উক্ত করণ) ........................................................................................................

14.(৪) আপনি করে থেকে এই বোধপত্র করাতে যাবেন কে বল করেনেন?

……………………………………….. আলে
বেছেনা না ……………………….. ৭৭
নিজঝর ……………………………….. ৯৯

14. (৫) আপনি কেন্দ্রে এই বোধপত্রকে ভাষক করার কথা বল করেনেন? (এই ধারণের একাধিক উক্তি হতে পারে)
ভাষকের বা বাণিজ্যিক প্রয়নে ………………………………… ১
বেছেনা কেন্দ্রে অনুবাদ করা ………………………………… ২
(উক্ত করণ) ……………………………………………………………………………
নিজঝর ………………………………………… ৬
(উক্ত করণ) ……………………………………………………………………………
বেছেনা না …………………………………… ৭৭
নিজঝর ………………………………………… ৯৯

এখন আমি আপনাকে আপনার শাসনিক অবস্থা সম্পর্কে আলোচনা কিছু শুরু করাকে চাই।

১২. আপনাকে কি অন্যতম কেন হাজারে বা বাণিজ্যিক জানিয়েছে যে আপনার উচ্চ স্তরে আছে?

যা ………………………………………….. ১
না …………………………………………. ০
নিজঝর……………………………………….. ৯৯

১৬. আপনাকে কি কথনে কেন হাজারে বা বাণিজ্যিক জানিয়েছে যে আপনার জায়ান্ডিস আছে?

যা ………………………………………….. ১
না …………………………………………. ০
নিজঝর……………………………………….. ৯৯

১৭. আপনি পরিবারকে কেন (স্ত্রী, ছেলে, বোন) কি হাতের লেখা ধরার আগন্ত আছে?

যা ………………………………………….. ১
না …………………………………………. ০
নিজঝর……………………………………….. ৯৯

১৮. সম্প্রতি কর্তব্য আপনি করপন্থ ৩০ মিনিটে সাকার থেকে কোনো প্রাকৃতিক পরিবর্তন করেন, তখন আপনি কিসের মাস্টার দিয়ে যান (যেমন: আপনি আজ কাজের তালিকা, কিঞ্চি ধন গাইন্টে চালু না)?
কথাটা না ........................................... ০
বড়তো ১-২ বার ..................................... ২
বড়তো ৩-৪ বার ..................................... ২
বড়তো ৫ বা এর বেশি বার ....................... ৩

১৯. হিসাব সংশোধনকারীর কাজ। অপবি কি করতেন হয় তার কাজের অনুসরণ পেতে পারি (যেমন: পিল, বলচ, ইলেক্ট্রনো) অথবা হয় তার কাজের করে গল্প (ক্যাথোলিক ইলেক্ট্রনো দেখুন) যাদের করতেন?

হা ............................................................ ১

না ........................................................... ০

বক্ষেত্র নহ .............................................. ৭৭

নিজের ........................................................ ৯৯

২০. অপবি যে ঘটন ঘটে, সেই একই ঘটন নিজের কেউ কি বুঝতেন করতেন?

হা ............................................................ ১

না ........................................................... ০

নিজের ........................................................ ৯৯

২১. গত ০১ শতাব্দীতের মধ্যে মানুষের পরিবারের কি কাজের ব্যবহার উত্তেজনা সৃষ্টির ঘটেছে। (যেমন: পরিবারের করার মূল্য, 

বিজ্ঞান, বিজ্ঞানী, সাক্ষাত্কার, সাক্ষাত্কার) 

হা ............................................................ ১

(উত্তর করান উপরের সংখ্যা দিন্তাহে) 

না ........................................................... ০

নিজের ........................................................ ৯৯

এখন আপনি কাজে যাচ্ছেন কবে আপনার মতে যাচ্ছেন কবে চাইবেন।

২২. অপবিতের বাতাসের মধ্যে কেন্দ্র প্রবাহকে সৃষ্টি করতে (যেমন: পাতা, জল, পাতা ইত্যাদি) যাচ্ছে?

উত্তর করান .................................................................

.................................................................

.................................................................

বক্ষেত্র নহ .............................................. ৭৭
কথা না ........................................... ০
নতুন ১-২ বর .................................... ১
nতুন ৩-৪ বর .................................... ২
নতুন ৫ বা এর বেশি বর ................................ ৩
নির্দেশ ............................................. ৯৯

১৯. অফিস অন্দর হামলার কথা। অপরিণতক্ষণে হস্তাক্ষর করার জন্য সামনের অনুলিপিত পত্রপত্রিকা (যেমন : মিল/বিড়ি, ইলেক্ট্রনিক) অথবা হস্তাক্ষর করার জন্য (হস্তাক্ষর সিলেটনেট দেবোগ্ন) যাবার কথা কোনো?
হা ......................................................... ১
না .................................................................. ০
কর্মপ্রদর্শন নয ........................................ ৭৭
নির্দেশ ..................................................... ৯৯

২০. অন্য জে ৪ বছর থাকেন, ঐহী কিছু কিছু গণমাধ্যম করার কথা কি পুলিশ করবে?
হা ............................................................... ১
না .................................................................. ০
নির্দেশ ..................................................... ৯৯

২১. পত্র ০১ তারিখের মধ্যে সামগ্রিক পরিষেবাকে কি করার কথা করার উদ্দেশ্যে নির্দেশ পত্র দুটি পত্র যাতে (যেমন- পরিষেবাকের করা মূল্য, বিদায়-নিদর্শন, নীতিসংস্থান, মাধ্যম-মূল্য, বাণিজ্য-কর্ম)
হা ............................................................... ১
(উদ্দেশ্য করন একটি ভাবেরর উপক্রমের নির্দেশ)
না .................................................................. ০
নির্দেশ ..................................................... ৯৯

একবারে আমি ভাবার সন্দেহে আপনার মতামত জানাতে চাইব।

২২. অপরাধের মতে সম্পর্কের মধ্যে সামগ্রিক করার জন্য সাস্তোত্তর করাতে (যেমন: পত-মাখ্যাপ, জন্ম, সাদা পাখি ইত্যাদি) যাবার কথা
উদ্দেশ্য করন .................................................................

কর্মপ্রদর্শন নয ........................................ ৭৭

০১
নিকটে ........................................ ১৯

২০. আপনি তিন তারিখের উপর মূল্যায়নকে তালিকাকে তফসিলের প্রাণের সময়ে আমন্ত্রণ?

হ্যা ........................................ ১

না .............................................. ০

জানি না .................................... ৮৬

নিকটে ........................................ ১৯

২০. (৪) বিশেষ করে, মূল্যায়নকে তালিকাকে তিন জন হতে পারে এবং আপনি আমন্ত্রণ?

উদ্ধৃতি করন ........................................

.................................................................

বহুজ না ..................................... ৭৭

জানি না ........................................ ৮৬

নিকটে ........................................ ১৯

২০. (৫) মূল্যায়নকে তালিকাকে তিন জন হতে পারে এবং আপনি আমন্ত্রণ?

উদ্ধৃতি করন ........................................

.................................................................

.................................................................

জানি না ........................................ ৮৬

নিকটে ........................................ ১৯

২৪. মূল্যায়নকে তালিকাকে তিন জন হতে পারে এবং আপনি আমন্ত্রণ?

উদ্ধৃতি করন ........................................

.................................................................

.................................................................

জানি না ........................................ ৮৬

নিকটে ........................................ ১৯

২৫. অবরোধক মূল্যায়নকে তালিকাকে যথেষ্ট সাবধান্তের জন্য। আপনি আপনার জীবনে সম্প্রসারণের ক্ষেত্রে মূল্যায়নকে তালিকাকে যথেষ্টের অভাব করেছিলেন?
২৩. বর্তমান দুখপাপমুক্ত তামাক ব্যবহারকারীদের জন্য কিছু অপরিকল্পনামূলক তামাক ব্যবহার করা ছেড়ে দেওয়া চেয়েছই?

হা ........................................... ১
(কারণ উল্লেখ করুন .................................................................)

না ........................................... ০

গবেষণা না ........................................... ৭৭

নিরক্ষর ........................................... ৯৯

২৭. বর্তমান দুখপাপমুক্ত তামাক ব্যবহারকারীদের জন্য গ্রহিত সাধারণ দুখপাপমুক্ততার অন্তর্জাতিক অনুমোদনকে কোন ব্যক্তি প্রদর্শন করেছেন?

........................................... উদ্যা

গবেষণা না ........................................... ৭৭

জানি না ........................................... ৮৮

নিরক্ষর ........................................... ৯৯

(সাম্যতার একদলীয় ৪ ব্যবস্থা দিয়ে সাম্যতার পেশ করা)
20 August 2009

Professor K Jamrozik  
School of Population Health and Clinical Practice

Dear Professor Jamrozik,

PROJECT NO: Smokeless tobacco and coronary heart disease: risks in Bangladesh  
H-117-2009

I write to advise you that the Human Research Ethics Committee has approved the above project. Please refer to the enclosed endorsement sheet for further details and conditions that may be applicable to this approval.

Approval is current for one year. The expiry date for this project is 31 August 2010. Where possible, participants taking part in the study should be given a copy of the Information Sheet and the signed Consent Form to retain.

Please note that any changes to the project which might affect its continued ethical acceptability will invalidate the project’s approval. In such cases an amended protocol must be submitted to the Committee for further approval. It is a condition of approval that you immediately report anything which might warrant review of ethical approval including (a) serious or unexpected adverse effects on participants (b) proposed changes in the protocol; and (c) unforeseen events that might affect continued ethical acceptability of the project. It is also a condition of approval that you inform the Committee, giving reasons, if the project is discontinued before the expected date of completion.

A reporting form is available from the Committee’s website. This may be used to renew ethical approval or report on project status including completion.

Yours sincerely,

[Signature]

Professor Garrett Culity  
Convenor  
Human Research Ethics Committee
Applicant: Professor K Jamrozik

Department: School of Population Health and Clinical Practice

Project Title: Smokeless tobacco and coronary heart disease: risks in Bangladesh

THE UNIVERSITY OF ADELAIDE HUMAN RESEARCH ETHICS COMMITTEE

Project No: H-117-2009

RM No: 00000309-405

APPROVED for the period until: 31 August 2010

subject to approval from the Ethical Review Committee of the International Centre for Diarrhoeal Disease Research, Bangladesh. It is noted that this study will be conducted by Dr Muhammad Aziz Rahman, PhD candidate.

Refer also to the accompanying letter setting out requirements applying to approval.

Professor Garrett Callaly
Convener
Human Research Ethics Committee

Date: 20 AUG 2009
Appendix IV: Ethics approval from Bangladesh

National Research Ethics Committee

Dr. Muhammad Aziz Rahman
Ph.D Student
The University of Adelaide
Australia.

Subject: Ethical Clearance

With reference to your application on the above subject, this is to inform you that your Research Proposal entitled “Smokeless tobacco and coronary heart disease: risks among non-smokers in Bangladesh” has been reviewed and approved by the National Research Ethics Committee (NREC).

You are requested to please note the following ethical guidelines as mentioned at page 2 (overleaf) of this memo.

Prof. Hafizul-Al-Rashid
MD, MSc, MPH, PhD, FRCP Edin
Director

Mohakhali, Dhaka-1212, Bangladesh, Phone : 8811395, 8828394, Fax : 880-2-8828820
E-mail : bmrc@effective.net
Appendix V: Signed statement of authorship

Statement of authorship from Mahmudur Rahman

A systematic review of epidemiological studies on the association between smokeless tobacco use and coronary heart disease
Journal of Public Health and Epidemiology (Accepted on November 15, 2011)

My contribution to this paper involved: Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed.................................................. Date........29-11-2011........

Is there any association between use of smokeless tobacco products and coronary heart disease in Bangladesh?
PLoS One (Revision submitted on November 28, 2011)

My contribution to this paper involved: Contributed in the design and provided support for the field activities in Bangladesh. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed.................................................. Date........29-11-2011........

Why do Bangladeshi people use smokeless tobacco products?
Asia Pacific Journal of Public Health (Submitted on July 01, 2011)

My contribution to this paper involved: Contributed in the design and provided support for the field activities in Bangladesh. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed.................................................. Date........29-11-2011........
Hospital controls vs. community controls: choice for a case-control study in Bangladesh
Epidemiologic Perspectives and Innovations (Submitted on October 13, 2011)

My contribution to this paper involved: Contributed in the design and provided support for the field activities in Bangladesh. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed: [Signature] Date: 29-11-2011

Rose Angina Questionnaire: validation with cardiologists' diagnoses to detect coronary heart disease in Bangladesh
The Southeast Asian Journal of Tropical Medicine and Public Health (Submitted on November 17, 2011)

My contribution to this paper involved: Contributed in the design and provided support for the field activities in Bangladesh. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed: [Signature] Date: 29-11-2011
Statement of authorship from Stephen Leeder

A systematic review of epidemiological studies on the association between smokeless tobacco use and coronary heart disease
*Journal of Public Health and Epidemiology (Accepted on November 15, 2011)*

My contribution to this paper involved: Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

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Is there any association between use of smokeless tobacco products and coronary heart disease in Bangladesh?
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Signed [Redacted] Date: 29 November 2011

Rose Angina Questionnaire: validation with cardiologists' diagnoses to detect coronary heart disease in Bangladesh

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My contribution to this paper involved: Contributed in the design and provided support for the field activities in Bangladesh. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed [Redacted] Date: 29 November 2011
Statement of authorship from Sohel Reza Chouchury

Is there any association between use of smokeless tobacco products and coronary heart disease in Bangladesh?
PLoS One (Revision submitted on November 28, 2011)

My contribution to this paper involved: Contributed in the design and provided support for the field activities in Bangladesh. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed.................................................. Date 29/11/11

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My contribution to this paper involved: Contributed in the design and provided support for the field activities in Bangladesh. Reviewed drafts of the manuscript, provided feedback, read and approved the final version of the manuscript. I give consent for Muhammad Aziz Rahman to present this paper for examination towards the Doctor of Philosophy.

Signed.............................................. Date 2.9/11/11
Appendix VI: Updated list of publications

The following list of publications has been updated before submission of the final hard-bound copy of this thesis in March 2012. Some of the manuscripts were published and accepted during the period of this thesis examination. Following the guideline of the Adelaide Graduate Centre, changes were not made in the original version of the thesis sent for examination on November 2011.


   Available online: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0030584


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
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, 95% CI 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 considered a public 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).

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 Spurrir and Mohammad Atzal 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 Thrombosis*[tiab], Coronary Vasospasm*[tiab], Myocardial Infarct*[tiab], Myocardial Stunning*[tiab], cardiogenic shock*[tiab], Myocardial Reperfusion Injur*[tiab] or Heart disease*[tiab].”

The search strategy was then used for ISI Web of Knowledge. The initial search yielded 6869 references on SLT and 52337 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 among 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, ICDDR, B 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;
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, 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 reported outcome as both fatal and non-fatal CHD. 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.

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

<table>
<thead>
<tr>
<th>Source</th>
<th>Study location (country)</th>
<th>Types of study</th>
<th>Recruitment and Follow-up year</th>
<th>Sample size</th>
<th>Gender</th>
<th>Age (yrs) at baseline</th>
<th>Types of SLT use as exposure</th>
<th>Types of CHD as outcome (only CHD data were considered)</th>
<th>Results presented in this table, based on the comparison groups</th>
<th>Key findings regarding association between SLT use and CHD</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive association between SLT use and CHD</td>
<td></td>
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</tr>
<tr>
<td>Bolinder et al. (1992)</td>
<td>Sweden</td>
<td>Cross-sectional</td>
<td>1971-74</td>
<td>97586</td>
<td>Men</td>
<td>16-65</td>
<td>SLT (types of SLT not defined)</td>
<td>Non-fatal CVD</td>
<td>Current SLT users vs. never tobacco users, (a)</td>
<td>Age 46-55yrs: OR = 1.6 (95%CI 0.7-3.5); Age 56-65yrs: OR = 1.5 (95%CI 1.1-1.9)</td>
<td>Results for men only; no separate reports for CHD or stroke, possibility of healthy worker effects on the association</td>
</tr>
<tr>
<td>Bolinder et al. (1994)</td>
<td>Sweden</td>
<td>Cohort</td>
<td>1971-74, 1974-85</td>
<td>84781</td>
<td>Men</td>
<td>16-65</td>
<td>SLT (types of SLT not defined)</td>
<td>Fatal CHD</td>
<td>Current SLT users vs. never tobacco users, (b)</td>
<td>Age 35-54yrs: RR = 2.0 (95%CI 1.4-2.9); Age 55-65yrs: RR = 1.2 (95%CI 1.0-1.5)</td>
<td>Results for men only; SLT use data old</td>
</tr>
<tr>
<td>Hergens et al. (2007)</td>
<td>Sweden</td>
<td>Cohort</td>
<td>1978-93, 1978-2004</td>
<td>118395</td>
<td>Men</td>
<td>16-65</td>
<td>Snuff</td>
<td>Fatal and non-fatal CHD</td>
<td>Current snuff users (never smoked) vs. never tobacco users, (c)</td>
<td>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 ≥50g/day and fatal CHD among 55-65 years: RR = 2.46 (95% CI 1.09-5.55)</td>
<td>Results for men only</td>
</tr>
<tr>
<td>Henley et al. (2005)</td>
<td>USA</td>
<td>Cohort</td>
<td>1959-72</td>
<td>77407 (CPS-I study)</td>
<td>Men</td>
<td>≥30</td>
<td>SLT (Chewing tobacco, snuff)</td>
<td>Fatal CHD</td>
<td>Current SLT users vs. never tobacco users, (d)</td>
<td>HR = 1.12 (95%CI 1.03-1.21)</td>
<td>Results for men only; SLT use data collected at baseline only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1962-1982-2000</td>
<td>113970 (CPS-II study)</td>
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<tr>
<td>Yatsuya et al. (2010)</td>
<td>USA</td>
<td>Cohort</td>
<td>1987-89, 1987-2008</td>
<td>14498</td>
<td>Both</td>
<td>45-64</td>
<td>SLT (types of SLT not defined)</td>
<td>Fatal and non-fatal CVD</td>
<td>Current SLT users (never smoked) vs. never tobacco users, (e)</td>
<td>HR = 1.31 (95% CI 1.06-1.61)</td>
<td>No separate reports for CHD or stroke</td>
</tr>
<tr>
<td>Nasir et al. (2010)</td>
<td>USA</td>
<td>Cross-sectional (Surveillance data analyses)</td>
<td>1999-2001</td>
<td>10332</td>
<td>Both</td>
<td>18-70+</td>
<td>SLT (types of SLT not defined)</td>
<td>Non-fatal CVD</td>
<td>Current SLT users vs. never tobacco users, (f)</td>
<td>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)</td>
<td>No separate reports for CHD or stroke</td>
</tr>
</tbody>
</table>
**Table 1. Contd.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Cohort</th>
<th>Year(s)</th>
<th>Number</th>
<th>Gender</th>
<th>Age Range</th>
<th>SLT Type</th>
<th>Outcome</th>
<th>current SLT users (never smoked) vs. non-current SLT users, (g)</th>
<th>Odds Ratio (CI)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johansson et al. (2005)</td>
<td>Sweden</td>
<td>Cohort 1988-89, 1988-2000</td>
<td>3120</td>
<td>Men</td>
<td>30-74</td>
<td>Snuff</td>
<td>Fatal and non-fatal CHD</td>
<td>Current SLT users (never smoked) vs. non-current SLT users, (g)</td>
<td>HR = 1.41 (0.61-3.28)</td>
<td>Results for men only, SLT use data collected at baseline only</td>
<td></td>
</tr>
<tr>
<td>Haglund et al. (2007)</td>
<td>Sweden</td>
<td>Cohort 1988-89, 1988-2003</td>
<td>5002</td>
<td>Men</td>
<td>16-74</td>
<td>Snuff</td>
<td>Fatal and non-fatal CHD</td>
<td>Current SLT users vs. never tobacco users, (h)</td>
<td>Non-fatal CHD: IRR = 0.77 (95%CI 0.51-1.15); Fatal CHD: MRR = 1.15 (95%CI 0.54-2.41)</td>
<td>Results for men only</td>
<td></td>
</tr>
<tr>
<td>Hansson et al. (2009)</td>
<td>Sweden</td>
<td>Cohort 1998-2002, 1998-2005</td>
<td>16642</td>
<td>Men</td>
<td>40-72</td>
<td>Snus</td>
<td>Fatal and non-fatal CHD</td>
<td>Current snus users (never smoked) vs. never tobacco users, (i)</td>
<td>RR = 0.85 (95%CI 0.51-1.41); Frequency and duration of snus use were not associated with CHD</td>
<td>Results for twin men only</td>
<td></td>
</tr>
<tr>
<td>Janzon et al. (2009)</td>
<td>Sweden</td>
<td>Cohort 1991-96, 1991-2004</td>
<td>27227</td>
<td>Men</td>
<td>45-73</td>
<td>Snuff</td>
<td>Fatal and non-fatal CHD</td>
<td>Current SLT users vs. never tobacco users, (j)</td>
<td>RR = 0.75 (95%CI 0.3-1.8)</td>
<td>Results for men only</td>
<td></td>
</tr>
<tr>
<td>Huhtasaari et al. (1992)</td>
<td>Sweden</td>
<td>Case-control 1989-91</td>
<td>1174 (586 cases &amp; 589 controls)</td>
<td>Men</td>
<td>35-64</td>
<td>Snuff</td>
<td>Fatal &amp; non-fatal CHD, Cases were selected from hospital records and death registers; controls were selected from population registers</td>
<td>Current SLT users vs. never tobacco users, (k)</td>
<td>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 0.87-2.30); No dose response relationship</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Huhtasaari et al. (1999)</td>
<td>Sweden</td>
<td>Case-control 1991-93</td>
<td>1374 (687 cases &amp; 687 matched controls)</td>
<td>Men</td>
<td>25-64</td>
<td>Snuff</td>
<td>Fatal &amp; non-fatal CHD, Cases were selected from hospital records and death registers; controls were selected from population registers</td>
<td>Current SLT users vs. never tobacco users, (l)</td>
<td>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)</td>
<td>Results for men only</td>
<td></td>
</tr>
<tr>
<td>Hergens et al. (2005)</td>
<td>Sweden</td>
<td>Case-control 1992-94</td>
<td>3242 (1432 cases &amp; 1810 matched controls)</td>
<td>Men</td>
<td>45-70</td>
<td>Snuff</td>
<td>Fatal &amp; non-fatal CHD, Cases were selected from hospital records and mortality register, controls were selected from communities</td>
<td>Current SLT users vs. never tobacco users, (m)</td>
<td>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)</td>
<td>Results for men only</td>
<td></td>
</tr>
</tbody>
</table>
Fatal CHD: OR = 1.12 (95% CI 0.38-3.29); Non-fatal CHD: OR = 0.82 (95% CI 0.46-1.43)

Cases & controls selected both from hospitals and communities

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, 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, 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; g) Adjusted for: Age, smoking, diabetes, hypertension, serum cholesterol level; 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, education; l) 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 activity, 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 | Mishi, 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 |
positive association between betel chewing alone and CHD (Guh et al., 2007; Lin et al., 2008). Although betel-juice does not contain tobacco, the association was thought to be due to the presence of substances in betel-juice 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-juice 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 underestimated 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 (Crichtley 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.

ACKNOWLEDGEMENT
The authors would like to express their sincere gratitude to late Professor Konrad Jamrozek, for his contribution in developing the concept of this research area.

REFERENCES


Is There Any Association between Use of Smokeless Tobacco Products and Coronary Heart Disease in Bangladesh?

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Abstract

Background: Most epidemiological studies exploring the association between smokeless tobacco (SLT) use and coronary heart disease (CHD) have been in Western populations, and have focused on SLT products used in those countries. Few studies come from South Asian countries. Our objective was to determine the association between SLT use and CHD among non-smoking adults in Bangladesh.

Methods: A matched case-control study of non-smoking Bangladeshi adults aged 40–75 years was conducted in 2010. Incident cases of CHD were selected from two cardiac hospitals. Community controls, matched to CHD cases, were selected from neighbourhoods, and hospital controls were selected from outpatient departments of the same hospitals. The Rose Angina Questionnaire (RAQ) was also used to re-classify cases and controls.

Results: The study enrolled 302 cases, 1,208 community controls and 302 hospital controls. Current use was higher among community controls (38%) compared to cases (33%) and hospital controls (32%). Current use of SLT was not significantly associated with an increased risk of CHD when community controls were used (adjusted OR 0.87, 95% CI 0.63–1.19), or when hospital controls were used (adjusted OR 1.00, 95% CI 0.63–1.60), or when both control groups were combined (adjusted OR 1.00, 95% CI 0.74–1.34). Risk of CHD did not increase with use of individual types except gul, frequency, duration, past use of SLT products, or using the RAQ to re-classify cases and controls. There was a significant association between gul use and CHD when both controls were combined (adjusted OR 2.93, 95% CI 1.28–6.70).

Conclusions: There was no statistically significant association between SLT use in general and CHD among non-smoking adults in Bangladesh. Further research on the association between gul use and CHD in Bangladesh along with SLT use and CHD in other parts of the subcontinent will guide public health policy and interventions that focus on SLT-related diseases.

Introduction

Smokeless tobacco (SLT), commonly used in many countries [1], is associated with various health effects. Epidemiological studies have consistently reported a significant positive association between SLT use and cancers of various organs such as oropharynx, oesophagus, stomach, pancreas, and lungs amongst others [2]. Studies also report a positive association between SLT use and oral diseases, dental diseases, hypertension, diabetes, poor reproductive outcomes, addiction, and all-cause mortality [2].

A number of studies have also reported a significant positive association between SLT use and risk factors for cardiovascular diseases (CVD) such as raised blood pressure and a less healthy lipid profile [3,4]. However, the results of epidemiological studies assessing the association between SLT use and CHD, stroke or CVD in general are inconsistent [5,6]. While several cohort [7,8,9] and case-control studies [10,11] have reported a significant positive association, other sufficiently powered cohort [12,13,14] and case-control studies [15,16,17] have not reported such an association. Some studies undertaken in Western countries (Sweden and USA) have found an association [7,8,9] whereas others have not [12,13,14]. South Asian SLT products differ from Western products in terms of constituents, nicotine concentration, manufacturing, and storage methods [18]. Usage patterns are also likely to be different and may explain the different results from studies conducted across various settings [6,19].
There are a limited number of studies from South Asian countries focusing on the association between SLT use and CHD. One Indian cohort study [20] and another multinational case-control study (INTERHEART) involving 52 countries [10] reported a significant positive association and did include South Asian SLT products. However, betel-quid and areca-nut were included as SLT products although these products do not contain tobacco. In addition, the INTERHEART study did not report results separately for any South Asian country [10]. A small number of Taiwanese studies [21,22,23] found a significant positive association between betel-quid chewing and CHD, but not with SLT use. The only study which has included SLT products available in Bangladesh [11], all of which contain tobacco, showed a significant positive association between SLT use and CHD (adjusted odds ratio 2.2, 95% confidence interval 1.1–4.5) and was conducted by the first author.

As a developing country in South-East Asia, Bangladesh has high rates of smoking and SLT usage. Half of those aged ≥15 years (43% = 41 million) use tobacco in some form [24]. The prevalence of SLT use has been estimated as 27% with similar rates in men (26%) and women (28%), but more prevalent in rural areas (29%) compared to urban areas (23%) [24]. Whilst a number of studies in Bangladesh have examined tobacco use [25,26,27], a small sample size (n = 207), included smokers, and recruited cases and controls from a hospital setting.

Betel-leaf (paan) chewing is a cultural tradition of Bangladeshi people extending back many centuries [28]. In Bangladesh, as in other countries of the subcontinent, people chew betel-leaf with/without SLT products routinely at various cultural and social events [29]. As there has been no large systematic study conducted in the Subcontinent, and the results of studies conducted in Western settings are inconsistent [6], we conducted the current study to determine whether there was any association between SLT use and CHD among non-smoking adults in Bangladesh.

Methods

Ethics statement

Informed written consent was requested from each participant in the prescribed consent form. Privacy and confidentiality were maintained regarding the collected data. The protocol including the information sheet and consent forms for this project was approved by The University of Adelaide Human Research Ethics Committee, Australia (H-117-2009) and the local ethics committee of Bangladesh Medical Research Council, Bangladesh (BMRC/NREG/2007–2010/125).

Study design and study sites

A matched case-control study was conducted in 2010. Data were collected through structured interviews. CHD cases were recruited from inpatient facilities of the National Institute of Cardiovascular Diseases (NICVD) and the National Heart Foundation Hospital and Research Institute (NHFH&RI), Dhaka, Bangladesh. Both hospitals are accessible to people from all socio-economic groups as minimal costs are associated with cardiac care. During the recruitment period, approximately 550 patients per day were admitted to the six cardiovascular units of NICVD and 110 patients per day were admitted to the seven cardiovascular units of NHFH&RI. Four hundred patients per day and 75 patients per day attended the outpatient facilities of the NICVD and the NHFH&RI respectively. Both hospital controls and community controls were selected in this study in order to assess whether results differed according to the use of different control groups. Hospital controls were recruited amongst individuals attending cardiac outpatient facilities of the NICVD and the NHFH&RI, while community controls were recruited from the neighbourhood households of CHD cases within Dhaka City Corporation (DCC) areas.

Study population

Inclusion criteria were: age 40–75 years, non-smoker, residence within DCC areas, and well enough to participate in a 20 minute interview. Non-smokers were defined as either (i) never smokers or (ii) ex-smokers who had not smoked a single puff in the past 10 years. This was because most studies suggest that the maximum reduction in CHD risk occurs within 4–14 years following smoking cessation [30,31,32]; and from a practical perspective, only including never smokers would have been difficult.

CHD cases

CHD patients admitted to the two hospitals and diagnosed as incident cases of CHD (diagnosis for the first time within the preceding twelve months) by hospital cardiologists, were selected as cases. Cardiologists diagnosed CHD cases based on clinical judgment (a combination of classical symptoms with positive results from electrocardiogram, cardiac enzymes, exercise tolerance test, or coronary artery angiogram). Either angina and/or myocardial infarction were included in the definition of CHD for the purpose of this study.

Community controls

Neighbourhood residents of the CHD cases, who had no self-reported cardiac disease, were selected as community controls. Control subjects were matched by age (±5 years), sex and socio-economic status (SES) to the corresponding case. If a suitable control subject could not be located in a suburb of the CHD case, the next adjacent suburb was used (this happened in 28% of cases).

Hospital controls

Hospital controls were also used in this study. This was to determine whether any systematic bias existed in the use of hospital controls as is often postulated in the literature [33,34]. These additional analyses are not the focus of this particular article and will be presented elsewhere. Patients, who attended cardiac outpatient facilities of the same hospitals and were diagnosed as not suffering from CHD by hospital cardiologists, were selected as hospital controls. It should be noted that unlike a developed country, many individuals with symptoms of chest pain or breathlessness attend outpatient facilities of cardiac hospitals for screening of cardiac disease; either self-referred or referred by a general practitioner in Bangladesh. About two-thirds (64%) of the hospital controls were selected from the hypertension clinic of NHFH&RI, which was the only available source of recruiting controls in that study setting. This poses a risk of potential bias because SLT use is known to be associated with hypertension [3]. Diagnoses for these patients included hypertension (62%), non-specific chest pain (48%), and gastric hyper-acidity (13%). Some patients were not assigned a diagnosis, and symptoms of palpitation (10%) or breathlessness (9%) were given in the case-notes. Each hospital control was matched with a corresponding case by age (±5 years) and sex.

Cases and controls re-classified by the Rose Angina Questionnaire (RAQ)

In addition to our study definition of cases and controls, we also used the RAQ [35] to re-classify study participants into RAQ cases and RAQ controls. Individuals responding affirmatively to the RAQ were re-classified as RAQ cases and the negative responders
were re-classified as RAQ controls as shown in Figure 1. It is to be noted that the RAQ cases and the RAQ controls were not matched.

Sample size
Sample size was calculated using Epi-info version 3.5.1. With 95% confidence intervals, 80% power, a control: case ratio of 4:1, a correlation for matched design of 0.1, an expected frequency of SLT use among controls of 25% [25], and a clinically significant odds ratio considered to be 1.5 [11,20], 302 cases and 1,208 controls were required for this study. Additionally, one hospital control was selected for each case (302 additional controls).

Study tool
A structured interview was conducted to measure exposure and confounding variables. Initially, a screening questionnaire was used to select eligible cases and controls. This included information on age, residence, smoking and heart disease status. Once informed consent was obtained, participants were asked a range of questions covering socio-demographic information, a detailed history of SLT use, and other known risk factors for CHD. Socio-demographic information included age, gender, marital status, highest level of education achieved, primary occupation and monthly house-rent as a proxy to socio-economic status.

Betel-leaf or areca-nut alone was not included as a SLT product, as they do not contain tobacco. If a respondent used any SLT product with/without betel-leaf or areca-nut in the last twelve months, he/she was categorized as a current SLT user. If a respondent ceased using SLT products for at least last twelve months, he/she was categorized as a past SLT user. If a respondent was not using any SLT product currently or in the past, he/she was categorized as never a tobacco user (as they were also non-smokers according to the participant selection criteria).

Using frequency and duration of SLT use, we categorized frequency into light use (less than once a day) and heavy use (at least once a day), duration into short duration (<10 years) and long duration (>10 years), and quit duration into short-term quit (2–10 years) and long-term quit (>10 years).

Information on known risk factors for CHD included self-reported history of hypertension, diabetes, family history of heart disease, level of physical activity, use of hormonal contraceptives for women, exposure to indoor passive smoking, and occurrence of acute psycho-social events within last one year.

Data collection
Reasons for non-participation were documented. If participants asked whether SLT could cause any health effect, interviewers

Figure 1. Re-classification of cases and controls using the Rose Angina Questionnaire (RAQ).
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only provided this information at the completion of the interview. Categorization of CHD cases according to the case definition and the RAQ was undertaken by the first author and selection of the majority of controls was undertaken in his presence. The first author trained the interviewers and undertook regular supervision of all data collection activities. In addition, the first author re-interviewed 4 cases (1%), 24 community controls (2%) and 6 hospital controls (2%) as a means of quality control of data collection.

Laboratory analysis

To enhance interpretation of the study results, samples of SLT products most commonly used within the DCC areas, were tested for nicotine. Purchased samples of paan-masala (3 samples), jarda (1 sample), and gul (1 sample) were analysed following extraction, steam distillation and silicotungstic acid gravimetric method [36] at the Institute of Food Science and Technology (IFST), Bangladesh Council of Scientific and Industrial Research (BCSIR). Nicotine concentration was reported in percentage by weight (% by wt.). Sada-pata, which is the natural tobacco leaf in dried form, was also used by study participants but was not tested for nicotine because of the natural variation of this product. A recent surveillance study reported nicotine concentrations in Bangladeshi sada-pata as 1.97% [37].

Data analysis

Analyses were performed using STATA version 10 statistical software. Initially, categorical variables were described as proportions for socio-demographic variables, SLT use, and risk factors for CHD. To determine the association between SLT use and CHD, cases and controls were compared using cross-tabulations at first. To statistically compare cases and controls, we used McNemar’s chi-squared ($\chi^2$) tests when the frequency in all of the cells of the cross-tabulation was $\geq 5$ and Fisher’s exact test otherwise. Univariate conditional logistic regression models [38] were fitted to determine the strength of the association between SLT use and CHD, with the effect of SLT use expressed as a matched odds ratios (ORs) with 95% confidence intervals (CIs). Then multivariate conditional logistic regression models were fitted to adjust for potential confounding variables. The most important confounder is the presence of hypertension; this is particular so with analysis using only hospital controls. Confounding variables were identified initially using a $\chi^2$ test relating the variables to CHD. If the p-value from the $\chi^2$ test was less than 0.20 and there was no missing data for the confounder, that variable was included into the final multivariate analysis. The adjusted ORs with 95% CIs finally determined the association between SLT use and CHD in this study. To determine whether the inclusion of ex-smokers could have biased the results, analyses were conducted separately for never-smokers, ex-smokers, and combining both groups. Data were analysed separately using community controls, hospital controls, and combining both groups. We also analysed data with all groups of re-classified cases and controls done by the RAQ to further explore the association between SLT use and CHD (Figure 1). As the RAQ cases and the RAQ controls were not matched, we used univariate and multivariate logistic regression models for these analyses.

Results

Study participants

Eligible participants included 311 hospital cases, 1293 community controls and 316 hospital controls. Nine potential hospital cases (3%), 85 potential community controls (7%), and 14 potential hospital controls (4%) did not consent to participate. Thus, the overall response rate was 94%. Results for the remaining 302 CHD cases from two cardiac hospitals, 1280 community controls and 302 hospital controls are presented in this paper.

Mean age of participants was 53 years (standard deviation ±8.5 years), 49.7% were men. Table 1 shows the distribution of different socio-demographic variables among cases and controls, and there were no significant differences in socio-demographic variables comparing cases and controls. Amongst the 1812 participants, 1292 (71%) were never-smokers. Never-smoking status was similar between cases (203 out of 302, 67%) and either community controls (864 out of 1208, 72%) or hospital controls (225 out of 302, 75%).

Risk factors for CHD

Table 1 shows the distribution of risk factors for CHD among cases and controls. More than two-thirds of hospital controls (67%) were hypertensive compared to half of cases (60%) and one-third of community controls (34%). The majority of these hospital controls were selected from the hypertension clinic of one study hospital which explains this difference.

Nicotine content of the SLT products

Nicotine was absent in all three commercial samples of paan-masala products tested. The selected samples of jarda and gul contained 0.96% and 5.48% nicotine respectively. Therefore, our data analysis included only three types of SLT products containing nicotine: jarda, sada-pata (1.97% nicotine) and gul.

Use of SLT products

Amongst the 1812 participants, 648 (36%) were current SLT users. Current use was higher among community controls (38%) compared to that of cases (33%) and hospital controls (32%). Quitting was more common among cases compared to either group of controls. Amongst the never-smoker participants, current use of SLT was more common among community controls (35%) than that of cases (25%) and hospital controls (30%). Amongst the ex-smoker participants, ever use, current use and quitting of SLT products were more common among cases compared to either group of controls. Table 2 shows the status of SLT use among the study participants.

Amongst the individual types of SLT products, use of jarda was more common compared to sada-pata and gul. Current use of jarda was slightly higher among community controls (26%) compared to either cases (21%) or hospital controls (24%). There was no difference between cases and controls for current use of sada-pata. Current use of gul was slightly more common among cases (5%) compared to either group of controls (2%). The majority of exclusive jarda, sada-pata or gul consumers were heavy users and long duration users. Mean duration of jarda use was 16 years (0.1–55 years), sada-pata 28 years (3–60 years), and gul 17 years (0.5–45 years). There was no difference between cases and controls for heavy use or long duration use of each SLT product.

Association between SLT use and CHD

Table 2, 3, 4 show the results of univariate and multivariate analyses. Among the socio-demographic variables and risk factor variables for CHD, age, hypertension, diabetes, and acute psychological stress were significantly associated with CHD when data were analysed using community controls, hospital controls or both controls. In addition, marital status and indoor passive smoking were significantly associated with CHD when data were analysed...
with hospital controls. There was no statistically significant association between current SLT use and CHD when community controls were used (adjusted OR 0.87, 95% CI 0.63–1.19), or hospital controls were used (adjusted OR 1.00, 95% CI 0.63–1.60), or when both controls were combined (adjusted OR 1.00, 95% CI 0.74–1.34). There was no association between ever use or cessation of SLT usage and CHD. Similar results were found when data were analysed separately for never-smokers and ex-smokers. Similarly, Table 3 shows that there was no statistically significant association between SLT use and CHD, when data were analysed using the RAQ classified cases and RAQ classified controls.

When we stratified our analyses according to younger (40–57 years) and older (58–75 years) age groups, there was no statistically significant association between current SLT use and CHD among younger and older participants, when community controls were used (younger: adjusted OR 1.08, 95% CI 0.73–1.60, older: adjusted OR 0.54, 95% CI 0.27–1.09), or hospital controls were used (younger: adjusted OR 1.14, 95% CI 0.59–2.19, older: adjusted OR 0.89, 95% CI 0.32–2.47), or when both controls were combined (younger: adjusted OR 1.19, 95% CI 0.82–1.72, older: adjusted OR 0.75, 95% CI 0.42–1.32). Results did not change when data were analysed separately for never-smokers and ex-smokers.

When we stratified our analyses further according to gender, there was no statistically significant association between current SLT use and CHD among men and women, when community controls were used (men: adjusted OR 1.30, 95% CI 0.81–2.10, women: adjusted OR 1.00, 95% CI 0.59–1.75).

### Table 1. Socio-demographic and risk factor variables for coronary heart disease (CHD) among the study participants.

<table>
<thead>
<tr>
<th>Socio-demographic variables</th>
<th>Total, N (%)</th>
<th>Cases, n(%)</th>
<th>Community Controls, n(%)</th>
<th>Hospital controls, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total study participants</td>
<td>1812</td>
<td>302</td>
<td>1208</td>
<td>302</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>53.0 (±8.5)</td>
<td>53.5 (±8.5)</td>
<td>53.1 (±8.5)</td>
<td>51.9 (±8.4)</td>
</tr>
<tr>
<td>Male participants</td>
<td>900 (49.7)</td>
<td>150 (49.7)*</td>
<td>600 (49.7)*</td>
<td>150 (49.7)*</td>
</tr>
<tr>
<td>Married (and living with spouse)</td>
<td>1414 (78.0)</td>
<td>232 (76.8)*</td>
<td>939 (77.8)*</td>
<td>243 (80.5)*</td>
</tr>
<tr>
<td>Highest level of education achieved</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>204 (11.3)</td>
<td>34 (11.3)*</td>
<td>151 (12.5)*</td>
<td>19 (6.3)*</td>
</tr>
<tr>
<td>Can sign names</td>
<td>212 (11.7)</td>
<td>27 (8.9)*</td>
<td>150 (12.4)*</td>
<td>35 (11.6)*</td>
</tr>
<tr>
<td>Primary</td>
<td>527 (29.1)</td>
<td>95 (31.5)*</td>
<td>338 (28.0)*</td>
<td>94 (31.2)*</td>
</tr>
<tr>
<td>Secondary</td>
<td>239 (13.2)</td>
<td>44 (14.6)*</td>
<td>153 (12.7)*</td>
<td>42 (14.0)*</td>
</tr>
<tr>
<td>Higher-secondary</td>
<td>197 (10.9)</td>
<td>33 (10.9)*</td>
<td>116 (9.6)*</td>
<td>48 (15.9)*</td>
</tr>
<tr>
<td>Above higher-secondary</td>
<td>418 (23.1)</td>
<td>66 (21.9)*</td>
<td>290 (24.0)*</td>
<td>62 (20.6)*</td>
</tr>
<tr>
<td>Primary occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Service holder</td>
<td>558 (30.8)</td>
<td>87 (28.8)*</td>
<td>369 (30.6)*</td>
<td>102 (33.8)*</td>
</tr>
<tr>
<td>Businessmen</td>
<td>262 (14.5)</td>
<td>42 (13.9)*</td>
<td>180 (14.9)*</td>
<td>40 (13.2)*</td>
</tr>
<tr>
<td>Housewife</td>
<td>741 (40.9)</td>
<td>126 (41.7)*</td>
<td>495 (41.0)*</td>
<td>120 (39.7)*</td>
</tr>
<tr>
<td>Retired</td>
<td>235 (13.0)</td>
<td>47 (15.6)*</td>
<td>149 (12.3)*</td>
<td>39 (12.9)*</td>
</tr>
<tr>
<td>Socio-economic status (SES) by monthly house-rent (HR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower SES (HR&lt;5000 BDT)</td>
<td>656 (36.2)</td>
<td>109 (36.1)*</td>
<td>433 (35.8)*</td>
<td>114 (37.7)*</td>
</tr>
<tr>
<td>Middle SES (HR 5000–10000 BDT)</td>
<td>930 (51.3)</td>
<td>152 (50.3)*</td>
<td>620 (51.3)*</td>
<td>158 (52.3)*</td>
</tr>
<tr>
<td>Higher SES (HR&gt;10000 BDT)</td>
<td>226 (12.5)</td>
<td>41 (13.6)*</td>
<td>155 (12.8)*</td>
<td>30 (9.9)*</td>
</tr>
<tr>
<td>Presence of other risk factors for CHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension*</td>
<td>796 (43.9)</td>
<td>180 (59.6)*</td>
<td>413 (34.2)*</td>
<td>203 (67.2)*</td>
</tr>
<tr>
<td>Diabetes**</td>
<td>446 (24.6)</td>
<td>129 (42.7)*</td>
<td>244 (20.2)*</td>
<td>73 (24.2)*</td>
</tr>
<tr>
<td>Family history of heart disease</td>
<td>421 (23.2)</td>
<td>94 (31.5)*</td>
<td>248 (21.5)*</td>
<td>79 (27.2)*</td>
</tr>
<tr>
<td>Undertook physical activity*</td>
<td>1116 (61.6)</td>
<td>179 (59.5)*</td>
<td>788 (65.3)*</td>
<td>149 (50.2)*</td>
</tr>
<tr>
<td>Use of hormonal contraceptives</td>
<td>60 (3.3)</td>
<td>9 (3.0)*</td>
<td>41 (3.4)*</td>
<td>10 (3.3)*</td>
</tr>
<tr>
<td>Exposure to indoor passive smoking*</td>
<td>321 (17.7)</td>
<td>58 (19.2)*</td>
<td>218 (18.0)*</td>
<td>45 (14.9)*</td>
</tr>
<tr>
<td>Acute psycho-social stress*</td>
<td>434 (24.0)</td>
<td>94 (31.1)*</td>
<td>265 (21.9)*</td>
<td>75 (24.8)*</td>
</tr>
</tbody>
</table>

Superscripts indicate which categories show a statistically significant (p<0.05) difference using chi-squared tests between cases and controls: same letter indicates no difference, different letter indicates a difference.

*Have you ever been told by a doctor or a health-worker that you have raised blood-pressure or hypertension?*

**Have you ever been told by a doctor or a health-worker that you have raised blood-glucose or diabetes?**

*Physical activity included moderate to vigorous physical activity for at least 30 minutes per week which made them huff and puff (where they can still talk but can't sing). There were three levels of physical activity: mild (1–2 times/week), moderate (3–4 times/week) and vigorous (>5 times/week). All these three levels were combined together in this table.

*Does anyone smoke inside the same room, where you live?*

*Such an incident that caused mental agony, sorrow, unhappiness or anxiety within last one year, like death of family members, divorce, separation, sudden job loss, unemployment, financial loss etc.*

doi:10.1371/journal.pone.0030584.t001
Table 2. Univariate and multivariate matched analysis showing the association between coronary heart disease and use of smokeless tobacco (by smoking status of the participants).

<table>
<thead>
<tr>
<th></th>
<th>Hospital cases vs. community controls</th>
<th>Hospital cases vs. hospital controls</th>
<th>Hospital cases vs. both controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hospital Cases, n(%)</td>
<td>Community Controls, n(%)</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Never users of any tobacco (Reference)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-smokers (total study participants)</td>
<td>302</td>
<td>1208</td>
<td>302</td>
</tr>
<tr>
<td>Ever users of SLT products</td>
<td>118 (39.1)</td>
<td>482 (39.9)</td>
<td>0.98</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>99 (32.8)</td>
<td>454 (37.6)</td>
<td>0.87</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>19 (6.3)</td>
<td>28 (2.3)</td>
<td>2.38</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>203</td>
<td>864</td>
<td>203</td>
</tr>
<tr>
<td>Ever users of SLT products</td>
<td>60 (29.6)</td>
<td>313 (36.2)</td>
<td>0.71</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>51 (25.1)</td>
<td>299 (34.6)</td>
<td>0.65</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>9 (4.4)</td>
<td>14 (1.6)</td>
<td>1.49</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>99</td>
<td>344</td>
<td>99</td>
</tr>
<tr>
<td>Ever users of SLT products</td>
<td>58 (58.6)</td>
<td>169 (49.1)</td>
<td>1.48</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>48 (48.5)</td>
<td>155 (45.1)</td>
<td>1.54</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>10 (10.1)</td>
<td>14 (4.1)</td>
<td>1.03</td>
</tr>
</tbody>
</table>

The variables those were significant ($p<0.20$) during initial univariate analysis, were selected as confounders and adjusted during multivariate analysis.

$^*$Adjusted for: age, hypertension, diabetes and acute psycho-social stress; matched for: age, sex, residential areas and monthly house rent.

$^*$Adjusted for: age, marital status, hypertension, diabetes, indoor smoking exposure and acute psycho-social stress; matched for: age and sex.

$^*$ Adjusted for: age, hypertension, diabetes and acute psycho-social stress; matched for: age, sex, residential areas and monthly house rent.

doi:10.1371/journal.pone.0030584.t002
Table 3. Univariate and multivariate unmatched analysis showing the association between coronary heart disease and use of smokeless tobacco among the re-classified cases and controls by the Rose Angina Questionnaire (RAQ).

<table>
<thead>
<tr>
<th></th>
<th>RAQ hospital cases vs. RAQ community controls</th>
<th>RAQ hospital cases vs. RAQ hospital controls</th>
<th>RAQ hospital cases vs. RAQ both controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RAQ Hospital Cases, n(%)</td>
<td>RAQ Community Controls, n(%)</td>
<td>RAQ Hospital Controls, n(%)</td>
</tr>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Never users of any tobacco (Reference)</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
</tr>
<tr>
<td>Non-smokers (total study participants)</td>
<td>194 1153</td>
<td>194 409</td>
<td>194 1562</td>
</tr>
<tr>
<td>Ever users of SLT products</td>
<td>78 (40.2) 458 (39.7)</td>
<td>81 (40.2) 143 (35.0)</td>
<td>78 (40.2) 601 (38.5)</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>69 (35.6) 431 (37.4)</td>
<td>69 (35.6) 129 (31.5)</td>
<td>69 (35.6) 560 (35.9)</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>9 (4.6) 27 (2.3)</td>
<td>9 (4.6) 14 (3.4)</td>
<td>9 (4.6) 41 (2.6)</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>132 823</td>
<td>132 295</td>
<td>132 1118</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>62 330</td>
<td>62 114</td>
<td>62 444</td>
</tr>
<tr>
<td>Current users of SLT products</td>
<td>36 (58.1) 162 (49.1)</td>
<td>36 (58.1) 53 (46.5)</td>
<td>36 (58.1) 215 (48.4)</td>
</tr>
<tr>
<td>Quitters of SLT products</td>
<td>32 (51.6) 149 (45.2)</td>
<td>32 (51.6) 44 (38.6)</td>
<td>32 (51.6) 193 (43.5)</td>
</tr>
</tbody>
</table>

The variables those were significant (p < 0.20) during initial univariate analysis, were selected as confounders and adjusted during multivariate analysis.

*Adjusted for: age, socioeconomic status, hypertension, diabetes, family history of heart disease, physical activities, indoor smoking and acute psycho-social stress.

*Adjusted for: marriage, level of education, socioeconomic status, hypertension, diabetes, indoor smoking and acute psycho-social stress.

*Adjusted for: age, socioeconomic status, hypertension, diabetes, family history of heart disease, indoor smoking and acute psycho-social stress.

doi:10.1371/journal.pone.0030584.t003
Table 4. Univariate and multivariate matched analysis showing the association between coronary heart disease and current use of different types of Bangladeshi smokeless tobacco (SLT) products (by smoking status of the participants).

<table>
<thead>
<tr>
<th></th>
<th>Hospital cases vs. community controls</th>
<th>Hospital cases vs. hospital controls</th>
<th>Hospital cases vs. both controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hospital Cases, n(%)</td>
<td>Community Controls, n(%)</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Never users of any tobacco (Reference)</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
</tr>
<tr>
<td>Non-smokers (total study participants)</td>
<td>302 1,208</td>
<td>302 302</td>
<td>302 1,510</td>
</tr>
<tr>
<td>Current users of any one SLT product</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jarda (0.96% nicotine)</td>
<td>63 (20.9) 314 (26.0)</td>
<td>0.75 0.53–1.06</td>
<td>0.79 0.55–1.21</td>
</tr>
<tr>
<td>Sada-pata (1.87% nicotine)</td>
<td>8 (2.6) 28 (2.3)</td>
<td>1.17 0.47–2.93</td>
<td>1.14 0.41–3.22</td>
</tr>
<tr>
<td>Gil (5.48% nicotine)</td>
<td>15 (5.0) 28 (2.3)</td>
<td>2.70 1.11–6.54</td>
<td>2.23 0.87–5.70</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>203 864</td>
<td>203 225</td>
<td>203 1,089</td>
</tr>
<tr>
<td>Current users of any one SLT product</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jarda (0.96% nicotine)</td>
<td>34 (16.7) 205 (23.7)</td>
<td>0.60 0.38–0.94</td>
<td>0.59 0.36–0.96</td>
</tr>
<tr>
<td>Sada-pata (1.87% nicotine)</td>
<td>5 (2.5) 21 (2.4)</td>
<td>0.95 0.34–2.68</td>
<td>0.90 0.27–2.98</td>
</tr>
<tr>
<td>Gil (5.48% nicotine)</td>
<td>7 (3.4) 18 (2.1)</td>
<td>1.44 0.37–5.55</td>
<td>1.33 0.31–5.69</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>99 344</td>
<td>99 77</td>
<td>99 421</td>
</tr>
<tr>
<td>Current users of any one SLT product</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jarda (0.96% nicotine)</td>
<td>29 (29.3) 109 (31.7)</td>
<td>1.44 0.71–2.90</td>
<td>1.51 0.71–3.24</td>
</tr>
</tbody>
</table>

The variables those were significant (p<0.20) during initial univariate analysis, were selected as confounders and adjusted during multivariate analysis.

*Adjusted for: age, hypertension, diabetes and acute psycho-social stress; matched for: age, sex, residential areas and monthly house rent.
*Adjusted for: age, marital status, hypertension, diabetes, indoor smoking exposure and acute psycho-social stress; matched for: age and sex.
*Adjusted for: age, hypertension, diabetes and acute psycho-social stress; matched for: age, sex, residential areas and monthly house rent.

doi:10.1371/journal.pone.0030584.t004
women: adjusted OR 0.62, 95% CI 0.38–0.99, or hospital controls were used (men: adjusted OR 1.08, 95% CI 0.46–2.55, women: adjusted OR 0.84, 95% CI 0.42–1.68), or when both controls were combined (men: adjusted OR 1.36, 95% CI 0.88–2.09, women: adjusted OR 0.73, 95% CI 0.47–1.14). Results did not change when data were analysed separately for never-smokers and ex-smokers.

Table 4 shows that there was no statistically significant association between use of *jarda* or *sada-paata* and CHD for current use, quitting or ever use during analyses by different control groups or by different smoking status. However, the product containing highest amount of nicotine (5.48%) in this study, *gul*, showed a significant positive association with CHD (adjusted OR 2.93, 95% CI 1.28–6.70), when data were analysed using both groups of controls. There was no statistically significant association between frequency or duration of each SLT product use and CHD, except use of *gul*. There was a significant positive association between heavy use of *gul* and CHD (adjusted OR 2.78, 95% CI 1.17–6.57), and long duration use of *gul* and CHD (adjusted OR 3.57, 95% CI 1.26–10.1) when both controls were used. There may have been a problem with lack of power to make stratified analyses with each SLT product to identify the association with CHD, as there were very few users of each SLT product in this study (Table 4).

### Discussion

In this study, there was no statistically significant association between SLT use in general and CHD among non-smoking adults in Bangladesh. However, there was a significant association between use of *gul* and CHD. This is very important because whilst in general our study did not find an association between SLT use and CHD, if nicotine content is higher in SLT (as it is in some other countries), it is likely to pose a significant risk for the development of CHD. No significant association was found for frequency or duration of each SLT product except *gul*. Heavy use and long duration of *gul* use was significantly associated with CHD. Results did not change when community controls, hospital controls, or both control groups were used during analyses, and when never-smoker, ex-smoker, or both groups were used. The results were the same for current users, quitters or ever users of SLT products. In addition, re-classification of cases and controls utilizing the RAQ did not change the findings of association between SLT use and CHD. Separate analyses with different age groups and gender did not change the results as well.

Findings of this study are supported by earlier case-control [15,16,17,39], cross-sectional [40] as well as cohort studies [12,13,14,41,42]. None of these case-control studies conducted in Sweden reported a statistically significant positive association between use of snuff and CHD, although the findings were for men only. Similar to case-control studies, none of these cohort studies have reported a significant association between SLT use and CHD. All of these cohort studies except the US study [12] included men only. The US study [12], which considered only fatal CHD, showed the same results when analysed separately for men (adjusted hazard ratio 0.6, 95% CI 0.3–1.2) and women (adjusted OR 1.4, 95% CI 0.8–2.2).

On the other hand, findings of this study are not supported by other cohort [7,9,30] and case-control studies [10,11]. The Swedish Construction Worker study [7] and the US Cancer Prevention Study [8] involving a larger cohort reported a significant positive association between SLT use and CHD. However, it is to be noted that both of these studies included men and fatal CHD only. Another US cohort study [9], which included both sexes as well as fatal and non-fatal CHD, reported a significant positive association between SLT use and CHD, but no separate results were reported for fatal and non-fatal CVD, or for CHD and stroke. All of these cohort studies included Western SLT products and populations. The only South Asian cohort study, conducted in India [20], showed a significant positive association between use of Indian SLT products and CHD among women (adjusted risk ratio 1.25, 95% CI 1.05–1.49), but not among men (adjusted risk ratio 0.89, 95% CI 0.75–1.05). This is also in contrast to what we have found in this study. The constituents of Indian SLT products are likely to be different from Bangladeshi SLT products, which could have resulted in the significant positive association in the Indian study. The INTERHEART [10] and the Bangladeshi case-control study [11] showed a significant positive association between SLT use and non-fatal CHD. All of these studies were limited by various methodological issues as described in the introduction to this paper and elsewhere [6].

The literature suggests inconsistent evidence regarding the association between SLT use and CHD among different age-groups. We did not find any difference in results by age, which is supported by another study that did not find any significant association among younger (35–54 years) and older (55–64 years) people [15]. On the other hand, whilst a cross-sectional study of Swedish construction workers did not find a significant association among younger workers (46–55 years) [40], the subsequent cohort study reported a significant association among young (35–54 years) as well as older workers (55–65 years) [7].

There was a significant association between use of *gul* and CHD in this study, although the numbers were not large enough to confirm this association from this study as mentioned before. *Gul* is the mixture of tobacco powder, molasses, alkaline modifiers and other ingredients prepared commercially, and used in other parts of South Asia including Bangladesh [1,37]. This product is kept between cheek and gum, used alone unlike other SLT products which are usually used with betel leaf in Bangladesh. This product was reported as having the highest nicotine concentration in this study. A recent survey of SLT products from different countries also reported higher nicotine concentration in Bangladeshi *gul* compared to other SLT products [37]. Frequency and duration of *gul* use was also significantly associated with CHD in the present study. Further well-powered study need to explore the association between this specific SLT product and CHD in a more detailed way.

Results from the existing research in Western countries are inconclusive; studies from South Asia are very limited and have some methodological constraints [6]. The current study addressed some of these methodological issues. Strengths of this study comprise including only non-smoking participants, a wider age range, both men and women, both community controls and hospital controls, and including exclusive SLT products from Bangladesh. Inclusion of non-smokers controlled for the potential strong confounding effects of smoking on CHD at the design stage. In addition, potential confounders were measured and adjusted for. This was particularly important for hypertension, which had the potential of introducing bias when data were analysed using hospital controls. Increasing the age limit of the participants in contrast to the earlier Bangladeshi case-control study helped assess the association between SLT use and CHD among a broader and more representative sample of Bangladeshi population. The consistent findings regardless of using either hospital controls or community controls support the accuracy of the study results. For the exposure variable, betel-quid or areca-nut was not included as a SLT product unlike other prior studies; rather selection of SLT products was supported by direct analysis of nicotine content.
Selecting subjects from the two tertiary care cardiac hospitals and the catchment areas within the DCC, which include people from all socio-economic strata, suggest our results are representative for urban dwellers in Bangladesh. However, the issue of different health care seeking behaviours should be kept in mind. Re-interviewing a percentage of both cases and controls ensured the quality of the collected data. Re-analysing data using the RAQ classification strengthened the study findings because milder or as yet undiagnosed CHD were identified from both hospitals and communities in this study.

The lack of an association between SLT use in general and CHD in this study can be explained in several ways. Nicotine concentration of some Bangladeshi SLT products, specifically gul is higher compared to commercial cigarettes (1.63%) or bidis smoking (2.12%) [43]. But more gradual and least peaked dosing of nicotine occurs for SLT use, although the blood concentration of nicotine remains similar for a daily SLT user and a smoker [44]. On the other hand, rapid dosing of nicotine occurs with smoking and this has the potential to result in much more intense cardiovascular stimulation [45]. Finally, SLT products do not contain carbon monoxide and polycyclic aromatic hydrocarbons, which are known to contribute to the cardiovascular effects of smoking [15, 45]. A significant association between gul use and CHD may be due to the higher nicotine concentration in the product itself along with the rapid absorption from buccal cavity to cause cardiovascular effects. It may also be due to other additives in gul having cardiovascular effects. Further studies need to confirm these hypotheses.

It was beyond the scope of this study to verify the self-reported diagnosis of non-CHD among the community controls by a qualified physician. Fatal CHD cases were not included in this study, because hospital death registers in Bangladesh are not well developed. In addition, collection of SLT exposure data from family members of deceased individuals would be less reliable compared to data collected from the users themselves. Reporting of the stratified analyses with each SLT product in this study has the potential to be biased as we had relatively small number of specific SLT users. We could not measure the amount of different SLT use from the study participants, as there are no standard pack sizes unlike snus or snuff. This limited us from including the amount during calculation of dose-response relationship between SLT use and CHD. However, as there was no association between SLT use and CHD, this missing information did not affect the result of this study. There is a chance of having interviewer-bias in this study, which can happen to any epidemiological study. But we had a structured questionnaire and the interviewers were trained to ask the exact question only, not try and interpret the questions for the respondents. However, as the interviewers could not be blinded, it is difficult to completely overcome this. Since our subjects were recruited from within Dhaka, our results may not be generalizable to the rural areas of Bangladesh. We attempted to measure and adjust for as many possible confounding variables as possible. Importantly, this included hypertension as previously discussed. However, it was not possible to measure body mass index (BMI) because we felt that urban dwellers in Bangladesh would be unlikely to invite interviewers into their homes to undertake height and weight measurements. Also, Bangladeshis do not tend to measure their own weight on a regular basis and so self-report data was also not considered feasible.

This study has implications for tobacco control policy. There is an ongoing debate regarding the use of SLT products as a safer alternative to active smoking and as a possible mechanism to encourage smoking cessation [2]. On the other hand, there is a concern that SLT use may potentiate tobacco smoking [46]. As tobacco control policies vary strikingly between countries [47], there is the potential of introducing Western SLT products as a harm-reduction agent into developing countries of South Asia [48]. Such products may contain ingredients, which could have unknown deleterious effects on CHD and other health conditions. In addition, SLT products and nicotine concentration also differ in other South Asian countries such as in India or Pakistan [1, 49].

This study did not find an association between SLT use in general and CHD among non-smoking Bangladeshi adults. This is the first large scale case-control study assessing the association between SLT use and CHD from a South Asian perspective. Despite the fact that the current study did not find an association between different Bangladeshi SLT products and CHD except gul, SLT use has an established risk for development of cancers and of dental diseases. Tobacco control campaigns should focus on these SLT-related diseases. Given the fact that the burden of tobacco-related illnesses are more among people of lower socio-economic status [25], as well as limited resources for health promotion activities in developing countries, policies supporting non-use of any form of tobacco are justified. Further research on the association between gul use and CHD in Bangladesh, along with SLT use and CHD in other parts of the subcontinent where SLT products may differ will guide public health policy and interventions to prevent SLT-related diseases. Because SLT use is not harmless, the strategic focus should be upon controlling both smoking and SLT use in Bangladesh.

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Author Contributions

Conceived and designed the experiments: MAR NS MAM MR SRC SL. Performed the experiments: MAR MR SRC. Analyzed the data: MAR. Contributed reagents/materials/analysis tools: NS MAM MR. Wrote the paper: MAR NS MAM SL.

References


