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Choice of Controls for a Case-control Study in Bangladesh: Hospital Controls versus Community Controls

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ABSTRACT

The study aimed to determine whether hospital controls could be used in case-control studies with minimal bias, where resource constraints limit recruitment of community controls. Hospital controls and community controls were compared for 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 and hospital controls were selected from cardiac hospitals. Community controls were selected from neighbourhoods of CHD cases. We 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. But they reported relatively less physical activity. Current use of SLT was higher amongst community controls compared to hospital controls, but was not significant (adjusted OR 0.81, 95% CI 0.58-1.12). 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 to 1.19, $p>0.05$), nor when hospital controls were used (adjusted OR 1.00, 95% CI 0.63 to 1.60, $p>0.05$). There were significant differences between two control groups 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.

Key words: Hospital controls, community controls, bias, smokeless tobacco, coronary heart disease, Bangladesh

INTRODUCTION

Selection of an appropriate control is crucial in a case-control study to avoid selection bias (Moritz *et al*., 1997; Grimes and Schulz, 2005). 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 (Grimes and Schulz, 2005). 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 (Tell *et al.*, 1991; Neupane *et al.*, 2010). 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) (Moritz *et al.*, 1997; Neupane *et al.*, 2010). In this instance, ORs would be decreased towards null if hospital controls are used (Neupane *et al.*, 2010).

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 (Tell *et al.*, 1991). 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 (Grimes and Schulz, 2005). The distribution of exposure variables may systematically differ between respondents and non-respondents, which could lead to bias (Neupane *et al.*, 2010). If the distribution of the exposure variable is high among the respondent community controls, the estimated ORs are likely to be decreased towards null.

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 (Infante-Rivard, 2003; Neupane *et al.*, 2010). In addition, healthcare seeking behaviour is likely to be comparable between cases and hospital controls, as both groups have accessed a hospital service (Wacholder *et al.*, 1992). 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 (West *et al.*, 1984; Tell *et al.*, 1991; Grimes and Schulz, 2005; Neupane *et al.*, 2010).

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.* (2010) reported the difference between hospital controls and community controls in a case-control study assessing the risk factors for Community-acquired Pneumonia (CAP) (Neupane *et al.*, 2010). 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 (Neupane *et al.*, 2010). 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 (Shibata *et al.*, 1998). 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 (Tell *et al.*, 1991).

There was an 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) (Rahman *et al.*, 2012). In Bangladesh, there is a lack of systematic registries of disease morbidity or mortality as in other developing countries, and many people do not seek medical care for CHD until symptoms become intolerable. This adds to the challenge of selecting CHD cases and appropriate controls. 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 study 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.

MATERIALS AND 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. Both hospitals are accessible to people from all socio-economic groups as minimal costs are associated with cardiac care. 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: Inclusion criteria were: age 40-75 years, non-smokers, residence within DCC areas (for at least one year), and well enough to undertake a 20 min interview. Non-smokers were defined as either (1) never smokers or (2) ex-smokers who had not smoked a single puff in the past 10 years (Kawachi *et al.*, 1993; Critchley and Capewell, 2003).

CHD cases: 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. 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.

Hospital controls: 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, only hospital controls were recruited from cardiac outpatient facilities. That 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 there. 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 (Hergens *et al.*, 2008). Diagnoses of hospital controls 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.

Community controls: 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. 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). Repeated (at the most three) attempts were taken to contact each eligible control, and requested him/her to participate in the study. If someone decided not to participate at the first contact, h/she was not contacted again.

Exclusion criteria: People below 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 give interviews, were excluded from the study.

Study tool: 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 included items regarding current and past use, as well as types of SLT products used. Details of SLT use are described elsewhere (Rahman *et al.*, 2012).

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 (Rahman *et al.*, 2002; Rahman and Zaman, 2008).

Data collection: 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% (World Health Organization-Bangladesh, 2006), a clinically significant odds ratio considered to be 1.5 (Gupta *et al.*, 2005; Rahman and Zaman, 2008); 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. Then these variables were 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, McNemar's chi-squared (χ^2) tests were used 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. Confounding variables were identified initially using a χ^2 test relating the variables to CHD. If the p-value from the χ^2 test was less than 0.20 and there was no missing data for the confounder, that variable was included into the final multivariate analyses. 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.

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 study.

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 1).

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.

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

Table 1: Socio-demographic and risk factor variables for coronary heart disease (CHD) among the study participants

	Total		Cases		Hospital controls		Community controls	
Socio-demographic variables	No.	%	No.	%	No.	%	No.	%
Total study participants	1812		302		302		1208	
Age (years)	53.0±8.5		53.5±8.5		51.9±8.4		53.1±8.5	
Age-groups (years)								
40-48	635	35.0	95	31.5	121	40.1[a]	419	34.7[a]
49-57	641	35.4	109	36.1	102	33.8[a]	430	35.6[a]
58-66	405	22.4	72	23.8	61	20.2[a]	272	22.5[a]
67-75	131	7.2	26	8.6	18	6.0[a]	87	7.2[a]
Male participants	900	49.7	150	49.7	150	49.7[a]	600	49.7[a]
Married (and living with spouse)	1414	78.0	232	76.8	243	80.5[a]	939	77.8[a]
Highest level of education achieved								
Illiterate	204	11.3	34	11.3	19	6.3[a]	151	12.5[b]
Can sign names	212	11.7	27	8.9	35	11.6[a]	150	12.4[a]
Primary	527	29.1	95	31.5	94	31.2[a]	338	28.0[b]
Secondary	239	13.2	44	14.6	42	14.0[a]	153	12.7[b]
Higher-secondary	197	10.9	33	10.9	48	15.9[a]	116	9.6[b]
Above higher-secondary	418	23.1	66	21.9	62	20.6[a]	290	24.0[a]
Primary occupation								
Service holder	558	30.8	87	28.8	102	33.8[a]	369	30.6[a]
Businessmen	262	14.5	42	13.9	40	13.2[a]	180	14.9[a]
Housewife	741	40.9	126	41.7	120	39.7[a]	495	41.0[a]
Retired	235	13.0	47	15.6	39	12.9[a]	149	12.3[a]
Socio-economic status (SES) by monthly house-rent (HR)								
Lower SES (HR <5000 BDT)	656	36.2	109	36.1	114	37.7[a]	433	35.8[a]
Middle SES (HR 5000-10000 BDT)	930	51.3	152	50.3	158	52.3[a]	620	51.3[a]
Higher SES (HR >10000 BDT)	226	12.5	41	13.6	30	9.9[a]	155	12.8[a]
Presence of other risk factors for CHD								
Hypertension	796	43.9	180	59.6	203	67.2[a]	413	34.2[b]
Diabetes	446	24.6	129	42.7	73	24.2[a]	244	20.2[a]
Family history of heart disease	421	23.2	94	31.5	79	27.2[a]	248	21.5[b]
Performed physical activities	1116	61.6	179	59.5	149	50.2[a]	788	65.3[b]
Use of hormonal contraceptives	60	3.3	9	3.0	10	3.3[a]	41	3.4[a]
Exposure to indoor smoking	321	17.7	58	19.2	45	14.9[a]	218	18.0[a]
Acute psycho-social stress[#]	434	24.0	94	31.1	75	24.8[a]	265	21.9[a]

Values within a row with different superscripts are significantly different at $p<0.05$ using chi-squared test, [#]Stress due to 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.

separately for never-smokers and ex-smokers (Table 2). 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.

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),

Table 2: Status of smokeless tobacco (SLT) use according to smoking exposure among the study participants

	Total		Cases		Hospital controls		Community controls	
Smokeless tobacco use	No.	%	No.	%	No.	%	No.	%
Total study participants (non-smokers)	1812	-	302	-	302	-	1208	-
Never-smokers	1292	71.3	203	67.2	225	74.5[a]	864	71.5[a]
Ex-smokers (quit >10 years ago)	520	28.7	99	32.8	77	25.5[a]	344	28.5[a]
Non-smokers (total study participants)	-	-	-	-	-	-	-	-
Ever users of SLT products	701	38.7	118	39.1	101	33.4[a]	482	39.9[b]
Current users of SLT products	648	35.8	99	32.8	95	31.5[a]	454	37.6[b]
Quitters of SLT products	53	2.9	19	6.3	6	2.0[a]	28	2.3[a]
Never-smokers	1292	-	203	-	225	-	864	-
Ever users of SLT products	444	34.4	60	29.6	71	31.6[a]	313	36.2[a]
Current users of SLT products	418	32.4	51	25.1	68	30.2[a]	299	34.6[a]
Quitters of SLT products	26	2.0	9	4.4	3	1.3[a]	14	1.6[a]
Ex-smokers	520	-	99	-	77	-	344	-
Ever users of SLT products	257	49.4	58	58.6	30	39.0[a]	169	49.1[a]
Current users of SLT products	230	44.2	48	48.5	27	35.1[a]	155	45.1[a]
Quitters of SLT products	27	5.2	10	10.1	3	3.9[a]	14	4.1[a]

Values within a row with different superscripts are significantly different at $p<0.05$ using chi-squared test

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 3). Use of individual SLT products was also not associated with choice of controls, when data were analysed data separately for never-smoker or ex-smoker participants, and for current use, quitting or ever use of SLT products.

DISCUSSION

In this study, a significant difference between hospital controls and community controls was found 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 (Ross and Wu, 1995). 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 (Kabir *et al.*, 2003). 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 most of them were considered to be hypertensive or under treatment for hypertension. In addition, there may be other unmeasured health problems that prevented them undertaking physical activity.

Table 3: Uuivariate 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)

	Cases vs. hospital controls					Cases vs. community controls					Hospital controls vs. community controls				
		Cares		Hospital			Cares		Commumity			Hospital		Commumity	
Parameter	p	OR	95% CI	Adj. OR*	95% CI	p	OR	95% CI	Adj. OR§	95% CI	p	OR	95% CI	Adj. OR¶	95% CI
Never users of any tobacco (Reference)		1.00		1.00			1.00		1.00			1.00		1.00	
Non-smokers (total study participants)															
Ever users of SLT products	0.108	1.33	0.94-1.87	1.11	0.71-1.71	0.896	0.98	0.74-1.29	0.96	0.71-1.30	0.032	0.72	0.55-0.96	0.87	0.64-1.18
Current users of SLT products	0.304	1.18	0.83-1.69	1.00	0.63-1.60	0.420	0.87	0.65-1.17	0.87	0.63-1.19	0.035	0.71	0.53-0.95	0.81	0.58-1.12
Quitters of SLT products	0.014	4.00	1.13-14.2	2.19	0.51-9.44	0.004	2.38	1.16-4.91	2.04	0.92-4.57	0.568	0.69	0.27-1.78	0.82	0.28-2.42
Never-smokers	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ever users of SLT products	0.736	0.92	0.59-1.45	1.11	0.59-2.10	0.091	0.71	0.49-1.02	0.66	0.44-0.99	0.181	0.81	0.57-1.15	0.96	0.65-1.43
Current users of SLT products	0.489	0.86	0.54-1.39	1.19	0.62-2.31	0.039	0.65	0.44-0.95	0.62	0.40-0.95	0.193	0.80	0.56-1.14	0.94	0.63-1.40
Quitters of SLT products	0.170	2.00	0.37-10.9	0.37	0.02-5.48	0.155	1.49	0.53-4.24	1.09	0.35-3.40	0.676	0.80	0.14-4.63	0.50	0.06-3.97
Ex-smokers	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ever users of SLT products	0.007	2.80	1.01-7.78	2.12	0.63-7.18	0.083	1.48	0.84-2.59	1.52	0.83-2.79	0.088	0.61	0.34-1.10	0.70	0.37-1.33
Current users of SLT products	0.018	2.20	0.76-6.33	0.85	0.20-3.55	0.210	1.54	0.84-2.83	1.50	0.78-2.89	0.083	0.60	0.31-1.13	0.78	0.38-1.59
Quitters of SLT products	0.037	Undef	Undef	Undef	Undef	0.009	1.03	0.30-3.60	0.91	0.15-5.49	0.717	0.66	0.16-2.74	0.28	0.03-2.46

The variables those were significant ($p<0.20$) during iuitial 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

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 (Rahman and Zaman, 2008). In that study (n = 207), prevalence of SLT use among hospital patients were less (22%) than that compared to the general population (32%) (World Health Organization-Bangladesh, 2006). 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 (Rahman *et al.*, 2002) and 27% by the recent Global Adult Tobacco Survey (GATS) (World Health Organization-Bangladesh, 2009). 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 studies reported higher prevalence of SLT use in rural areas than urban settings in Bangladesh (Rahman *et al.*, 2002; Flora *et al.*, 2009).

Community controls 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 (Hergens *et al.*, 2008; Martin *et al.*, 2010). 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. On the other hand, there might be under-reporting of hypertension by community controls resulting an over-estimation of the reported ORs when data were analysed using community controls. Because hypertension is an important potential confounder, it was adjusted 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 (Lee, 2011). Although community controls were screened out by self-reporting, hospital controls were screened out by the 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, this issue was addressed 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.

There was no 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 (Huhtasaari *et al.*, 1992, 1999; Hergens *et al.*, 2005; Wennberg *et al.*, 2007) as well as cohort studies (Hergens *et al.*, 2007; Hansson *et al.*, 2009; Janzon and Hedblad, 2009). 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 (Teo *et al.*, 2006) 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 diagnoses of non-CHD among the community controls by a qualified physician. In addition, four hospital controls could not be included for each case in the same way 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. Blood pressure could not be measured but data on self reported history of hypertension were collected for both cases and controls. The possibility of excluding undiagnosed cases of hypertension exists. This was addressed by controlling hypertension (categorized as presence or absence) through multivariate analyses.

CONCLUSIONS AND RECOMMENDATIONS

There was 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 within South Asian context, reporting the comparison between two groups of controls. Results of this study are more credible as the exposure of cases was compared to both hospital controls and community controls, which allowed 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 can consider selecting hospital controls for a case-control study if potential confounders are carefully considered, measured and adjusted for.

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