

Socio-economic disparities in heart disease in the Republic of Lebanon: findings from a population-based study

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ABSTRACT

Background Socio-economic inequalities in the incidence of heart disease exist in developed countries. No data are available on the relation between heart disease and socio-economic status in Arab countries. This study examined the relation between heart disease and socio-economic status (income and education) among adults in Lebanon.

Methods The study examined data from 7879 respondents aged 40 years or more in the 2004 Lebanese Survey of Family Health. The dependent variable was reported heart disease. The main independent variables were education and household income. The analysis adjusted for the classic risk factors of coronary heart disease (CHD), namely smoking, diabetes mellitus, hypertension, hypercholesterolaemia, age, sex and other socio-demographic variables. Bivariate associations were calculated using χ^2 tests. Adjusted ORs for heart disease were calculated using multivariate logistic regression models.

Results 7.5% of respondents reported cardiac disease, 15.2% hypertension, 10.1% diabetes, 3.2% hypercholesterolaemia and 47.5% smoked at the time or previously. After adjustment for the classic risk factors of CHD, reported heart disease was inversely associated with education (OR=1.53, 95% CI 1.15 to 2.04, for those with less than elementary and OR=1.34, 95% CI 1.00 to 1.80, for those with elementary education). Reported heart disease was also inversely associated with income (OR=1.40, 95% CI 1.09 to 1.80, for those in the lowest income bracket). Past smoking, hypertension, age, male sex, marriage and residence in Beirut were all significantly associated with reported cardiac disease.

Conclusions In Lebanon, adults with lower income and educational levels had a higher prevalence of heart disease independent of the risk factors of CHD.

INTRODUCTION

Coronary heart disease (CHD) is a complex disease without a precisely defined aetiology and pathogenesis but with well-established independent risk factors, namely tobacco smoking, diabetes mellitus, hypertension and hypercholesterolaemia.^{1–5} Male sex and older age are two additional non-modifiable independent risk factors.^{1–6} Although the causal pathways of these risk factors remain under investigation, it is believed that they play a causative role in at least 80% of all cases of CHD.^{1 2 4} This seems to be a worldwide phenomenon, applying not only to high-income, mostly European origin, societies, but also to middle- and low-income countries, where more than 80% of the global burden of cardiovascular disease occurs.^{4 6}

The vast majority of these countries have undergone an epidemiological transition from the predominance of rheumatic heart disease in the beginning of the last century to the current situation where CHD accounts for the vast majority of heart disease.^{6 7}

Furthermore, it has long been known that there are socio-economic inequalities in the incidence and mortality of heart disease. In developed economies, lower economic, educational and occupational levels have been associated with higher incidence and mortality from heart disease.⁸ These socio-economic determinants are believed to be responsible for the development of the classic major risk factors for heart disease and to act mostly through the intermediacy of these classic risk factors in the pathogenesis of heart disease. A recent study in the UK suggested that the classic risk factors account for most of the socio-economic inequality in the prevalence and mortality of CHD⁹; however, this finding is not fully accepted by social epidemiologists and may not necessarily hold in other settings.^{10 11}

Few data exist on the epidemiology and nature of heart disease in the Arab world. The available data point to high incidence and prevalence of CHD and its major risk factors and high mortality.^{6 12} As in many middle-income developing countries, the incidence and mortality of CHD in some Arab countries are higher than those in most developed countries.^{12–17} Furthermore, CHD seems to present at younger age and afflict a higher proportion of males in the Arab countries compared with other developing countries.⁴ Although data from some developing countries suggest an epidemiological transition of CHD from higher- to lower-income strata,¹⁸ the relationship between socio-economic status and prevalence of heart disease in the Arab world remains unknown. This study examines the association between adult heart disease and social and economic variables in the Republic of Lebanon using population-based household survey data. Specifically, the study will test whether socio-economic status, measured by education, income and the related income gradient, is significantly associated with reported heart disease and whether such associations persist after adjusting for the classic risk factors of CHD.

METHODS

Data

This study utilised household data from the Lebanese Survey for Family Health, which was conducted by the Ministry of Social Affairs and the

Pan-Arab Project for Family Health (PAPFAM) in 2004.¹⁹ The PAPFAM survey used a standard questionnaire instrument designed for large regional survey programmes and was preceded by a pilot study testing the validity and reliability of the wording of its questions. The survey followed a stratified, two-stage probability sampling design. The sample was drawn by dividing Lebanon into 15 geographical areas, with a random sample drawn from each area in two stages. In the first stage, a systemic random sample of 449 primary sampling units was drawn. In the second stage, a random sample of 7098 main housing units was selected from these primary sampling units. A total of 6505 households were found and visited in these dwellings. Interviews were completed for 5532 households (85% response rates). Data were collected between April and November 2004 by well-trained interviewers using face-to-face interviews. For this study, a subsample ($n=7879$) of all persons aged 40 years and older found in the surveyed households was selected for analysis. This study analysed data collected using one of four instruments used in the survey, a household questionnaire containing basic demographic and socio-economic data on households and household members.

The outcome variable in this study is self-reported heart disease, which, in more than 97% of subjects, was diagnosed by a healthcare provider. The PAPFAM survey included a module on chronic diseases containing questions on 24 diseases for all family members. These included heart disease (without further specification) and the classic risk factors for CHD, namely hypertension, diabetes mellitus and hypercholesterolaemia. Information on tobacco smoking history was obtained in another module of the survey. For each household member, up to two chronic diseases were reported, in addition to one question about medical diagnosis of the reported diseases. In this study, any member who chose heart disease as one of the two reported chronic diseases was considered a case. Socio-economic status was measured by two variables, total monthly household income and completed education. Household income was first divided into quintiles at the household level before merging it with the household members' data. It was subsequently transformed into three groups (low, middle and high). The variable 'completed education' consisted of four levels: less than elementary, elementary, preparatory, and secondary or higher education. Data on the classic independent risk factors for CHD obtained from the survey were included in the analysis, specifically history of hypertension, diabetes mellitus, hypercholesterolaemia and smoking status (current, past smoker, never smoked). Socio-demographic factors including age (40–49, 50–59, 60–69, 70 and above), sex, marital status (single, married, previously married), labour force participation (active, non-active) and region of residence (the Bekaa Valley, North, Mount Lebanon, South and Nabatia, and Beirut) were also used in the analysis.

Analysis

Descriptive analyses of all variables used in the study were first undertaken. The associations between reported heart disease and classic risk factors and socio-economic and demographic variables were then assessed using χ^2 tests of associations. Adjusted ORs of heart disease were then calculated from multivariate logistic regression models. Two regression models were performed; one with education and another with income because preliminary analysis showed that education was highly associated with income. Sampling weights were used in the analysis in order to correct for non-response and unequal probability of selections. The statistical analyses were performed

using the SPSS for Windows (version 16; SPSS, Chicago, Illinois) statistical software program.

RESULTS

Overall, 7.5% of respondents (those 40 years of age and older) reported heart disease, 15.2% reported hypertension, 10.1% reported diabetes mellitus, and 3.2% reported hypercholesterolaemia (table 1). Nearly half of respondents smoked, 36.8% reporting current smoking, and 10.7% reporting past smoking. There were more females (52.4%) than males in the sample, and over a third of respondents were in the younger age group, 40–49 years. The median age of the study population was 55 years. Education was low, with 31% of respondents having had less than elementary education, and only 24.8% having had secondary or higher education. Of all respondents, 32% came from low-income households and 23.9% from high-income households. Labour force participation was relatively low at 46.7%, mainly due to low economic activity among women. The vast majority of respondents were currently married (77%), and only 9.4% were single. Mount Lebanon had the largest proportion of respondents (40.4%), and the Bekaa Valley had the smallest (11.1%), followed by Beirut (13.3%). For some of the variables, there were missing values, but these amounted to less than 1% of the respondents. Given these very small proportions, no imputations of missing values were required, as the excluded values would have had no effect on the overall findings.

With the notable exception of hypercholesterolaemia, all of the classic risk factors for CHD were associated with a higher prevalence of reported heart disease. Reported heart disease was higher among males and older people as expected, but it was also higher among the married or previously married, non-participants in labour force, those from poorer households and people of lower educational level. As shown in table 2, all four classic risk factors for CHD (tobacco smoking, hypertension, diabetes mellitus and hypercholesterolaemia) were also inversely related to educational level and income, with the exception of hypercholesterolaemia and income.

Table 3 shows the adjusted ORs for reported heart disease. Model 1 displays the ORs for reporting heart disease by socio-economic variables only. As shown in the table, both income and education were significantly associated with reporting heart disease. A socio-economic gradient, similar to dose–response association, was also evident for both variables. The odds for reporting heart disease were 2.8 (95% CI 2.19 to 3.63) for persons with less than elementary education, 1.8 (95% CI 1.37 to 2.37) for those with elementary education, and 1.4 (95% CI 1.03 to 1.90) for those with preparatory education, all compared with respondents with secondary education and higher. Similarly, persons with the lowest income were 1.52 (95% CI 1.21 to 1.92) times more likely to report heart disease compared with those in the highest income bracket, but there was no statistically significant gradient for income and heart disease.

Two additional models are displayed in the table, one with education and another with income, both adjusted for classical risk factors and other relevant socio-demographic factors. In model 2, the association between reported heart disease and education was attenuated but remained statistically significant after controlling for the classic risk factors and the other socio-demographic factors. The OR of reporting heart disease was higher for those with less than elementary (OR=1.53, 95% CI 1.15 to 2.04) and elementary education (OR=1.34, 95% CI 1.00 to 1.80) compared with those with secondary and higher education. An educational gradient for heart disease was

Table 1 Characteristics of the study population (adults 40 years of age and older) and proportion of reported heart disease in relation to background variables, Lebanon 2004

Variable	Total subjects (N=7879)		Subjects reporting heart disease		p Value*
	N	Percentage	N	Percentage	
Heart disease					
Yes	594	7.5			
No	7285	92.5			
Sex					
Male	3751	47.6	322	8.6	<0.001
Female	4128	52.4	271	6.6	
Age					
70+	1296	16.5	241	18.6	<0.001
60–69	1593	20.2	172	10.8	
50–59	2124	27.0	115	5.4	
40–49	2866	36.4	65	2.3	
Tobacco smoking					
Current smoker	2880	36.8	131	4.5	<0.001
Past smoker	837	10.7	172	20.6	
Never smoked	4112	52.5	288	7.0	
Hypertension					
Yes	1201	15.2	162	13.5	<0.001
No	6678	84.8	432	6.5	
Diabetes mellitus					
Yes	793	10.1	107	13.5	<0.001
No	7085	89.9	487	6.9	
Hypercholesterolaemia					
Yes	251	3.2	18	7.2	0.828
No	7628	96.8	575	7.5	
Education					
Less than elementary	2424	31.0	274	11.3	<0.001
Elementary	1988	25.4	149	7.5	
Preparatory	1463	18.7	87	5.9	
Secondary and higher	1938	24.8	84	4.3	
Income					
Low	2523	32.0	230	9.1	<0.001
Middle	3474	44.1	248	7.1	
High	1881	23.9	116	6.2	
Labour-force participation					
Inactive	4161	53.3	380	9.1	<0.001
Active	3644	46.7	210	5.8	
Marriage					
Previously married	1072	13.7	151	14.1	<0.001
Married	6043	77.0	429	7.1	
Single	736	9.4	14	1.9	
Region					
Beirut	1048	13.3	109	7.5	<0.001
South and Nabatia	1282	16.3	86	10.4	
Mount Lebanon	3186	40.4	248	7.8	
North	1491	18.9	96	6.4	
Bekaa valley	872	11.1	54	6.2	

*p Values (two-tailed) from χ^2 tests.

therefore evident in these data, with a statistically significant trend ($p < 0.04$). In this multivariate model, which included education and socio-demographic variables, only reported hypertension and past smoking in addition to age and sex were significantly associated with reported heart disease, but not diabetes and hypercholesterolaemia. Respondents with hypertension were 1.24 times (95% CI 1.01 to 1.53) more likely to report heart disease than those without hypertension. Past-smokers had higher OR of reporting heart disease (OR=2.31, 95% CI 1.85 to 6.88) compared with never smokers, but current smokers had a lower OR of reporting heart disease (OR=0.75, 95% CI 0.60 to 0.94) than never smokers. Males were significantly more likely (OR=1.44, 95% CI 1.13 to 1.83) to report

heart disease, and older respondents were also more likely to report heart disease compared with younger respondents. The OR for those aged 70 and above years was the highest at 4.90 (95% CI 3.48 to 6.88). An age gradient was also apparent with younger persons consistently less at risk for heart disease compared with older respondents. Finally, marital status and region were also associated with reported heart disease. Married (OR=2.81, 95% CI 1.58 to 4.97) and previously married (widowed or divorced) respondents (OR=3.65, 95% CI 2.02 to 6.60) were more likely to report heart disease than the never-married respondents. Lastly, those living in Beirut were more likely to report heart diseases (OR=1.86, 95% CI 1.20 to 2.89) than those living in the Bekaa Valley.

Table 2 Relation between coronary heart disease risk factors and socio-economic characteristics in Lebanon

Variable	Smoker		p Value*	Hypertension		p Value*
	N	Percentage		N	Percentage	
Education						
Below elementary	1036	42.9	<0.001	532	22.0	<0.001
Elementary	1030	52.1		312	15.7	
Preparatory	780	53.7		181	12.4	
Secondary and higher	851	44.1		173	8.9	
Income						
Low	1180	47.0	<0.024	443	17.6	<0.001
Middle	1693	49.0		533	15.3	
High	843	45.2		225	12.0	
Variable	Diabetes mellitus		p Value*	High cholesterol		p Value*
	N	Percentage		N	Percentage	
Education						
Below elementary	347	14.3	<0.001	76	3.1	<0.002
Elementary	211	10.6		85	4.3	
Preparatory	113	7.7		48	3.3	
Secondary and higher	122	6.3		41	2.1	
Income						
Low	275	10.9	<0.018	83	3.3	0.926
Middle	360	10.4		110	3.2	
High	158	8.4		58	3.1	

*p values (two-tailed) from χ^2 tests.

Model 3 in table 3 shows the adjusted ORs for reported heart disease with income, instead of education, as the index of socio-economic status. As in model 1, respondents in the lowest income bracket had significantly higher odds of reporting heart disease (OR=1.40, 95% CI 1.09 to 1.80) than the richest respondents. Similar associations were found between reported heart disease and hypertension, smoking status, sex, age, marital status and region when income was used instead of education to index socio-economic status.

DISCUSSION

This study shows a significant association between the prevalence of reported heart disease and socio-economic status in adults 40 years of age and older residing in the Republic of Lebanon. It suggests that among the citizens and residents of Lebanon, a developing middle-income country with a human development index of 0.796,²⁰ those with a lower educational level and a lower household income have higher prevalence of heart disease. A socio-economic gradient of heart disease, previously noted in affluent predominantly Western countries,⁸ is also evident in Lebanon. This finding is consistent with the worldwide epidemiological transition of coronary heart disease from a disease of the privileged to a disease of the lower socio-economic groups.^{6 18 21–24} The study also shows a significant association in Lebanon between heart disease and three of the classic risk factors for coronary heart disease, namely tobacco smoking, diabetes mellitus and hypertension, but no such association with hypercholesterolaemia. All four risk factors are more prevalent in the lower-education group and, with the exception of hypercholesterolaemia, in the lower-income groups. The association between heart disease and socio-economic status persisted after adjusting for age, sex and all four independent risk factors, possibly suggesting other mechanisms through which socio-economic factors contribute to the development of heart disease in this predominantly younger population. Interestingly, the study suggests that heart disease has a higher prevalence in married people and an even higher

prevalence in previously married (widowed and divorced) persons compared with those never married, independently of age, other risk factors and socio-economic factors. This finding is consistent with previously reported data on the association of heart disease and marital status in Western countries^{25 26} and suggests a possible role for marital or parenting stress as well as the stresses of separation and bereavement in the development or precipitation of heart disease.

This study also confirms the relevance of the classic risk factors of coronary heart disease and their applicability to societies other than the predominantly wealthy and European-origin societies in which they were originally identified. It also reveals the high prevalence of some of these risk factors in this predominantly young population. The prevalence of tobacco smoking (47.5%, combined past and current, of adults 40 years or older), is likely a reasonably accurate estimate and is one of the highest in the world. Prevalence of hypertension (15.2%) and diabetes (10.1%) are likely underestimates but are still fairly high. These would all predict an ever-increasing burden of coronary heart disease. The lack of a statistically significant association between reported heart disease and reported hypercholesterolaemia is surprising. No definite inferences can be reached, however, in view of the low reported prevalence of hypercholesterolaemia. The latter is likely due to underdiagnosis of dyslipidaemia in the study population and under-reporting in this type of household surveys. Studies from neighbouring Arab countries have in fact reported a much higher prevalence of dyslipidaemia.¹² The same probably also applies to hypertension and diabetes mellitus, which in the early stages might go undiagnosed for a period for time. Another surprising finding is the lack of a significant association between heart disease and reported current smoking, as opposed to past smoking, despite adjustment for age. This could possibly also be explained by the nature of these self- and proxy-reported data. Heart disease is often a compelling reason for smoking cessation, whereas current smokers might not be inclined to seek medical care in the absence of disease symptoms. The study did not take into consideration the duration and extent of smoking among current and former

Table 3 Association between reported heart disease and the classic risk factors for coronary heart disease, socio-economic variables and demographic characteristics, Lebanon 2004

Variable	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Education			
Less than elementary	2.82 (2.19 to 3.63)	1.53 (1.15 to 2.04)	—
Elementary	1.80 (1.37 to 2.37)	1.34 (1.00 to 1.80)	—
Preparatory	1.40 (1.03 to 1.90)	1.27 (0.95 to 1.55)	—
Secondary and higher	1	1	
Income			
Low	1.52 (1.21 to 1.92)	—	1.40 (1.09 to 1.80)
Middle	1.17 (0.93 to 1.47)	—	1.17 (0.92 to 1.48)
High	1	—	1
Smoking status			
Current		0.75 (0.60 to 0.94)	0.75 (0.60 to 0.94)
Past		2.31 (1.85 to 6.88)	2.33 (1.87 to 2.92)
Hypertension			
		1.24 (1.01 to 1.53)	1.24 (1.00 to 1.53)
Diabetes mellitus			
		1.24 (0.97 to 1.53)	1.24 (0.98 to 1.58)
Hypercholesterolaemia			
		0.79 (0.48 to 1.30)	0.80 (0.49 to 1.32)
Male sex			
		1.44 (1.13 to 1.83)	1.43 (1.11 to 1.82)
Age			
40–49		1	1
50–59		2.01 (1.47 to 2.76)	2.10 (1.53 to 2.88)
60–69		3.28 (2.39 to 4.51)	3.55 (2.60 to 4.83)
70+		4.90 (3.48 to 6.88)	5.37 (3.87 to 7.44)
Labour-force participation			
Active		1	1
Inactive		1.22 (0.95 to 1.55)	1.25 (0.98 to 1.59)
Marital status			
Married		2.81 (1.58 to 4.97)	3.01 (1.70 to 5.33)
Previously married		3.65 (2.02 to 6.60)	3.91 (2.17 to 7.06)
Region			
Bekaa valley		1	1
North		0.99 (0.69 to 1.42)	0.99 (0.69 to 1.42)
Mount Lebanon		1.29 (0.94 to 1.78)	1.28 (0.93 to 1.77)
South and Nabatia		1.05 (0.73 to 1.52)	1.05 (0.73 to 1.52)
Beirut		1.86 (1.20 to 2.89)	1.83 (1.27 to 2.62)

smokers, owing to the lack of requisite data. That would have been a better indicator of the exposure to tobacco smoke.

Previous studies suggested that societal factors operate mostly through established risk factors, and hence that the elimination, even if it were possible, of these risk factors would eliminate most of coronary artery disease.^{9–11} Because of the persistence of the association between measures of socio-economic status and heart disease despite adjustment for the classic risk factors, this study suggests that there might be other intermediaries through which societal factors can influence the development of heart disease. The elucidation of such mechanisms, which might be more important in certain societies, would be essential for the implementation of effective preventive strategies. Psychosocial distress could be such an intermediary. Previous studies have suggested an immediate role for psychological distress in heart disease, perhaps as a trigger of acute events,^{27–28} other studies established a role for psychological distress as an upstream risk factor for CHD possibly acting through the intermediacy of life style factors, such as tobacco smoking, physical inactivity and poor dietary habits.^{29–30} Data from the INTERHEART study suggested a very important role for psychological distress as a risk factor for myocardial infarction in the Arab Middle Eastern Countries, especially in females.⁴ Lebanon is a country that has witnessed several conflicts over the past century, and

especially over the past three decades, and it is reasonable to imagine that such conflicts caused high levels of psychological distress. Psychological distress and other risk factors such as physical inactivity, obesity, dietary patterns and alcohol consumption were not taken into consideration in this study. Although they all, with the possible exception of alcohol consumption, operate to a great extent through established risk factors, it is conceivable that part of their effect is mediated through other mechanisms. Although studies from Western societies suggested that the socio-economic disparities in the classic risk factors account for the major part of the socio-economic gradient of CHD,^{9–11} this might not be the case in non-European ethnic groups and in low- and intermediate-income societies. It is conceivable that psychosocial stress plays multiple complex roles, directly and indirectly, in the development of CHD and its clinical presentations.

This study suffers from several other limitations. First, although more than 97% of the diagnoses were reportedly made by medical professionals, the data are self- and proxy-reported. Although a previous study suggested the reliability and validity of such data in the Lebanese context,³¹ the data undoubtedly underestimate the real prevalence of the medical conditions in question. People of lower socio-economic status are less likely to seek primary health maintenance medical care, and as a consequence certain conditions, notably hypertension and hypercholesterolaemia, might go undiagnosed for longer periods of time than in people of higher education and more means. This phenomenon could have played a role in weakening the associations detected in this study, suggesting perhaps that there is even a stronger inverse relation between heart disease and socio-economic status. Another limitation of the study is the fact that only two chronic diseases were captured for each subject in the survey data. For subjects with heart disease and more than one risk factor, information on second, third and possibly fourth risk factors was not captured. This phenomenon also likely weakened the detected associations. These two deficiencies could explain the low reported prevalence of hypertension and hypercholesterolaemia in this study, compared with data obtained from other sources.^{32–34} In view of this inherent tendency to underestimation of true prevalence, the prevalence of reported diabetes mellitus in the study population is surprisingly high. It is comparable with the prevalence of diabetes mellitus obtained in other population-based studies and in neighbouring countries. This suggests an even higher prevalence of diabetes mellitus in the study population.^{12 35 36}

Furthermore, the study survey grouped all heart disease under one category and did not define it further. The analysis looked at the relation between this grouped heart disease category and the risk factors for CHD. This assumed that the majority of heart disease in the study population is coronary heart disease. While this might be a reasonable assumption based on available data,^{34 37–40} the uncovered associations might have been further weakened by grouping all types of heart disease under one category. The study did not examine gender differences in the association between heart disease and other variables. This was due to the low numbers and decreased power of the analysis in gender-based groups. Gender-based analysis would have been of interest vis-à-vis smoking status, educational level and labour force participation, variables that are known to have a large gender-based variability in Arab Middle Eastern countries. Although Lebanon has the highest percentage of female smokers and one of the highest female education levels of the Arab countries,¹⁹ the prevalence of smoking and educational level among men is likely higher, especially in rural and non-urban

areas. The diverse religious and cultural composition of Lebanon makes further interpretation of the results and their applicability to cultural subgroups difficult. The higher reporting of heart disease in Beirut might be attributed to the urban lifestyle and its well established effects on the incidence of CHD. Finally, the findings of this study were based on data from a cross-sectional survey, thereby preventing inferences of causation. Although the direction of some associations reported was clear (eg, age and heart disease), reverse causality cannot be ruled out, given the cross-sectional nature of the study design.

Despite its limitations, this is the first study examining the socio-economic disparities in heart disease in an Arab Middle Eastern country. It suggests that heart disease might be more prevalent in people with lower educational level and lower income, independently of the major classic medical risk factors. It also suggests the possible presence of other socio-economically determined factors and mechanisms mediating the development of heart disease. The elucidation of these mechanisms and, more importantly, improvement in education and decrease in poverty would be important steps in the development of effective preventive strategies against cardiovascular disease in the region. This study should serve as an impetus for future population-based cohort studies examining cardiovascular disease and its risk factors in the Arab Middle Eastern countries.

Competing interests None.

Contributors TR formulated the research plan in consultation with MK. TR wrote the Introduction and Discussion sections and drafted all versions of the manuscript. He modified the tables and assembled all references. MK analysed the data and drafted the Methods and Results sections. He also commented on the entire manuscript. NA-R contributed to data analysis and prepared the initial versions of the tables and commented on the manuscript. SA came up with the initial study concept which was subsequently modified by TR. She also commented on the manuscript.

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