# Association of Patient Characteristics with Risk of Rheumatic Heart Disease in First-Degree Relatives of Index Cases in Nepal

Saurya Dhungel

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Committee:

Nona Sotoodehnia

Annette L. Fitzpatrick

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University of Washington

## Abstract

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Saurya Dhungel

Chair of the Supervisory Committee:

Nona Sotoodehnia, MD, MPH

Department of Medicine

Rheumatic heart disease (RHD) is associated with significant morbidity and mortality, particularly in low- and middle-income countries. First-degree relatives (FDR) of RHD patients share known risk factors for RHD: poverty, poor living conditions, crowding, poor hygiene, and potential shared genetic characteristics that lead to higher RHD risk. We sought to determine whether FDR screening would be a high-yield method of screening patients for RHD to allow for timely preventive measures. This was a cross-sectional study based in two tertiary care centers in Nepal. RHD patients (n=102) were given the opportunity to invite their FDRs for RHD screening. A total of 234 FDRs without clinically recognized RHD participated in the RHD screening. Patients were screened using echocardiography by cardiologists at the two sites and RHD was adjudicated by a committee of cardiologists and echo-sonographers at the University of Washington according to the World Heart Federation classification of "definite" or “borderline” RHD. We assessed prevalence of RHD among FDRs and compared them with prior school-based screening results in Nepal. We examined whether index case characteristics (age, sex, socio-economic status (SES) and family history of having RHD) were associated with likelihood

of the index case having at least one FDR with borderline or definite RHD using multi-variable adjusted logistic regression. The mean ages of the 102 index RHD cases and of the 234 FDRs were 29.6 and 29.0 years, respectively. 74% of the RHD cases and 58% of the FDRs were women. Among the 234 FDRs, 19 (8.1%; 95% CI 5.1%-12.6%) had borderline or definite RHD of which 8 (3.4%; 95% CI 1.6%-6.9%) had definite RHD. Prior screening efforts in Nepal have been limited to examining children in schools and have yielded a prevalence of 0.1%-3.7% for borderline or definite RHD. Of the 102 index cases participating in this study, 17.6% had at least one FDR with borderline or definite RHD. Index case age, sex, SES, family history of having RHD were not associated with likelihood of having an FDR screen positive for RHD. Of the 52 child-parent relationships where the index case was the child, no parent had borderline or definite RHD. Of the 111 sibling-sibling relationships, 8 FDRs (12.5%) screened positive for borderline or definite RHD. Of the 71 parent-child relationships where the index case was the parent, 11 children (15.5%) screened positive for borderline or definite RHD. Our study demonstrates that screening FDRs of known RHD cases is a high-yield method of identifying previously unrecognized RHD. Identification of FDRs with RHD can encourage these patients to receive earlier treatment with penicillin prophylaxis to prevent further reinfection and valvular damage. Coupled with a penicillin prophylaxis program, adoption of FDR screening into the national RHD screening strategy in RHD-endemic countries like Nepal could improve RHD care worldwide.

## Introduction

RHD is one of the most common cardiovascular diseases in low- and middle-income countries (LMICs).[1] RHD is a sequela of Acute Rheumatic Fever (ARF) caused by Group A *Streptococcus* (GAS). Antigenic mimicry along with abnormal host response is considered the key to pathogenesis of RHD.[2] Cardiac involvement which starts from childhood shows evidence of inflammation, leading to permanent damage of heart valves, primarily the mitral valve.[3] RHD leads to significant morbidity and mortality, with 18% of patients developing heart failure and 10% dying within 10 years of RHD diagnosis.[4]

Studies have shown that prevalence of RHD is higher in women than men across all age groups.[5,6] Women are more likely to develop RHD and suffer its clinical sequelae.[5] A cohort study that performed transthoracic echocardiography studies had a sex ratio of female to male RHD diagnosed cases of 1.6 in eastern Nepal.[5] Similarly, a study done in rural India found that the prevalence of RHD is higher among females with a prevalence of RHD of 10.3 per 1000 in females and 3.6 per 1000 in males.[6]

RHD impacts humans across their lifespan, with incidence starting in childhood, and peak prevalence between 25-45 years. While it is a disease of poverty, affecting more than 33 million people in LMICs, RHD also continues to be a problem in non-endemic countries such as the United States, primarily through immigration.[7] First-degree relatives (siblings, parents, and children) of RHD patients share known risk factors for RHD: poverty, poor living conditions, crowding, poor hygiene, and potential shared genetic characteristics that lead to higher RHD risk.[8,9] Known risk factors for RHD also include poverty, poor living conditions, overcrowding, and poor hygiene.[9,10] Genetic factors have been found to be associated with higher RHD risk.[9,10] Thus, first-degree relatives of RHD patients likely share known environmental and genetic risk factors for RHD. In an echocardiographic screening in Uganda, nearly 17% of siblings of definite RHD cases had definite RHD compared to 3% for siblings of non-RHD controls.[11] *There is a dearth of information and evidence on potentially high-yield approaches, such as screening of first-degree relatives of RHD patients, to identify asymptomatic and early-stage RHD patients who may benefit from penicillin prophylaxis.*

The only known treatment is penicillin therapy, which helps prevent further damage to the heart by repeated Group A Streptococcal (GAS) infection.[12] Benzathine penicillin G remains the mainstay of treatment to delay and prevent sequelae among ARF and RHD patients by preventing repeat GAS infections.[13] It is a cheap, safe, effective and proven means to improve the clinical outcomes in ARF and RHD patients.[14] However, a major obstacle exists to the optimal utilization of this penicillin prophylaxis largely because RHD is initially asymptomatic.[10] Therefore, only a fraction of those who would benefit receive penicillin prophylaxis treatment. Identifying individuals at elevated risk is of great public health importance in LMICs.[9] Furthermore, RHD is endemic in Nepal.[15] Nepal has a national level Benzathine penicillin prophylaxis (BPP) program, where all RHD patients can receive BPP free of charge.[16] Because of its endemicity and the national commitment to RHD treatment, Nepal is an ideal place to study RHD.

This study examines the prevalence of RHD among first degree relatives of RHD patients. We compared RHD prevalence among first degree relatives (FDR) of index RHD cases to screened school-age children, which is the most common RHD screening practice in Nepal. The difference between prevalence will help to highlight the importance of considering first-degree relatives as a high-risk group and incorporating them in national screening programs for RHD. We will also examine whether specific RHD patient characteristics, such as sex, age, or socioeconomic (SES) factors modify the chances for family member to have RHD. The overarching goal of this study is to determine whether FDR are an appropriate population for RHD screening in Nepal allowing opportunity for timely prevention. This study could provide a base for further studies to be conducted that could explore the opportunities and challenges of incorporating the screening approach for FDRs in Nepal. Ultimately, this may guide the development of a screening model that may be replicable in other RHD endemic settings.

## Methods

### Study design and setting

This observational study was cross-sectional in design. This study was a component of the University of Washington– Dhulikhel Hospital Kathamndu University Hospital joint UW-Nepal study set at two tertiary care centers in Nepal: Manmohan Cardiothoracic, Vascular and Transplant Center and Dhulikhel Hospital. RHD cases were selected from a comprehensive electronic RHD registry of 2348 RHD patients from these two sites in Kathmandu, Nepal, that was created from August 2018.

### Study subjects

The study subjects were leveraged from the joint UW-Nepal study to assess the feasibility of screening first degree relatives for RHD. The original study had sampled 128 cases from the RHD registry of 2348 cases at between November 2019 – July 2020. Of these 128 index cases, 102 consented to participate and recruited a total of 234 their FDRs to be enrolled in the study. All underwent RHD screening. Thus, the present study included a total of 102 index cases and 234 FDRs.

### Exposure

The exposures of interest were age of index cases, sex of index cases, and SES deprivation score of RHD index case. Age is evaluated as a continuous variable and sex as a binary variable (male/female). The SES deprivation score was derived from socio-economic factors of the index case such as type of cooking fuel, lack of access to improved drinking water, lack of access to electricity, status of roof and floor in house, lack of asset ownership, presence of child mortality in the family, inadequate years of schooling and lack of school attendance of household members. All socio-economic factors were self-reported by the index cases in response to questions that provided binary options for answers – yes or no.

The description of the eight SES deprivation indicators for the index case were as follow: 1)Type of cooking fuel indicated deprivation if the household of the index case cooks with any of the following fuel - dung, wood, or charcoal; 2) Lack of improved drinking water evaluated if the

household does not have access to improved/safe drinking water in a 30-minute roundtrip walk from home of the index case; 3) Lack of access to electricity; 4) Status of flooring and roofing indicated deprivation if the household has either dirt, sand, or dung on the floor or if the roof is made of thatch/palm leaf, sod, rustic mat, wood planks; 5) Lack of asset ownership estimated if the household does not own at least two of these assets: radio, TV, telephone, bicycle, motorbike, or refrigerator, and does not own a car or truck; 6) Child mortality determined if there had been a child who died in the index case's household in the five years preceding the survey; 7) Years of schooling assessed if any household member aged 10 years or older of the index case has not completed 5 years of schooling; 8) School attendance assessed if any school-aged child in the index case's household is not attending school up to the age at which they would complete grade 8. We created the SES deprivation score from the responses to these eight questions asked to assess their socio-economic status. The SES deprivation score was a continuous variable with every 'yes' answered for the questions evaluating SES increasing the score with a possible range from 0-8.

**Outcome**

We compared the RHD status among FDRs to other RHD screening studies in Nepal. The RHD status of FDRs were determined through echocardiography. The echocardiograms were obtained by Nepalese cardiologists at the two study sites collected from November 2019 to July 2020 (date). The studies were then transferred to the UW for review. A committee of cardiologists and echo sonographers at the UW adjudicated the outcome using the World Heart Federation (WHF) criteria for echocardiographic diagnosis of RHD.[17] Each FDR was assessed to have either (i) no evidence of RHD, (ii) borderline evidence, or (iii) definite evidence of RHD as defined by the WHF.

The outcome of interest was defined as the **index case** with at least one FDR with WHF-defined borderline or definite evidence of RHD. We examined these cases to determine if specific RHD patient characteristics, such as sex, age, SES factors or family history of having RHD, modify the chances for FDRs to have RHD. Furthermore, we considered a secondary analysis to evaluate the associations between index case characteristics and RHD status of FDRs as the outcome to take the correlation of a group of FDRs with a single index case into account.

**Covariates**

We *a priori* defined a limited set of confounding variables for adjustment in models. While estimating the association between the exposures and RHD status of index case with at least one FDR with WHF-defined borderline/definite RHD, we adjusted for age and sex of index case. Other demographic variables that were assessed descriptively were:

a) Ethnicity (5 categories – Brahmin/Chettri, Madhesi, Dalits, Janajati, Muslim); b) Education (5 categories – no education, Informal education, Basic education, Secondary education, More than secondary education); c) Occupation (6 categories - Professional/technical, clerical, sales and services, skilled labour, unskilled labour, and agriculture); and d) Religion (5 categories – Hindu, Buddhist, Muslim, Kirat, Christian). We also created descriptive statistics for the following

variables: e) history of prior RHD related hospital admission; f) Mode of diagnosis of RHD (whether the RHD was diagnosed in index case incidentally or symptomatically); g) BPP status (signifies whether the RHD index case is on BPP for secondary prophylaxis); and h) Family history of RHD. The following clinical variables were also obtained at time of echocardiographic screening of index cases and available as continuous variables: i) body mass index (BMI); j) heart rate; k) systolic blood pressure; and l) diastolic blood pressure. We also assessed some FDR characteristics such as: m) sex of FDR (binary variable - male and female) n) age of FDR (continuous variable) o) familial relationship of case and FDR (3 categories: Parent-Child, Child-Parent, Sibling-Sibling.)

**Data collection and steps to assure data quality**

The EPIQ echocardiographic ultrasound platform was used by trained cardiologists in Nepal to determine the outcome, i.e. RHD status of FDRs. Data on the remaining exposure variables – age, sex, and other covariates - were collected through questionnaires administered to index cases by trained research assistants in Nepal as part of enrollment into the RHD registry. Covariate information on FDRs was obtained as part of the screening study on the day of enrollment. In order to ensure data quality, the results found by echocardiogram screenings in Nepal were sent to UW for final clinical verification and adjudication. The necessary edition and cross checking was done immediately after data collection. Data were cleaned, recoded and analyzed through R studio Version 1.4.1717.

**Statistical Analyses**

We calculated the prevalence of RHD among all first-degree relatives, those less than 40 years of age, and those less than 15 years of age, and compared it with other published prevalence rates of RHD in Nepal. Confidence intervals were constructed using robust variance estimators that took into account the correlation of each group of FDRs with their index case. The proportion and confidence intervals of the borderline or definite RHD were presented from the studies.

We used multi-variable adjusted logistic regression with robust standard errors to evaluate whether index case characteristics were associated with the outcome of an index case having at least one FDR with ‘borderline or definite RHD.’ Results were presented as odds ratios (OR) with 95% confidence intervals. We estimated the effects of the factors of interest (age of index case, sex of index case, SES deprivation score and family history of RHD), while controlling for age of index case and sex of index case as confounders in our models, using logistic regression. Additionally, we have provided a supplemental table that adjusted for SES deprivation score and family history of having RHD along with sex and age of index cases. The general form of the multi-variable adjusted logistic model is given by: $\text{Logit}(p)=\alpha + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \ldots$, where $p = 0..05$, $\alpha = 95\%$, $\beta = 20\%$ i.e. power of the study was 80% and $x_1$ is exposure variables (age, sex, SES deprivation score or family history of RHD); $x_2$ and $x_3$ and sex and age of index cases while calculating the estimate for SES deprivation score and family history of RHD.

Furthermore, we created an analytic model for the secondary analysis using Generalized Estimating Equations (GEE) with an independent working correlation and robust standard errors. This model evaluated whether index case characteristics were associated with RHD status of FDRs after adjusting for age of FDRs, sex of FDRs and familial relationship of FDRs as confounders. While adjusting FDR characteristics, GEE had to be applied to take into account the correlation of each group of FDRs with their index case as the data was comprised of groups of one or more FDRs per index case.

We exponentially transformed the estimates obtained through logit in natural log scale. By applying the exponential transformation, we transformed the data back to its original scale to facilitate a more intuitive interpretation.

**Results**

There were a total of 102 index cases who had invited 234 FDRs for the screening. The mean age of the index cases and their first-degree were 29.6 and 29.0, respectively (Table 1). 73.5% of index cases and 57.7% of FDRs were female. The study participants were predominantly of Brahmin/Chettri orJanajatis ethnicity (Table 1). 72.5% of index cases and 66.2% of FDRs were Hindus. One-third of the index cases had completed up to higher secondary education and 42.3% of the FDRs had completed basic education to grade 8. Since almost three fourth of index cases were female, the majority of the proportion of occupation for index cases was homemaker (36.3%), owing to the gender roles prevalent in Nepal.

In theory, the SES deprivation score could have ranged from 0 (no SES deprivation indicators) to 8 (all SES deprivation indicators present). However, in our dataset, no individual had more than five SES deprivation indicators. Thus, the SES deprivation score ranged from 0 to 5 with a median score of 1, mean score of 1.4 and standard deviation of 1.44. 89.2% of the index cases were diagnosed symptomatically and only 9.8% were diagnosed incidentally. 90.2% were on BPP prophylaxis through injection. 47.1% of the index cases reported being admitted to a hospital due to RHD. 85.2% of the index cases reported not having a family history of RHD, whereas 6% index cases reported having a family history of RHD. The descriptive assessment of the socio-demographic variables stratified by two categories of index cases and FDRs – index cases with at least one FDR with borderline or definite RHD and index cases without any FDR with RHD; FDRs with borderline or definite RHD and FDR without any RHD is present in Supplementary Table 1.

The prevalence of borderline or definite RHD was 8.1% among all 234 FDRs (Table 2). Because the goal of treatment is to identify those with clinically unrecognized RHD who might benefit from antibiotic treatment, we restricted the analyses to those FDRs younger than 40 years of age. Among these 173 FDRs, 11% had borderline or definite RHD. By contrast, none of FDRs 40 years or older had any evidence of RHD.

The prevalence of borderline or definite RHD among FDRs less than or equal to 15 years of age from this study was compared with seven RHD prevalence studies done in Nepal (Supplemental

Table 2). The prevalence of RHD among FDRs less than or equal to 15 years is 19.4% (95% CI: 10.8% - 31.7%). Taking the correlation of a group of FDRs with their index cases, the confidence intervals of the proportion of RHD among FDRs was 19.4% (95% CI: 11.5% - 30.6%). The seven other prevalence studies done in Nepal had screened school children with the age range of 5-18 years. Four out of the seven studies followed the WHF criteria for stratifying RHD[5,15,18,19], while one of the studies used Australian RHD guidelines 2012, which still consisted of stratifying RHD into borderline and definite.[20] The other two studies also did not use WHF criteria and presented prevalence of RHD without stratifying into borderline and definite.[21,22] The cumulative prevalence of borderline or definite RHD in a study by Shrestha et al. that screened through World Heart Federation (WHF) criteria through echocardiogram was 1.06%[5,18] and in three different studies screened through auscultation followed by echocardiogram was 0.1%, 1% and 3.7 %.[5,19,23] Whereas the prevalence of RHD was 0.09% in a study that implied World Health Organization (WHO) Echocardiography criteria for RHD 2005 and screened through auscultation followed by echocardiogram.[21] In another study that screened only through echocardiogram based on the Australian RHD guidelines 2012, the prevalence of borderline or definite RHD was 0.73%.[20] Furthermore, the prevalence of RHD was 0.3% in another study that used rapid antigen detection followed by echocardiogram screening.[22] The prevalence of borderline or definite RHD when index case and FDRs were siblings was 7.2% (Table 3). The prevalence of borderline or definite RHD among children with the mother as index cases was 17.74%. There was no prevalence of RHD among children and parents when the index cases were father and children respectively.

In a RHD screening study on FDRs done in Uganda, the prevalence of borderline or definite RHD was 12.8% when the index case and the FDR were siblings and 6.1% when child was the index case and mother the FDR (Supplemental Table 3).[11] There was no prevalence of RHD among the father when the child was an index case in that study, similar to the findings in our study. None of the FDRs included in that study were children.[11]

At least one of the symptoms of RHD and RF (arthritis, carditis, chorea, erythema marginatum, dyspnea, lower extremity edema, heart palpitation, weakness, sore throat) was present in 94.4% of index cases with at least one FDR with borderline or definite RHD (Supplemental Table 4). Similarly, 89.3% of index cases with none of the FDRs with RHD had at least one symptom of RHD and RF. Furthermore, 47.4% of the FDRs with borderline or definite RHD had at least one of the symptoms.

In our dataset, the 19 FDRs with borderline or definite RHD were related to 18 separate index cases (Table 4). The remainder of the of the 215 FDRs were related to 84 index cases. Thus, we examined the outcome of any index case with at least one FDR with WHF-defined borderline/definite RHD (n=18) vs. all other index cases (n=84) (Table 4). There was no association of age or SES with likelihood of index case having an FDR with RHD. There was a suggestion that female index cases had a 2-fold higher odds of having an FDR with borderline or definite RHD compared with male cases but the confidence interval was wide (95% CI: 0.53-7.53) and the association was not significant. Similarly, index cases with a family history of RHD tended to have a five-fold higher odds of having at least one FDR with borderline or definite

RHD (OR: 5.4 95% CI: 0.99 – 29.33) compared to index cases who do not have family history of RHD, however the confidence interval was wide due to small numbers of those with a positive family history. We also calculated the estimate using the mid-p method to address the small cell size in the family history of RHD, which would provide even wider confidence intervals.[24] Using this method, the odds of index cases with family history of RHD having at least one FDR with borderline or definite RHD was 5.27 times (95% CI: 0.84 – 33.33) compared to index cases who do not have family history of RHD. The association was not significant.

For our secondary analysis, we adjusted for sex and age of FDR, assessing the relationship between case and FDR, along with age and sex of index cases through GEE which addressed the correlation that exists between different FDR groups with an index case (Supplemental Table 7). For the secondary analysis we considered the RHD status of FDRs as the outcome (19 FDRs with borderline or definite RHD vs 215 FDRs without RHD). The association between sex of index case, age of index case and SES deprivation score was not significantly associated with the FDRs having RHD. However, there was a suggestion in the data that family history of RHD in index cases was associated with the RHD status of their FDRs, although the cell sizes were small. We estimate that the odds of index cases with family history of RHD having FDRs with borderline or definite RHD is 4.34 times (95% CI: 0.99 – 29.33) compared to index cases without family history of RHD. We also calculated the estimates after adjusting for SES deprivation score and family history along with age and sex of index case and FDRs using GEE (Supplemental Table 8). However, none of the exposure variables were significantly associated with their FDR having borderline or definite RHD.

**Discussion**

This is a unique study conducted to explore the association between characteristics of index cases and the odds of RHD in first-degree relatives in Nepal. 17.6% of index cases had at least one FDR with borderline or definite RHD. This indicates that screening FDRs of index cases is a high yield screening method. The majority of the index cases were female as well as the index cases who had at least one FDR with RHD. Moreover, the majority of the FDRs who were screened and who had borderline or definite RHD were also female. This finding is consistent with findings from other RHD studies that reported higher prevalence of RHD among females than males.[5,6] The Brahmin/Chettri and Janajati were most common ethnicities owing to their large population around cities where the two tertiary sites in Nepal were located. Almost 9 out 10 of the index cases in the registry had been diagnosed symptomatically. This indicates that more effective and high-yielding screening methods need to be in place so that incidental diagnosis may be ascertained. All of the FDRs in the study who had borderline or definite RHD were less than 40 years old. The prevalence of borderline or definite RHD amongst FDRs in the study was 11% which suggests that FDR screening could result in even higher yield among younger populations. Because those who have RHD for longer are more likely to be symptomatic, the younger population may have higher prevalence of having asymptomatic RHD and should be screened.

These results indicate that screening FDRs of index cases for RHD is a high-yield screening

method. Among all the FDRs screened in the study, only FDRs below 40 years of age had RHD. The proportion of RHD among FDRs less than 40 years was 11% in this study. Screening FDRs is a high yield as compared to other screening studies done in Nepal, which have screened school children. The range of prevalence of RHD from other screening studies done in school children in Nepal ranged from 0.09% - 3.7%. The prevalence of RHD among FDRs less than 15 years of age in this study was 19.4% (CI: 10.8% - 31.7%). When taking into account the correlation of different FDRs to a single index case, the CI for the prevalence is narrower at 11.5% - 30.6%. The high prevalence of RHD among FDRs of comparable age to other screening studies done in Nepal shows that screening FDRs of an index case is an extremely high-yielding screening method.

This study looked at the familial relation between cases and FDRs with borderline or definite RHD. There was a 7.2% prevalence of borderline or definite RHD among siblings of index cases. In a RHD screening study conducted in Uganda that screened FDRs of school children, siblings represented a particularly high-risk group that could be targeted for echocardiographic screening as the prevalence of RHD in siblings of index cases was 12.8% ($n_{screened} = 156$).[11] None of the children who were index cases had any parents with RHD in our study. Similarly, none of the fathers of index cases had RHD in the screening study done in Uganda.[11] 6.1% of index casers' mothers had RHD in the Ugandan study ($n_{screened} = 50$).[11] Since, the Ugandan study was a school-based screening, it did not have children as FDR. In our study, children of index mothers had 17.74% of borderline or definite RHD and none of the children of index fathers had RHD. However, we do not interpret that having a female index parent has a higher risk of having a child with borderline or definite RHD as our study is underpowered due to small sample size.

For both crude and adjusted associations with age and sex of index case, none of the exposure – sex, age, family history of RHD and SES deprivation score of index cases had a statistically significant association with their FDR having borderline or definite RHD. Thus, we do not have enough evidence to reject that age, sex, SES deprivation score and family history of RHD are not associated with having at least one FDR who have borderline or definite RHD. Although, the association was statistically non-significant, the odds of the female index cases having at least one FDR with borderline or definite RHD was 1.89 (CI: (0.49 – 7.37) times higher than male index cases adjusting for age. Previous literature has shown that the prevalence of RHD is higher among women than men.[5,6] The odds of index cases with family history of RHD was also higher compared to index cases without family history of RHD (OR = 5.4; 95% CI: 0.99 – 29.33) in our study. This is consistent with findings from other studies that have shown higher risk of RHD amongst FDRs of RHD cases compared to non-cases.[11,25,26] Moreover, in our secondary analysis which had the RHD status of the FDRs as the outcome, an index case having a family history of RHD was associated with their FDRs having borderline or definite RHD. However, the interpretation of this result should be taken with caution as the cell sizes were small as only six index cases who had a family history of RHD were found. Adjusted for sex, the odds of having at least one FDR with borderline or definite RHD for every unit increase in age was the same (OR = 1.00; 95% CI = 0.96 – 1.07). Although not significant, the odds of having at least one FDR with borderline or definite RHD decreased with every unit increase in SES deprivation

score (OR adjusted with age and sex = 0.91 ;  95% CI: 0.62 – 1.33). In contrast to the literature suggesting that socio-economic status may be a risk factor for RHD[8,9], this study found no association of SES conferring additional risk for FDRs. However, the SES deprivation was based on only eight variables related to cooking fuel, access to improved drinking water, access to electricity, status of roof and floor in house, asset ownership, child mortality in the family, years of schooling and school attendance of household members. Future studies should include other evaluation metrics for SES to assess and compare the association between SES and RHD outcome.

**Limitations**

Several limitations deserve consideration in our findings.  Selection bias was a limitation as our index cases were accessed in a tertiary care center in Nepal, which may indicate relatively more severe cases. Thus, the interpretation of the results for associations between index case characteristics and their FDRs having RHD should be viewed cautiously regarding generalizability in a community setting. On average, we had 2.3 FDRs for each index case resulting in most FDRs for each index patient not being examined. Selection bias of which FDRs were screened could have influenced these associations. For example, if index cases preferentially brought family members for screening who had health concerns suggestive of RHD, it may have led to spuriously higher rates of RHD among FDRs.  Conversely, if difficulty of travel allowed only healthier FDRs to make the trip for the screening, then the true association would be attenuated. Moreover, information regarding family size was not collected to determine the total number of FDRs per index case. The socio-economic status variables were self-reported and may be subjected to non-differential misclassification due to social desirability bias. Moreover, missing data was not imputed. Because we were limited by small sample size, it was not possible to conduct tests for effect modification despite having multiple co-variates (sex of FDRs, age of FDRs, familial relation between case and FDR, BMI, BP, Heart rate, mode of diagnosis) that could potentially interact with the exposure to have significantly differential outcome across various strata. Also, due to small size of the cells, we adjusted only for age and sex of index cases. We did not adjust for additional confounders such as age of FDR, sex of FDR, familial relationship between case and FDR, though these seem like potential confounders. Finally, , due to the cross-sectional nature of the study, we are not able to draw causal inference between the patient characteristics and the RHD status of their FDRs and we can only provide the estimates of their associations.

**Conclusion**

Screening FDRs is a high yield screening method. Our study suggested that all FDRs need to be screened. Although, the index case characteristics in this study were not associated with having at least one FDR with borderline or definite RHD, further FDR screening studies with larger sample sizes should be done to examine the associations between the index case characteristics and FDRs having RHD. Moreover, if screening FDR can be incorporated into the national RHD screening strategy of a RHD endemic country like Nepal, it can identify

asymptomatic and early-stage RHD patients who would benefit from the national prophylactic program of Benzathine penicillin prophylaxis. Implementation of similar screening models, coupled with prophylactic programs in other RHD endemic low resource settings like Nepal, may ultimately have an impact on the global RHD landscape.

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**Tables**

**Table 1: Characteristic of index cases and First-degree relatives (FDRs)**

| | **Index cases (n = 102)** | **FDR (n= 234)** |
|---|---|---|
| **Tertiary care centre in Nepal** | | |
| Dhulikhel Hospital | 36 (35.29) | 93 (39.74) |
| MCVTC | 66 (64.71) | 141 (60.26) |
| **Age** | | |
| Mean (SD) | 29.6 (9.89) | 29.0 (16.9) |
| Median [Min, Max] | 30 [10, 63] | 27 [5, 80] |
| **Sex** | | |
| Female | 75 (73.5%) | 135 (57.7%) |
| **ethnicity** | | |
| Brahmin/Chettri | 50 (49.0%) | 81 (34.6%) |
| Dalit | 1 (1.0%) | 2 (0.9%) |
| Janajati | 46 (45.1%) | 132 (56.4%) |
| Madhesi | 0 (0%) | 0 (0%) |
| Muslim | 1 (1.0%) | 4 (1.7%) |
| Others | 4 (3.9%) | 2 (0.9%) |
| Missing | 0 (0%) | 13 (5.6%) |
| **religion** | | |
| Buddhism | 26 (25.5%) | 58 (24.8%) |
| Christianity | 1 (1.0%) | 4 (1.7%) |
| Hindu | 74 (72.5%) | 155 (66.2%) |
| Muslim | 1 (1.0%) | 3 (1.3%) |
| others | 0 (0%) | 2 (0.9%) |
| Missing | 0 (0%) | 12 (5.1%) |
| **Level of education** | | |
| No education | 10 (9.8%) | 23 (9.8%) |
| Basic (1-8) | 22 (21.6%) | 99 (42.3%) |
| Secondary (9-12) | 30 (29.4%) | 67 (28.6%) |
| More than secondary (Higher than 12) | 34 (33.3%) | 26 (11.1%) |
| Informal education | 6 (5.9%) | 12 (5.1%) |
| Missing | | 7 (3.0%) |
| **occupation** | | |
| agriculture | 1 (1.0%) | 27 (11.5%) |

| | | |
|---|---|---|
| home-maker | 37 (36.3%) | 50 (21.4%) |
| gov employee | 5 (4.9%) | 8 (3.4%) |
| non-gov employee | 12 (11.8%) | 18 (7.7%) |
| self-employed | 23 (22.5%) | 26 (11.1%) |
| student | 21 (20.6%) | 90 (38.5%) |
| unemployed | 3 (2.9%) | 1 (0.4%) |
| retired | 0 (0%) | 5 (2.1%) |
| migrant worker | 0 (0%) | 2 (0.9%) |
| Missing | 0 (0%) | 7 (3.0%) |
| **SES deprivation** | | |
| Household cooks with word or charcoal | 33 (32.4%) | - |
| No access to drinking water | 5 (4.9%) | - |
| No electricity | 2 (2.0%) | - |
| Poor condition of roof and floor | 30 (29.4%) | - |
| No ownership of more than one asset | 13 (12.7%) | - |
| Household members of 10 years and above not completing five years of schooling | 52 (51.0%) | - |
| school-aged child in the household is not attending school up to the age at which they would complete grade 8. | 5 (4.9%) | - |
| Child mortality in last 5 years in household | 3 (2.9%) | - |
| **SES_score** | | |
| Mean (SD) | 1.40 (1.44) | - |
| Median [Min, Max] | 1.00 [0, 5.00] | - |
| **Mode of RHD diagnosis** | | |
| incidental | 10 (9.8%) | - |
| symptomatic | 91 (89.2%) | - |
| Missing | 1 (1.0%) | |
| **On BPP prophylaxis** | 101 (99.0%) | - |
| **Mode of administration of BPP** | | |
| Injection | 92 (90.2%) | - |

| | | |
|---|---|---|
| Pills | 9 (8.8%) | - |
| Missing | 1 (1.0%) | - |
| **Ever been admitted in hospital due to RHD** | 48 (47.1%) | - |
| **Family history of RHD** | | - |
| Yes | 6 (5.9%) | - |
| No | 87 (85.2%) | - |
| Unknown | 8 (7.84%) | - |
| Missing | 1 (0.01%) | - |
| **BMI (Mean, SD)** | 23.8 (4.73) | 21.5 (13.5) |
| **Heart rate** | 79.5 (11.8) | 82.2 (46.8) |
| **Systolic blood pressure** | 109 (12.2) | 116 (12.8) |
| **Diastolic blood pressure** | 73.4 (8.94) | 75.2 (15.0) |

**Table 2: Proportion of FDRs with evidence of RHD on echocardiogram screening**

| Age group of FDR | FDR without RHD | FDR with borderline or definite | Proportion of outcome with 95% CI (uncorrelated) | FDR with definite RHD (n = 8) | Proportion of outcome with 95% CI (uncorrelated) |
|---|---|---|---|---|---|
| Overall (n = 234) | 215 | 19 | 0.081 (0.051-0.126) | 8 | 0.034(0.016-0.069) |
| Less than 40 years (n = 173) | 154 | 19 | 0.110 (0.070 – 0.168) | 8 | 0.046 (0.022-0.092) |
| 40 years or older (n = 61) | 61 | 0 | 0 (0.00 – 0.074) | 0 | 0 (0.00 – 0.074) |

**Table 3: Proportion of FDRs who screened positive for RHD stratified by familial relationships of cases and FDRs**

| Case-FDR relationships | Number of FDRs in the study (n) | Number of FDRs with borderline or definite RHD | Proportion and CI of borderline or definite RHD (%) |
|---|---|---|---|
| Child-parent | 52 | 0 | 0 (0 – 8.57) |
| Sibling – sibling | 111 | 8 | 7.2 (3.39 – 14.14) |
| Brother-brother | 8 | 1 | 12.5 (0.32 – 52.65) |
| Brother-sister | 7 | 1 | 14.29 (0.36 – 57.87) |
| Sister-brother | 35 | 3 | 8.57 (2.24 – 24.19) |
| Sister-sister | 61 | 3 | 4.91 (1.28 – 14.60) |
| Parent-child | 71 | 11 | 15.49 (8.35 – 26.46) |
| Mother-child | 62 | 11 | 17.74 (9.60 - 29.95) |
| Father-child | 9 | 0 | 0 (0.00 – 33.63) |

*Note: First value of the relation is case and the relation following the '-' is of the FDR

**Table 4: Association of index case characteristics with having FDR with RHD**

| | **Index cases who FDR have borderline or definite RHD (n =18)** | **Index cases whose FDR do not have RHD (n = 84)** | **Crude odds ratio for index cases whose FDR has borderline or definite RHD (95%CI)** | **OR after adjusting for sex and age of index cases (95%CI)** |
|---|---|---|---|---|
| Sex of index case (female vs male) | | | | |
| Male | 3 (16.7%) | 24 (28.6%) | 1 (Reference) | 1 (Reference) |
| Female | 15 (83.3%) | 60 (71.4%) | 2.0 (0.53 – 7.53) | 1.89 (0.49 – 7.37) |
| Age of index case as continuous variable | - | - | 1.02 (0.97 – 1.07) | 1.00 (0.96 – 1.07) |
| SES deprivation score as continuos variable | - | - | 0.89 (0.62 – 1.30) | 0.91 (0.62 – 1.33) |
| Family history of RHD | | | | |
| No | 15 (83.3%) | 81 (96.4%) | 1 (Reference) | 1 (Reference) |
| Yes | 3 (16.7%) | 3 (3.6%) | 5.40 (0.99 – 29.33) | 4.90 (0.87 – 27.47) |

**Supplemental Tables**

**Supplemental Table 1: Characteristics of index cases and FDRs according to their RHD status**

| | Index cases (n = 102) | Index cases with borderline or definite RHD FDR (n = 18) | Index case whose FDR do not have RHD (n= 84) | FDR (n= 234) | FDR with borderline or definite RHD (n = 19) | FDR without RHD (n = 215) |
|---|---|---|---|---|---|---|
| **Tertiary care centre in Nepal** | | | | | | |
| Dhulikhel Hospital | 36 (35.29) | 5 (27.77) | 31 (36.90) | 93 (39.74) | 5 (26.31) | 88 (40.93) |
| MCVTC | 66 (64.71) | 13 (72.23) | 53 (73.10) | 141 (60.26) | 14 (73.69) | 127 (59.07) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Age** | | | | | | |
| Mean (SD) | 29.6 (9.89) | 30.8 (9.44) | 29.3 (10.0) | 29.0 (16.9) | 16.1 (8.01) | 30.2 (17.0) |
| Median [Min, Max] | 30 [10, 64] | 32 [12, 48] | 30 [10, 63] | 27.0 [5.00, 80.0] | 13.0 [7.00, 35.0] | 28.0 [5.00, 80.0] |
| | | | | | | |
| **Sex** | | | | | | |
| Male | 27 (26.5%) | 3 (16.7%) | 24 (28.6%) | 99 (42.3%) | 8 (42.1%) | 91 (42.3%) |
| Female | 75 (73.5%) | 15 (83.3%) | 60 (71.4%) | 135 (57.7%) | 11 (57.9%) | 124 (57.7%) |
| **ethnicity** | | | | | | |
| Brahmin/Chettri | 50 (49.0%) | 9 (50.0%) | 41 (48.8%) | 81 (34.6%) | 8 (42.1%) | 73 (34.0%) |
| Dalit | 1 (1.0%) | 0 (0%) | 1 (1.2%) | 2 (0.9%) | 1 (5.3%) | 1 (0.5%) |
| Janajati | 46 (45.1%) | 9 50.0%) | 37 (44.0%) | 132 (56.4%) | 7 (36.8%) | 125 (58.1%) |
| Madhesi | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Muslim | 1 (1.0%) | 0 (0%) | 1 (1.2%) | 4 (1.7%) | 0 (0%) | 4 (1.9%) |
| Others | 4 (3.9%) | 0 (0%) | 4 (4.8%) | 2 (0.9%) | 0 (0%) | 2 (0.9%) |
| Missing | | | | 13 (5.6%) | 3 (15.8%) | 10 (4.7%) |
| **religion** | | | | | | |
| Buddhism | 26 (25.5%) | 4 (22.2%) | 22 (26.2%) | 58 (24.8%) | 2 (10.5%) | 56 (26.0%) |
| Christianity | 1 (1.0%) | 0 (0%) | 1 (1.2%) | 4 (1.7%) | 0 (0%) | 4 (1.9%) |
| Hindu | 74 (72.5%) | 14 (77.8%) | 60 (71.4%) | 155 (66.2%) | 14 (73.7%) | 141 (65.6%) |
| Muslim | 1 (1.0%) | 0 (0%) | 1 (1.2%) | 3 (1.3%) | 0 (0%) | 3 (1.4%) |
| others | 0 (0%) | 0 (0%) | 0 (0%) | 2 (0.9%) | 0 (0%) | 2 (0.9%) |
| Missing | 0 (0%) | 0 (0%) | 0 (0%) | 12 (5.1%) | 3 (15.8%) | 9 (4.2%) |
| **Level of education** | | | | | | |
| No education | 10 (9.8%) | 2 (11.1%) | 8 (9.5%) | 23 (9.8%) | 1 (5.3%) | 22 (10.2%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Basic (1-8) | 22 (21.6%) | 2 (11.1%) | 20 (23.8%) | 99 (42.3%) | 12 (63.2%) | 87 (40.5%) |
| Secondary (9-12) | 30 (29.4%) | 8 (44.4%) | 22 (26.2%) | 67 (28.6%) | 4 (21.1%) | 63 (29.3%) |
| More than secondary (Higher than 12) | 34 (33.3%) | 5 (27.8%) | 29 (34.5%) | 26 (11.1%) | 0 (0%) | 26 (12.1%) |
| Informal education | 6 (5.9%) | 1 (5.6%) | 5 (6.0%) | 12 (5.1%) | 1 (5.3%) | 11 (5.1%) |
| Missing | | | | 7 (3.0%) | 1 (5.3%) | 6 (2.8%) |
| **occupation** | | | | | | |
| agriculture | 1 (1.0%) | 0 (0%) | 1 (1.2%) | 27 (11.5%) | 1 (5.3%) | 26 (12.1%) |
| home-maker | 37 (36.3%) | 9 (50.0%) | 28 (33.3%) | 50 (21.4%) | 3 (15.8%) | 47 (21.9%) |
| gov employee | 5 (4.9%) | 2 (11.1%) | 3 (3.6%) | 8 (3.4%) | 1 (5.3%) | 7 (3.3%) |
| non-gov employee | 12 (11.8%) | 1 (5.6%) | 11 (13.1%) | 18 (7.7%) | 0 (0%) | 18 (8.4%) |
| self-employed | 23 (22.5%) | 3 (16.7%) | 20 (23.8%) | 26 (11.1%) | 1 (5.3%) | 25 (11.6%) |
| student | 21 (20.6%) | 3 (16.7%) | 18 (21.4%) | 90 (38.5%) | 12 (63.2%) | 78 (36.3%) |
| unemployed | 3 (2.9%) | 0 (0%) | 3 (3.6%) | 1 (0.4%) | 0 (0%) | 1 (0.5%) |
| retired | 0 (0%) | 0 (0%) | 0 (0%) | 5 (2.1%) | 0 (0%) | 5 (2.3%) |
| migrant worker | 0 (0%) | 0 (0%) | 0 (0%) | 2 (0.9%) | 0 (0%) | 2 (0.9%) |
| Missing | 0 (0%) | 0 (0%) | 0 (0%) | 7 (3.0%) | 1 (5.3%) | 6 (2.8%) |
| **SES deprivation score** | | | | | | |
| **Cooking fuel** | | | | | | |
| no | 69 (67.6%) | 13 (72.2%) | 56 (66.7%) | - | - | - |
| yes | 33 (32.4%) | 5 (27.8%) | 28 (33.3%) | - | - | - |
| **Drinking water** | | | | | | |
| no | 97 (95.1%) | 17 (94.4%) | 80 (95.2%) | - | - | - |
| yes | 5 (4.9%) | 1 (5.6%) | 4 (4.8%) | - | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| **electricity** | | | | | | |
| no | 100 (98.0%) | 18 (100%) | 82 (97.6%) | - | - | - |
| yes | 2 (2.0%) | 0 (0%) | 2 (2.4%) | - | - | - |
| **Floor and roof** | | | | | | |
| no | 72 (70.6%) | 14 (77.8%) | 58 (69.0%) | - | - | - |
| yes | 30 (29.4%) | 4 (22.2%) | 26 (31.0%) | - | - | - |
| **Asset ownership** | | | | | | |
| no | 89 (87.3%) | 15 (83.3%) | 74 (88.1%) | - | - | - |
| yes | 13 (12.7%) | 3 (16.7%) | 10 (11.9%) | - | - | - |
| **years_of_schooling** | | | | | | |
| no | 50 (49.0%) | 9 (50.0%) | 41 (48.8%) | - | - | - |
| yes | 52 (51.0%) | 9 (50.0%) | 43 (51.2%) | - | - | - |
| **school_attendance** | | | | | | |
| no | 97 (95.1%) | 18 (100%) | 79 (94.0%) | - | - | - |
| yes | 5 (4.9%) | 0 (0%) | 5 (6.0%) | - | - | - |
| **child_mortality_** | | | | | | |
| no | 99 (97.1%) | 18 (100%) | 81 (96.4%) | - | - | - |
| yes | 3 (2.9%) | 0 (0%) | 3 (3.6%) | - | - | - |
| **SES_score** | | | | | | |
| Mean (SD) | 1.40 (1.44) | 1.22 (1.35) | 1.44 (1.46) | - | - | - |
| Median [Min, Max] | 1.00 [0, 5.00] | 1.00 [0, 4.00] | 1.00 [0, 5.00] | - | - | - |
| **Mode of RHD diagnosis** | | | | | | |
| incidental | 10 (9.8%) | 1 (5.6%) | 9 (10.7%) | - | - | - |
| symptomatic | 91 (89.2%) | 16 (88.9%) | 75 (89.3%) | - | - | - |
| Missing | 1 (1.0%) | 1 (5.6%) | 0 (0%) | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **BPP prophylaxis status** | | | | | | |
| yes | 101 (99.0%) | 18 (100%) | 83 (98.8%) | - | - | - |
| no | 1 (1.0%) | 0 (0%) | 1 (1.2%) | - | - | - |
| **Mode of administration of BPP** | | | | | | |
| Injection | 92 (90.2%) | 17 (94.4%) | 75 (89.3%) | - | - | - |
| Pills | 9 (8.8%) | 1 (5.6%) | 8 (9.5%) | - | - | - |
| Missing | 1 (1.0%) | 0 (0%) | 1 (1.2%) | - | - | - |
| **Hospital admission due to RHD** | | | | | | |
| yes | 48 (47.1%) | 5 (27.8%) | 43 (51.2%) | - | - | - |
| no | 54 (52.9%) | 13 (72.2%) | 41 (48.8%) | - | - | - |
| **Family history of RHD** | | | | | | |
| yes | 6 (5.9%) | 3 (16.7%) | 3 (3.6%) | - | - | - |
| no | 87 (85.3%) | 12 (66.7%) | 75 (89.3%) | - | - | - |
| unknown | 8 (7.8%) | 3 (16.7%) | 5 (6.0%) | - | - | - |
| Missing | 1 (1.0%) | 0 (0%) | 1 (1.2%) | - | - | - |
| **BMI** | | | | | | |
| Mean (SD) | 23.8 (4.73) | 24.5 (4.03) | 23.6 (4.88) | 21.5 (13.5) | 18.1 (6.65) | 21.8 (13.9) |
| Median [Min, Max] | 23.6 [12.2, 37.3] | 23.4 [17.6, 33.7] | 23.6 [12.2, 37.3] | 21.6 [0, 166] | 18.7 [2.60, 32.1] | 21.8 [0, 166] |
| Missing | 2 (2.0%) | 0 (0%) | 2 (2.4%) | 4 (1.7%) | 0 (0%) | 4 (1.9%) |
| **HR** | | | | | | |
| Mean (SD) | 79.5 (11.8) | 78.4 (9.85) | 79.8 (12.2) | 82.2 (46.8) | 82.6 (22.3) | 82.1 (48.7) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Median [Min, Max] | 78.0 [60.0, 123] | 78.0 [60.0, 102] | 78.0 [60.0, 123] | 78.0 [0, 726] | 88.0 [0, 104] | 78.0 [0, 726] |
| Missing | 4 (3.9%) | 0 (0%) | 4 (4.8%) | 24 (10.3%) | 0 (0%) | 24 (11.2%) |
| **SBP** | | | | | | |
| Mean (SD) | 109 (12.2) | 111 (11.1) | 109 (12.5) | 116 (12.8) | 110 (10.5) | 117 (12.9) |
| Median [Min, Max] | 110 [80.0, 140] | 110 [90.0, 130] | 110 [80.0, 140] | 120 [78.0, 150] | 110 [79.0, 120] | 120 [78.0, 150] |
| Missing | 10 (9.8%) | 0 (0%) | 10 (11.9%) | 43 (18.4%) | 3 (15.8%) | 40 (18.6%) |
| **DBP** | | | | | | |
| Mean (SD) | 73.4 (8.94) | 75.0 (9.24) | 73.0 (8.89) | 75.2 (15.0) | 72.9 (20.2) | 75.4 (14.5) |
| Median [Min, Max] | 70.0 [60.0, 90.0] | 80.0 [60.0, 90.0] | 70.0 [60.0, 90.0] | 80.0 [0, 100] | 80.0 [0, 90.0] | 80.0 [0, 100] |
| Missing | 9 (8.8%) | 0 (0%) | 9 (10.7%) | 44 (18.8%) | 3 (15.8%) | 41 (19.1%) |

**Supplemental Table 2: Comparison of prevalence of RHD in FDRs of age group <30 with other published studies**

| Year of publicaton | Name of study | Range of age in years of participants | Screening method | Categorization of RHD (borderline vs defininte vs non-WHF) | Screening population | Location | Proportion of borderline or defnite RHD (95% CI) |
|---|---|---|---|---|---|---|---|
| | Overall FDRs in present study | 5-80 | Echocardiograph in tertiary care centre | Borderline and defininte | FDR of index case at tertiary care centre | Dhulikhel and Kathmandu | 0.081 (0.051-0.126) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Present study with uncorrelated CI | 5-15 | Echocardiograph in tertiary care centre | Borderline and defininte | FDR of index case at tertiary care centre | Dhulikhel and Kathmandu | 0.194 (0.108 – 0.317); correlated CIs: 0.194 (0.115 – 0.306)^ |
| 2021 | Nikesh R. Shrestha, Surendra Uranw et al. | 5-16 | echocardiogram | Borderline and defininte | Children in government and private schools | Sunsari (urban & rural) | 0.0106 (0.830 – 0.134) |
| 2019 | Shankar Laudari et al. | 5-16 | Auscultation followed by echocardiogram | Borderline and Definite | School children | Chitwan and Nawalparasi | 0.0259 (0.0191 – 0.0348)* |
| 2019 | Prakash Raj Regmi et al. | 5-16 | Echocardiogram | Non-WHF (Australian RHD guideline 2012) was used; categorization of definite and borderline still present | Children in government and private schools | Jajarkot (rural) | 0.0073 (0.0054 – 0.0099)* |
| 2016 | Nikesh R. Shrestha, Prahlad Karki et al. | 5-15 | Auscultation & echocardiogram | Borderline & definite | School children | *Sunsari* (84.5% rural vs 15.5% urban) | 0.0102 (0.0075 – 0.0130) |
| 2013 | Dipanker Prajapati et al. | 5-16 | auscultation & echocardiogram | World Health Organization's Echocardiograp | Children in governmen | *Kathmandu* and *Lalitpur* (both | 0.0009 (0.0006 – 0.0012)* |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | hy criteria for RHD in 2005 | t schoo ls | urban and rural; Kathma ndu and Lalitpur are districts with metropo litan cities | |
| 2012 | Nikesh R. Shrestha, Bindu Kalesan et al. | 5-15 | auscultati on & echocard iogram | Definite and borderline | Scho ol childr en | *Sunsari* (urban) | 0.0370 (0.0064 – 0.1384) |
| 2003 | KC Man Bahadur et al. | 5-18 | rapid antigen detection test followed by echocard iogram in children suspecte d of having RHD or history of RF | RF according to modified John's criteria and RHD according to non-WHF criteria (just mentions RHD without stratifying severity) | Childr en in gover nmen t schoo ls | *Kathma ndu, Lalitpur* and *Bhaktap ur* (all 3 districts have mostly urban and some rural areas) | 0.0030 (0.0008 – 0.0095)* |

^Taking correlation of multiple FDRs of a single index case into account

*CIs that were calculated as they were not presented in the study

**Supplemental Table 3: Comparison with Uganda study**

| RHD +ve categories (case-FDR) | Mean age of FDRs in Uganda study (SD) | RHD amongst screened FDRs of cases in Uganda study ($n_{total}$=235; $n_{child\text{-}mother}$ = 50; $n_{child\text{-}father}$ = 60; $n_{sibling\text{-}sibling}$ = 156 ) | Mean age of FDRs in present study (SD) | RHD among FDRs from present study [$n_{total}$=234; $n_{child\text{-}mother}$ = 31 ; $n_{child\text{-}father}$ = 21 ; $n_{sibling\text{-}sibling}$ = 111; $n_{parent\text{-}child}$ = 71 ($n_{father\text{-}child}$ = 9 ; $n_{mother\text{-}child}$ = 62)] |
|---|---|---|---|---|
| Total FDRs | | 23/235 (9.78%) | 29.01 (16.91) | 19/234 (8.11%) |
| Child-mother | 36.2 (6.48) | 3/50 (6.1%) | 49.51 (11.33) | 0/31 (0%) |
| Child-father | 44 (7.38) | 0/29 | 53.00 (11.86) | 0/21 (0%) |
| Sibling – sibling | 11.5 (4.63) | 20/156 (12.8%) | 28.34 (11.43) | 8/111 (7.2%) |
| Parent-child | - | - | 13.86 (7.20) | 11/71 (15.49%) |

*First relation is the case and the relation following the '-' is of the FDR

**Supplemental Table 4: Symptoms of RHD and RF in index cases and FDRs with borderline or definite RHD**

| S.No. | Index cases with FDR who have RHD (n = 18) | Index case with RHD -ve FDR (n= 84) | FDRs who have RHD (n = 19) |
|---|---|---|---|
| arthritis_recode | | | |
| yes | 11 (61.1%) | 55 (65.5%) | 2 (10.5%) |
| no | 7 (38.9%) | 29 (34.5%) | 17 (89.5%) |
| carditis_recode | | | |
| yes | 6 (33.3%) | 18 (21.4%) | 2 (10.5%) |
| no | 12 (66.7%) | 66 (78.6%) | 17 (89.5%) |
| chorea_recode | | | |
| yes | 2 (11.1%) | 16 (19.0%) | 1 (5.3%) |
| no | 16 (88.9%) | 68 (81.0%) | 18 (94.7%) |
| erythem_recode | | | |
| yes | 2 (11.1%) | 3 (3.6%) | 0 (0%) |
| no | 16 (88.9%) | 81 (96.4%) | 19 (100%) |
| dyspnea_recode | | | |
| yes | 11 (61.1%) | 50 (59.5%) | 5 (26.3%) |
| no | 7 (38.9%) | 34 (40.5%) | 14 (73.7%) |
| lower_edema_recode | | | |
| yes | 10 (55.6%) | 29 (34.5%) | 1 (5.3%) |
| no | 8 (44.4%) | 55 (65.5%) | 18 (94.7%) |
| heart_palpitation_recoded | | | |
| yes | 9 (50.0%) | 44 (52.4%) | 2 (10.5%) |
| no | 9 (50.0%) | 40 (47.6%) | 17 (89.5%) |
| weakness_recode | | | |
| yes | 9 (50.0%) | 36 (42.9%) | - |
| no | 9 (50.0%) | 48 (57.1%) | - |
| Sore throat | | | |
| Yes | - | - | 5 (26.3%) |
| no | - | - | 14 (73.7%) |
| Any symptoms | | | |
| Yes | 17 (94.4%) | 75 (89.3%) | 9 (47.4%) |
| No | 1 (5.6%) | 9 (10.7%) | 10 (52.6%) |

**Supplemental Table 5: Proportion of FDRs with borderline or definite RHD among index cases**

| Age group of index case | Index case with at least 1 FDR with borderline or definite RHD | Index case with FDR who don't have RHD | Proportion of outcome with 95% CI |
|---|---|---|---|
| Overall | 18 | 84 | 0.176 (0.110 – 0.267) |

**Supplemental Table 6: Adjusted association for sex, age, SES deprivation score and family history of RHD**

| | Index cases whose FDR have borderline or definite RHD (n = 18) | Index cases whose FDR do not have RHD (n = 84) | Adjusted odds ratio for index cases who FDR have borderline or definite RHD (95%CI) |
|---|---|---|---|
| Sex of index case (female vs male) | | | |
| Male | 3 | 24 | 1 (Reference) |
| Female | 15 | 60 | 1.56 (0.39 – 6.24) |
| Age of index case as continuous variable | - | - | 1.01 (0.96 – 1.07) |
| SES deprivation score as continuous variable | - | - | 0.94 (0.64 – 1.40) |
| Family history of RHD | | | |
| No | 15 | 81 | 1 (Reference) |
| Yes | 3 | 3 | 4.74 (0.83 – 26.91) |

Note: Each of the exposure variables were adjusted with remaining exposure variables

**Supplemental Table 7: Adjusted association between exposure and RHD status of FDR taking correlation into account and adjusting for:** sex of index case, age of index case, sex of FDR, age of FDR & familial relationship between case and FDR

| | **Adjusted odds ratio for FDR with borderline or definite RHD (95%CI)** |
|---|---|
| Sex of index case (female vs male) | |
| Male | 1 (Reference) |
| Female | 1.03 (0.25 – 4.26) |
| Age of index case as continuous variable | 0.99 (0.92 – 1.07) |
| SES deprivation score as continuous variable | 0.77 (0.51 – 1.16) |
| Family history of RHD | |
| No | 1 (Reference) |
| Yes | 4.34 (1.06 – 17.67)* |

*Statistically significant

**Supplemental Table 8: Adjusted association between exposure and RHD status of FDR taking correlation into account and adjusting for:** sex of index case, age of index case, sex of FDR, age of FDR & familial-relationship between case and FDR, SES deprivation score and family history of RHD

| | FDR with borderline or definite RHD (n =19) | FDR without borderline or definite RHD (n = 215) | Adjusted odds ratio for index cases who FDR have borderline or definite RHD (95%CI) |
|---|---|---|---|
| Sex of index case (female vs male) | | | |
| Male | - | - | 1 (Reference) |
| Female | - | - | 0.95 (0.22 – 4.20) |
| Age of index case as continuous variable | - | - | 1.00 (0.92 – 1.07) |
| SES deprivation score as continuous variable | - | - | 0.80 (0.52 – 1.24) |
| Family history of RHD | | | |
| No | - | - | 1 (Reference) |
| Yes | - | - | 3.71 (0.77 – 18.00) |