Original Investigation

Prevalence of Subclinical Rheumatic Heart Disease in Eastern Nepal
A School-Based Cross-sectional Study

Nikesh R. Shrestha, MD; Prahlad Karki, MD; Rajan Mahto, MBBS; Keshar Gurung, MD; Naveen Pandey, MD; Krishna Agrawal, MD; Martina Rothenbühler, MSc; Philip Urban, MD; Peter Jüni, MD; Thomas Pilgrim, MD

IMPORTANCE Although rheumatic heart disease has been nearly eradicated in high-income countries, 3 in 4 children grow up in parts of the world where it is still endemic.

OBJECTIVES To determine the prevalence of clinically silent and manifest rheumatic heart disease as a function of age, sex, and socioeconomic status and to estimate age-specific incidence.

DESIGN, SETTING, AND PARTICIPANTS In this school-based cross-sectional study with cluster sampling, 26 schools in the Sunsari district in Eastern Nepal with 5467 eligible children 5 to 15 years of age were randomly selected from 595 registered schools. After exclusion of 289 children, 5178 children were enrolled in the present study from December 12, 2012, through September 12, 2014. Data analysis was performed from October 1, 2014, to April 15, 2015.

EXPOSURES Demographic and socioeconomic characteristics were acquired in a standardized interview by means of a questionnaire customized to the age of the children. A focused medical history was followed by a brief physical examination. Cardiac auscultation and transthoracic echocardiography were performed by 2 independent physicians.

MAIN OUTCOMES AND MEASURES Rheumatic heart disease according to the World Heart Federation criteria.

RESULTS The median age of the 5178 children enrolled in the study was 10 years (interquartile range, 8-13 years), and 2503 (48.3%) were female. The prevalence of borderline or definite rheumatic heart disease was 10.2 (95% CI, 7.5-13.0) per 1000 children and increased with advancing age from 5.5 (95% CI, 3.5-7.5) per 1000 children 5 years of age to 16.0 (95% CI, 14.9-17.0) in children 15 years of age, whereas the mean incidence remained stable at 1.1 per 1000 children per year. Children with rheumatic heart disease were older than children without rheumatic heart disease (median age [interquartile range], 11 [9-14] years vs 10 [8-13] years; $P = .03$), more commonly female (34 [64.2%] vs 2469 [48.2%]; $P = .02$), and more frequently went to governmental schools (40 [75.5%] vs 2792 [54.5%]; $P = .002$). Silent disease (n = 44) was 5 times more common than manifest disease (n = 9).

CONCLUSIONS AND RELEVANCE Rheumatic heart disease affects 1 in 100 schoolchildren in Eastern Nepal, is primarily clinically silent, and may be more common among girls. The overall prevalence and the ratio of manifest to subclinical disease increase with advancing age, whereas the incidence remains stable at 1.1 per 1000 children per year. Early detection of silent disease may help prevent progression to severe valvular damage.

Invited Commentary page 96

Supplemental content at jamacardiology.com

Author Affiliations: Department of Cardiology, Neuro Cardio and Multispeciality Hospital, Biratnagar, Nepal (Shrestha, Gurung); Department of Internal Medicine, B. P. Koirala Institute of Health Sciences, Dharan, Nepal (Karki, Mahto, Pandey, Agrawal); Clinical Trials Unit, University of Bern, Bern, Switzerland (Rothenbühler); Department of Cardiology, Hôpital de la Tour, Geneva, Switzerland (Urban); Applied Health Research Centre, Li Ka Shing Knowledge Institute of St. Michael's Hospital, and Department of Medicine, University of Toronto, Toronto, Ontario, Canada (Jüni); Department of Cardiology, Bern University Hospital, Bern, Switzerland (Pilgrim).

Corresponding Author: Thomas Pilgrim, MD, Department of Cardiology, Bern University Hospital, Freiburgstrasse 10, CH-3010 Bern, Switzerland (thomas.pilgrim@insel.ch).

JAMA Cardiol. 2016;1(1):89-96. doi:10.1001/jamacardio.2015.0292
Published online March 2, 2016. Corrected on April 20, 2016.

Three in 4 children grow up in parts of the world where rheumatic heart disease (RHD) is endemic.[1-3] Nearly eradicated in high-income countries, RHD ranks among the important noncommunicable diseases in low- and middle-income countries. It is a sentinel of social inequality and a physical manifestation of poverty and continues to be a substantial health care challenge in less privileged regions of the world. An autoimmune response to group A β-hemolytic streptococcal pharyngitis results in acute rheumatic fever, affecting the large joints, brain, skin, and heart. Recurrent bouts of rheumatic fever insidiously propel clinically silent valvular damage to clinically manifest heart disease, resulting in a quarter of a million premature deaths every year.[1]

Early detection of clinically silent valvular disease and timely implementation of secondary antibiotic prevention may prevent progression to manifest disease and motivated the implementation of echocardiographic screening programs in sub-Saharan Africa, Oceania, and Southeast Asia.[4-7] The mean prevalence of clinically silent RHD is 21 per 1000 children, with large heterogeneity among reports across various endemic regions. This prevalence outweighs the prevalence of manifest disease by a factor of 7 to 8.[8] The World Health Organization (WHO) global action plan targets a relative reduction of noncommunicable disease mortality by 25% by the year 2025 and prioritizes RHD control programs in endemic regions through early detection.[9] An understanding of prevalence and incidence of the condition and risk factors associated with susceptibility to disease is needed to guide active surveillance and secondary prevention. The objectives of the study were to determine the prevalence of clinically silent and manifest RHD as a function of age, sex, and socioeconomic status and to estimate the age-specific incidence from available prevalence data.

Methods

Study Design and Setting

We performed a school-based cross-sectional study of RHD among children in the Sunsari district in Eastern Nepal. Nepal has a Human Development Index of 0.540 and ranks at 145 among all 187 listed countries in the Human Development Report issued by the United Nations Development Programme.[10] The Sunsari district belongs to the Outer Terai of the Koshi zone, is situated in the eastern developmental region of Nepal, and spreads over an area the size of New York City. Nepal's third largest city, Dharan, is the economic and political center of the district and is surrounded by 52 villages with a total population of approximately 760 000 inhabitants. The study was planned in collaboration with the district education office. The observational survey was based on schools rather than communities with the intention to pilot integration of a regular screening program into the educational system. Among a total of 595 registered schools, 503 (84.5%) were located in rural areas; 370 schools (73.6%) in the rural areas had a governmental administration, and 79 schools (85.9%) in urban areas were private.

The design of the study has been previously described.[11] We applied random cluster sampling stratified by the location and administration of the schools to reflect the socioeconomic demographic distribution of the population in Eastern Nepal.[12] We selected rural to urban schools in a ratio of 3:1 and governmental to private schools in a ratio of 2:1.

The study was accompanied by a public campaign reporting on RHD in local print media and local radio. Because of a high rate of illiteracy, we screened an educational movie on RHD for the orientation of children and parents. After permission of the district education office, school principals and teachers were approached in a first step and gave written informed consent for participation in the study. Subsequently, all children from a selected school were asked to participate in the observational survey and included unless the children themselves or their parents or primary caregivers actively withdrew consent. Data were deidentified. The study was conducted according to the Declaration of Helsinki and was registered with ClinicalTrials.gov (identifier NCT 01550068).[13] The study was approved by the institutional review board of B.P. Koirala Institute of Health Sciences and the Nepal Health Research Council and was given an exempt status by the ethics committee of the University of Bern, Bern, Switzerland.

Data Collection

All selected schools were visited at least twice by a team of 2 physicians (N.R.S., R.M., K.G., N.P., or K.A.) and 1 nurse to include children who were absent at an earlier visit. Data on social background and medical history were acquired in a standardized interview by means of a questionnaire customized to the age of the children. Demographic characteristics and socioeconomic variables were documented along with a short medical history followed by a physical examination (eTable 1 in the Supplement). Cardiac auscultation and echocardiographic screening were performed by 2 independent physicians (R.M., K.G., N.P., or K.A.) masked to the findings of each other. Because of a lack of power sources in most schools, echocardiography was performed using a battery-operated portable ultrasound machine (Samsung Medison MySonoU6). Patients with clinical and/or echocardiographic findings suggestive of cardiac disease underwent an independent confirmatory examination. All children with signs of RHD were included in a prospective registry. Secondary antibiotic prophylaxis was recommended in children with definite RHD, whereas yearly echocardiographic follow-up without antibiotic prevention is performed among children with borderline disease. Study data were collected and managed using REDCap electronic data capture tools hosted at the Clinical Trials Unit of the University of Bern, Bern, Switzerland.[14] A pilot study[15] was performed to evaluate the feasibility of collecting information on individuals, performing data collection and echocardiographic screening, identifying barriers to implementation, and streamlining the process for the main study.

Definitions

We defined RHD according to the World Heart Federation (WHF) criteria for individuals 20 years or younger and categorized RHD as definite or borderline. In brief, definite RHD requires the combination of at least 2 morphologic criteria with pathologic regurgitation or mitral stenosis or borderline disease of the aortic and mitral valves. *Borderline RHD* is defined

by at least 2 morphologic features or the presence of pathologic mitral or aortic regurgitation.[16]

Clinically manifest disease was recorded in the presence of any heart murmur in combination with borderline or definite RHD. Clinically silent or subclinical disease was documented if echocardiographic evidence of RHD according to the WHF criteria was not accompanied by an audible heart murmur. The socioeconomic score was calculated using the method suggested by Kuppuswamy[17] and adapted by Ghosh and Ghosh.[18]

Statistical Analysis

Baseline characteristics and clinical findings are presented as frequencies for categorical variables and medians (interquartile ranges [IQRs]) for continuous variables. The association between sex and age with respect to school attendance was evaluated using the Mann-Whitney test. We compared characteristics of children with RHD and children without RHD using the χ^2 or Fisher test, with the Wilcoxon rank sum test used for continuous variables. We included all baseline characteristics in univariable and multivariable multilevel logistic regression models if the univariable was $P < .02$ for the difference across groups. We controlled for cluster effects (schools) and adjusted for the setting of the school (governmental vs private and urban vs rural). The prevalence of borderline and definite RHD according to age was modeled overall and separately by sex using Poisson regression. Because no follow-up data were available, we estimated the incidence from prevalence according to age using the method described by Leske and colleagues.[19] This method has 3 underlying assumptions. First, we assume that the mortality rate among the study population is constant and does not depend on age. Second, we assume that the mortality rate among children and adolescents younger than 16 years is independent of RHD. Third, we assume that there is no disease regression and that disease progression is constant over time. eFigure 1 in the Supplement provides further information regarding the described method. We used the WHO child growth standards and the corresponding Stata statistical software package, version 13.1 (StataCorp) to assess height, weight, and body mass index (calculated as the weight in kilograms divided by height in meters squared) of the study population according to the presence of RHD.

Results

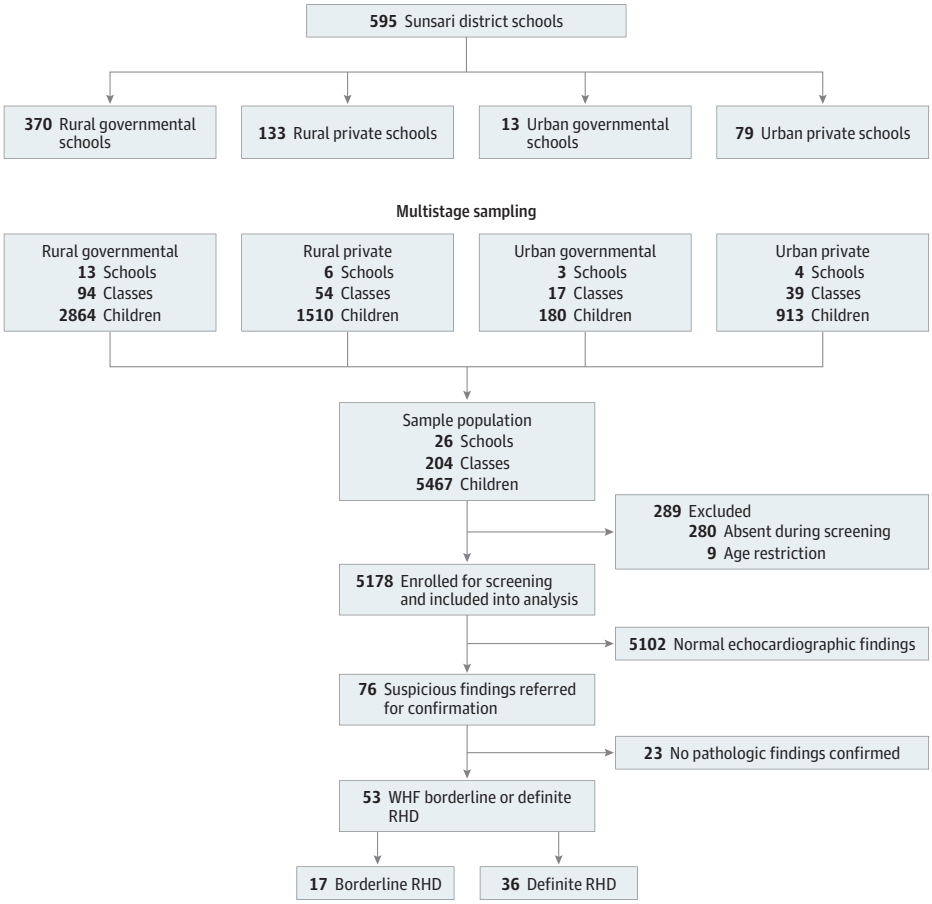
From December 12, 2012, through September 12, 2014, a total of 5467 eligible children from 26 randomly selected schools were invited to undergo active surveillance for RHD. Data analysis was performed from October 1, 2014, to April 15, 2015. After exclusion of 289 children because of absence during screening visits (n = 280) or ineligible age (n = 9), 5178 children (94.7%) were enrolled for echocardiographic screening (**Figure 1**). A total of 4150 children (80.1%) were living in rural areas, whereas 1028 children (19.9%) were living in an urban environment; 16 governmental and 10 private schools contributed 2832 (54.7%) and 2346 (45.3%) children, respectively. Demographic and socioeconomic characteristics are summarized in **Table 1**. The median age of the children was 10 years (IQR, 8-13 years), and 2503 (48.3%) were female. The sex distribution of school attendees across age categories is illustrated in eFigure 2 in the Supplement. No significant interaction was found between age and sex with respect to school attendance ($P = .09$). Most children lived in tin shacks (n = 3483 [67.3%]) or mud houses (n = 530 [10.2%]) in families with 2 adults (IQR, 2-4) and 3 children (IQR, 2-3). Although most children lived in families with a television connection (n = 3625 [70.0%]) and cellular telephone (n = 4770 [92.1%]), few had an Internet connection (n = 326 [6.3%]), a car (n = 56 [1.1%]), or a motorbike (n = 899 [17.4%]). One in every 5 children indicated that his/her parents were illiterate, and almost half of the parents were unemployed or unskilled workers.

Seven children had a documented history of acute rheumatic fever, and 12 reported symptoms suggestive of acute rheumatic fever; none of either group was found to have echocardiographic lesions consistent with RHD according to the WHF criteria. Findings from clinical examination are summarized in **Table 2**. Cardiac auscultation revealed a heart murmur in 664 children (12.8%). Relative to the echocardiographic findings, the sensitivity and specificity of a cardiac murmur for diagnosis of RHD were 17.0% and 87.2%, respectively.

The prevalence of borderline or definite RHD according to the WHF criteria was 10.2 (95% CI, 7.5-13.0) per 1000 children. Thirty-six children had definite RHD, and 17 had borderline disease. Detailed echocardiographic findings are summarized in eTable 2 in the Supplement. Children with definite or borderline RHD were older compared with children with no RHD (median age [IQR], 11 [9-14] years vs 10 [8-13] years; $P = .03$) and more commonly female (34 [64.2%] vs 2469 [48.2%]; $P = .02$). The prevalence of RHD was higher among girls (13.8 per 1000 children; 95% CI, 9.2-18.3) compared with boys (7.2 per 1000 children; 95% CI, 4.0-10.3) (eFigure 3 in the Supplement). The overall prevalence of RHD corrected for underschooling of girls was 10.4 per 1000 children (95% CI, 7.7-13.1). Children with RHD more frequently went to governmental schools compared with children without RHD (40 [75.5%] vs 2792 [54.5%]; $P = .002$) (Table 1).

The prevalence of RHD increased across age categories from 5.5 per 1000 children 5 years of age (95% CI, 3.5-7.5) to 16.0 per 1000 children 15 years of age (95% CI, 14.9-17.0). The corresponding estimated incidence was 1.1 per 1000 children per year, without evidence of a change in incidence across age categories (eFigure 1 in the Supplement). Clinically silent disease (n = 44) was 5 times more common than clinically manifest disease (n = 9). Children with silent RHD were younger than children with clinically manifest disease (median age [IQR], 10.5 [9-13] years vs 14 [11-15] years; $P = .05$). Manifest disease was exceptionally rare in primary school children and was increasingly detected in the early teenage years (**Figure 2**). In a multivariable analysis, older age (odds ratio, 1.11; 95% CI, 0.99-1.25; $P = .049$) and female sex (odds ratio, 1.86; 95% CI, 1.05-3.29; $P = .03$) were associated with an increased risk of RHD, whereas individual socioeconomic determinants were not (**Figure 3**). Although children were generally smaller than the 50th percentile on WHO growth charts, we identified no difference in growth in children with RHD compared with children without RHD (eFigure 4 in the Supplement).

Figure 1. Flowchart According to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement



The flowchart illustrates the sampling procedure and screening procedure. The Inaruwa and Itahari municipalities were excluded. RHD indicates rheumatic heart disease; WHF, World Heart Federation.

Discussion

In this school-based cross-sectional study, the prevalence of borderline or definite RHD among schoolchildren in Eastern Nepal amounted to 10.2 (95% CI, 7.5-13.0) per 1000 children 5 to 15 years of age. Rheumatic heart disease was more common in girls compared with boys. The prevalence increased across age categories in a nearly linear fashion. Correspondingly, the estimated incidence remained approximately stable at 1.1 per 1000 children per year. The prevalence of subclinical RHD was 5 times higher compared with manifest disease, and the ratio of manifest to subclinical disease increased with increasing age.

The observed prevalence of echocardiographically documented RHD of 10.2 (95% CI, 7.5-13.0) per 1000 children among schoolchildren in Eastern Nepal in our study was considerably lower compared with a pooled estimate from population-based surveys in Southeast Asia, suggesting a prevalence of 28 (95% CI, 17-50) per 1000 children.[4,6,8,20] Reports[4,6-8,21-30] from Africa, Oceania, and Latin America documented a prevalence of 7.9 (95% CI, 2.9-21.4), 14.0 (95% CI, 7.7-25.5), and 4.1 (95% CI, 2.4-7.1) per 1000 children, respectively. The most recent active surveillance program in Nepal, including 9420 students 5 to 18 years of age in the Kathmandu Valley, documented a RHD prevalence of 1.2 per 1000 population as assessed by cardiac auscultation only, comparable to the rate of 1.7 per 1000 children with RHD manifesting with a heart murmur in our study.[31] Several reasons may account for the heterogeneity across reports. Prevalence varies as a function of socioeconomic context, sampling strategy, and diagnostic criteria applied. In addition, differences in streptococcal strains and genetic host susceptibility may contribute to heterogeneity.[32] Multistage sampling was used to approximately reflect the socioeconomic distribution of the entire region. Although we accounted for governmental and private schools and rural and urban location of these schools, sampling was based on school lists and was not strictly community based. Screening among school-going children may underestimate the true burden of disease because of an association between school attendance and socioeconomic status.[8,26] Primary school attendance in Nepal is 96% for boys and 91% for girls.[33] Consistently, girls accounted for 48.3% of children in the present survey, reflecting the lower schooling rate for girls compared with boys.[33] In our study, the prevalence of RHD was higher among girls (13.8 per 1000 children; 95% CI, 9.2-18.3) compared with boys (7.2 per 1000 children; 95% CI, 4.0-10.3). After correction for un-

Table 1. Sociodemographic Characteristics[a]

Characteristic	Overall (N = 5178)	Healthy (n = 5125)	Borderline or Definite RHD (n = 53)	*P* Value
Individual Characteristics				
Age, median (IQR), y	10 (8-13)	10 (8-13)	11 (9-14)	.03
Female sex	2503 (48.3)	2469 (48.2)	34 (64.2)	.02
Family Characteristics				
Type of house				
Kachcha (mud roof)	530 (10.2)	520 (10.2)	10 (18.9)	.30
Tin (tin roof)	3483 (67.3)	3451 (67.4)	32 (60.4)	
Wooden (wooden roof)	129 (2.5)	128 (2.5)	1 (1.9)	
Pakka (cement roof)	129 (2.5)	128 (2.5)	1 (1.9)	
No. of rooms				
≤3	2659 (51.4)	2631 (51.4)	28 (52.8)	.50
4-6	2123 (41.0)	2100 (41.0)	23 (43.4)	
≥7	394 (7.6)	392 (7.7)	2 (3.8)	
No. of family members				
Adults per household, median (IQR)	2 (2-4)	2 (2-4)	2 (2-3)	.22
Children per household, median (IQR)	3 (2-3)	3 (2-3)	3 (2-3)	.27
Overcrowding	1302 (25.2)	1285 (25.1)	17 (32.1)	.26
Possessions				
Car (≥1)	56 (1.1)	56 (1.1)	0 (0.0)	>.99
Motorbike (≥1)	899 (17.4)	892 (17.4)	7 (13.2)	.42
Television connection (≥1)	3625 (70.0)	3594 (70.1)	31 (58.5)	.07
Cellular telephone (≥1)	4770 (92.1)	4719 (92.1)	51 (96.2)	.44
Internet connection	326 (6.3)	323 (6.3)	3 (5.7)	>.99
Property of books (≥10)	4264 (82.4)	4216 (82.3)	48 (90.6)	.15
Estimated family income per month, $				
<23	74 (1.4)	74 (1.4)	0 (0.0)	.33
23-69	707 (13.7)	696 (13.6)	11 (20.8)	
70-115	1720 (33.3)	1699 (33.2)	21 (39.6)	
116-173	1027 (19.9)	1017 (19.9)	10 (18.9)	
174-230	649 (12.6)	646 (12.6)	3 (5.7)	
231-461	825 (16.0)	819 (16.0)	6 (11.3)	
>461	166 (3.2)	164 (3.2)	2 (3.8)	
Characteristics of primary caregiver				
Age of primary caregiver, median (IQR), y	37 (33-41)	37 (33-41)	37 (34-42)	.46
Educational level of primary caregiver				
Illiterate	1148 (22.2)	1137 (22.2)	11 (20.8)	.54
Primary school or literate	1683 (32.5)	1660 (32.4)	23 (43.4)	
Middle school certificate	872 (16.8)	863 (16.8)	9 (17.0)	
High school certificate	1097 (21.2)	1089 (21.2)	8 (15.1)	
Intermediate or post-high school diploma	219 (4.2)	219 (4.3)	0 (0.0)	
Graduate or postgraduate	120 (2.3)	118 (2.3)	2 (3.8)	
Profession or honors	39 (0.8)	39 (0.8)	0 (0.0)	
Occupation of primary caregiver				
Unemployed	988 (19.1)	984 (19.2)	4 (7.5)	.01
Unskilled worker	1230 (23.8)	1207 (23.6)	23 (43.4)	
Semiskilled worker	686 (13.2)	680 (13.3)	6 (11.3)	
Skilled worker	506 (9.8)	503 (9.8)	3 (5.7)	
Shop-owner, farmer	1385 (26.7)	1374 (26.8)	11 (20.8)	
Semiprofessional	100 (1.9)	97 (1.9)	3 (5.7)	
Professional	283 (5.5)	280 (5.5)	3 (5.7)	
Socioeconomic status score, median (IQR)	10 (8-13)	10 (8-13)	9 (7-12)	.14
Characteristics of the school				
Urban	1028 (19.9)	1017 (19.8)	11 (20.8)	.87
Governmental	2832 (54.7)	2792 (54.5)	40 (75.5)	.002

Abbreviations: IQR, interquartile range; RHD, rheumatic heart disease.

[a] Data are presented as number (percentage) of children unless otherwise indicated. Differences across groups are estimated using the χ^2 or Fisher exact test or logistic regression for categorical variables and Wilcoxon rank sum test for continuous variables. Overcrowding is defined as number of family members divided by number of rooms of 2.5 or more.

Table 2. Clinical Findings[a]

Finding	Overall (N = 5178)	Normal (n = 5125)	Borderline or Definite RHD (n = 53)	*P* Value
z score, median (IQR)				
Height	−1 (−2 to −1)	−1 (−2 to −1)	−1 (−2 to 0)	.65
Weight[b]	−1 (−2 to −1)	−1 (−2 to −1)	−2 (−3 to −1)	.29
BMI	−1 (−1 to 0)	−1 (−1 to 0)	−1 (−2 to −0)	.33
Waist circumference, median (IQR)	57 (53 to 64)	57 (53 to 64)	59 (54 to 64)	.39
Cardiac murmur, No. (%)	664 (12.8)	655 (12.8)	9 (17.0)	.36
History of ARF, No. (%)	7 (0.1)	7 (0.1)	0 (0.0)	>.99
Joint pain	449 (8.7)	441 (8.6)	8 (15.1)	.10
Signs of ARF[c]	12 (0.2)	12 (0.2)	0	>.99

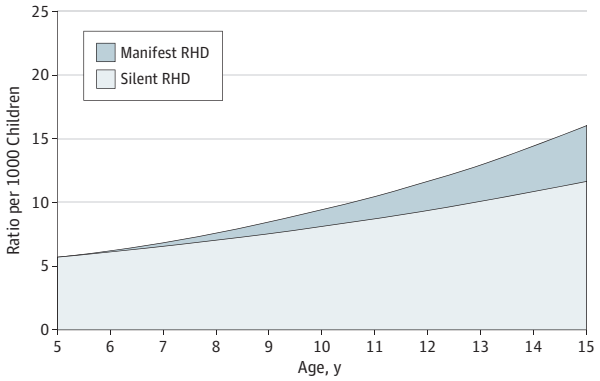
Abbreviations: ARF, acute rheumatic fever; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; RHD, rheumatic heart disease.

[a] Differences across groups are estimated using the χ^2 or Fisher exact test or logistic regression for categorical variables and the Wilcoxon rank sum test for continuous variables.

[b] World Health Organization child growth standards for weight are only available for children up to 10 years old, which reduces the sample size for this item to 2048 (16 children with borderline or definite RHD).

[c] Signs of ARF, including migrating arthritis, erythema marginatum, subcutaneous nodules, or chorea.

Figure 2. Ratio of Silent and Manifest Rheumatic Heart Disease (RHD) According to Age



The prevalence of silent and manifest RHD was estimated using Poisson regression.

derschooling of girls, the overall prevalence is estimated to be higher than observed in the present survey (10.4 per 1000 children; 95% CI, 7.7-13.1). Under the assumption that underschooling may be associated with lower socioeconomic status, the true burden of disease may be even higher.

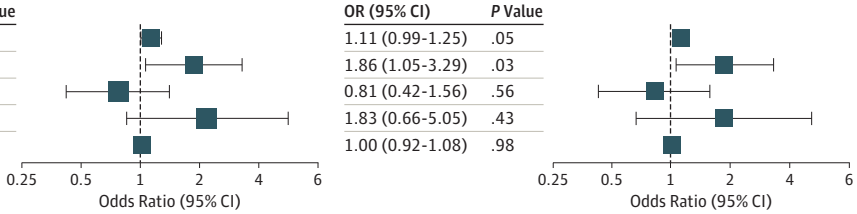
Several studies[34-40] reported a higher prevalence of RHD among females, whereas others did not.[4,8,41] Although a higher cumulative exposure to β-hemolytic streptococci may contribute to a higher prevalence among young child-rearing mothers, it is less likely to explain differences among children. The consequence of a female preponderance of RHD may be further amplified once girls reach child bearing age because severe valvular damage, particularly mitral stenosis, increases the risk of complications during birth not only for the mother but also for the child. A previous study[42] of 9463 pregnant women documented a prevalence of significant RHD in 5 of 1000 women with a mean age of 25 years. Maternal and fetal or neonatal mortality amounted to 20% among women with a pregnancy complicated by RHD.

In contrast to previous analyses from Southeast Asia, we used the recently propagated WHF criteria[16] for diagnosis. The WHF criteria are more specific and less sensitive compared with the WHO criteria used in previous reports.[6-8,43] Still, concerns have been raised that borderline RHD could be a normal variant.[43] The correlation between subclinical valvular lesions and subsequent burden of symptomatic RHD has to be thoroughly assessed. It remains unclear which proportion of subclinical lesions progress to severe valvular damage. Previous analyses[6,20,28,44] in small patient cohorts with limited duration of follow-up suggested regression of approximately one-third of functional lesions, whereas morphologic changes were less likely to improve. Moreover, the efficacy of early detection of subclinical disease and timely implementation of secondary antibiotic prevention need to be determined in longitudinal studies. A recent report[41] from the Southeast Pacific documented that 90% of all children with RHD received antibiotic prevention, and three-quarters had stable disease.

Consistent with previous reports,[7,23] we observed a steady increase of prevalence with advancing age. The higher prevalence of RHD with older age was paralleled by a greater ratio of clinically detectable disease with increasing age. Both observations may underscore the importance of cumulative exposure to progression of disease. In line with previous reports,[4,6-8,21,23,24,28] clinically silent disease was 5 times more frequent compared with clinically manifest disease. In addition, the sensitivity of a cardiac murmur for diagnosis of RHD was very low. The absolute risk of developing clinically manifest and eventually symptomatic disease is a function of the pool of silent disease and disease duration. It may be hypothesized that the pathologic mechanism of cumulative exposure not only increases prevalence but also accelerates progression of disease. As a result of this propagation through exposure, endemic regions with a very high prevalence of RHD may also have a higher ratio of advanced disease in younger children compared with regions with lower prevalence. As a consequence, the optimal age for screening may be a function of prevalence; endemic regions with very high prevalence may benefit from screening at a younger age and additional screening compared with regions with lower prevalence.

Figure 3. Predictors of Rheumatic Heart Disease (RHD)

	Univariable model, OR (95% CI)	*P* Value	Multivariable model, OR (95% CI)	*P* Value
Age	1.12 (1.01-1.24)	.03	1.11 (0.99-1.25)	.05
Female sex	1.84 (1.04-3.24)	.04	1.86 (1.05-3.29)	.03
Television connection	0.76 (0.42-1.39)	.38	0.81 (0.42-1.56)	.56
Property of books (≥10)	2.17 (0.83-5.66)	.11	1.83 (0.66-5.05)	.43
Socioeconomic score	1.01 (0.94-1.09)	.78	1.00 (0.92-1.08)	.98



We controlled for cluster effects (schools) and adjusted for school characteristics (governmental vs private, urban vs rural). All baseline characteristics with a difference between children with RHD and children without RHD of $P < .20$ were included in the univariable and multivariable models.

The present study has several limitations. First, the number of children detected with RHD was modest, thus limiting the robustness of prevalence estimates according to age. Second, the present analysis is open to selection bias. School attendance is likely to be associated with socioeconomic status and health status. The school-based rather than community-based design of our study may undermine the burden of disease in the least privileged population most vulnerable to disease. Conversely, every school was visited at least twice to reduce the number of absentees to a minimum. Moreover, in a recent meta-analysis[8] of active surveillance programs, no significant interaction between prevalence of RHD in school-based vs community-based studies has been documented. Third, we did not assess interrater reliability of echocardiographic findings. All children with suspicious findings were, however, examined by a second cardiologist (N.R.S.), and diagnosis of RHD was based on a consensus decision. Fourth, we assumed a constant mortality rate for the model used for the estimation of incidence and did not account for mortality secondary to RHD. Mortality may, however, not be entirely negligible in populations with endemic streptococcal infections because children with the findings may be more susceptible to acute rheumatic fever that can be fatal. Fifth, our findings provide no insights into the importance of subclinical valvular lesions on prognosis. Longitudinal studies are needed to evaluate the efficacy of early detection of clinically silent disease on progression of disease and development of congestive heart failure.

Conclusions

Rheumatic heart disease affects approximately 1 in 100 schoolchildren in Eastern Nepal, is primarily clinically silent, and may be more common among girls. The overall prevalence and the ratio of manifest to subclinical disease increase with advancing age, whereas the estimated incidence remains stable at 1.1 per 1000 children per year.

ARTICLE INFORMATION

Correction: This article was corrected on April 20, 2016, to add an Open Access note to the Article Information section.

Accepted for Publication: November 29, 2015.

Published Online: March 2, 2016. doi:10.1001/jamacardio.2015.0292.

Open Access: This article is published under *JAMA Cardiology*'s open access model and is free to read on the day of publication.

Author Contributions: Drs Shrestha and Pilgrim had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Shrestha, Karki, Agrawal, Rothenbühler, Urban, Pilgrim.
Acquisition, analysis, or interpretation of data: Shrestha, Mahto, Gurung, Pandey, Agrawal, Rothenbühler, Jüni, Pilgrim.
Drafting of the manuscript: Shrestha, Mahto, Gurung, Pandey, Agrawal, Rothenbühler, Pilgrim.
Critical revision of the manuscript for important intellectual content: Shrestha, Karki, Rothenbühler, Urban, Jüni, Pilgrim.
Statistical analysis: Shrestha, Rothenbühler, Jüni, Pilgrim.
Obtained funding: Rothenbühler, Urban, Pilgrim.
Administrative, technical, or material support: Shrestha, Karki, Pandey, Agrawal, Rothenbühler, Urban, Pilgrim.
Study supervision: Shrestha, Karki, Agrawal, Jüni, Pilgrim.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: The study was funded by research grants from the UBS Optimus Foundation (Dr Pilgrim) and the Foundation Coeur de la Tour from Switzerland (Drs Shrestha and Pilgrim).

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

REFERENCES

1. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. *Lancet Infect Dis*. 2005;5(11):685-694.

2. Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. *Lancet*. 2012;379(9819):953-964.

3. Population Reference Bureau. 2013 World Population Data Sheet. http://www.prb.org/Publications/Datasheets/2013/2013-world-population-data-sheet/data-sheet.aspx. Published 2013. Accessed March 31, 2014.

4. Marijon E, Ou P, Celermajer DS, et al. Prevalence of rheumatic heart disease detected by echocardiographic screening. *N Engl J Med*. 2007;357(5):470-476.

5. Carapetis JR, Hardy M, Fakakovikaetau T, et al. Evaluation of a screening protocol using auscultation and portable echocardiography to detect asymptomatic rheumatic heart disease in Tongan schoolchildren. *Nat Clin Pract Cardiovasc Med*. 2008;5(7):411-417.

6. Saxena A, Ramakrishnan S, Roy A, et al. Prevalence and outcome of subclinical rheumatic heart disease in India: the RHEUMATIC (Rheumatic Heart Echo Utilisation and Monitoring Actuarial Trends in Indian Children) study. *Heart*. 2011;97(24):2018-2022.

7. Beaton A, Okello E, Lwabi P, Mondo C, McCarter R, Sable C. Echocardiography screening for rheumatic heart disease in Ugandan schoolchildren. *Circulation*. 2012;125(25):3127-3132.

8. Rothenbühler M, O'Sullivan CJ, Stortecky S, et al. Active surveillance for rheumatic heart disease in endemic regions: a systematic review and meta-analysis of prevalence among children and adolescents. *Lancet Glob Health*. 2014;2(12):e717-e726.

9. World Health Organization. Global action plan for the prevention and control of NCDs 2013-2020. http://www.who.int/nmh/events/ncd_action_plan/en. Accessed April 24, 2014.

10. United Nations Development Programme. Human development reports. http://hdr.undp.org/en/content/human-development-index-hdi. Accessed April 21, 2015.

11. Pilgrim T, Kalesan B, Karki P, et al. Protocol for a population-based study of rheumatic heart disease prevalence and cardiovascular outcomes among schoolchildren in Nepal. *BMJ Open*. 2012;2(3):e001320.

12. United Nations Statistical Division. Nepal. http://data.un.org/CountryProfile.aspx?crName=Nepal#Environment. Accessed January 3, 2015.

13. ClinicalTrials.gov. Rheumatic Heart Disease School Project. NCT01550068. https://clinicaltrials.gov/ct2/show/NCT01550068. Accessed January 21, 2016.

14. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap): a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.

15. Shrestha NR, Kalesan B, Karki P, et al. Rheumatic heart disease: pilot study for a population-based evaluation of prevalence and cardiovascular outcomes among schoolchildren in Nepal. *BMJ Open*. 2012;2(5):2.

16. Reményi B, Wilson N, Steer A, et al. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease: an evidence-based guideline. *Nat Rev Cardiol*. 2012;9(5):297-309.

17. Kuppuswamy B. *Manual of Socioeconomic Status (Urban)*. Delhi, India: Manasayan; 1981.

18. Ghosh A, Ghosh T. Modification of Kuppuswamy's Socioeconomic Status Scale in context to Nepal. *Indian Pediatr*. 2009;46:1105.

19. Leske MC, Ederer F, Podgor M. Estimating incidence from age-specific prevalence in glaucoma. *Am J Epidemiol*. 1981;113(5):606-613.

20. Bhaya M, Beniwal R, Panwar S, Panwar RB. Two years of follow-up validates the echocardiographic criteria for the diagnosis and screening of rheumatic heart disease in asymptomatic populations. *Echocardiography*. 2011;28(9):929-933.

21. Bhaya M, Panwar S, Beniwal R, Panwar RB. High prevalence of rheumatic heart disease detected by echocardiography in school children. *Echocardiography*. 2010;27(4):448-453.

22. Anabwani GM, Amoa AB, Muita AK. Epidemiology of rheumatic heart disease among primary school children in western Kenya. *Int J Cardiol*. 1989;23(2):249-252.

23. Kane A, Mirabel M, Touré K, et al. Echocardiographic screening for rheumatic heart disease: age matters. *Int J Cardiol*. 2013;168(2):888-891.

24. Webb RH, Wilson NJ, Lennon DR, et al. Optimising echocardiographic screening for rheumatic heart disease in New Zealand: not all valve disease is rheumatic. *Cardiol Young*. 2011;21(4):436-443.

25. Baroux N, Rouchon B, Huon B, Germain A, Meunier JM, D'Ortenzio E. High prevalence of rheumatic heart disease in schoolchildren detected by echocardiography screening in New Caledonia. *J Paediatr Child Health*. 2013;49(2):109-114.

26. Roberts K, Maguire G, Brown A, et al. Echocardiographic screening for rheumatic heart disease in high and low risk Australian children. *Circulation*. 2014;129(19):1953-1961.

27. Cramp G, Stonehouse M, Webb R, Webb R, Chaffey-Aupouri G, Wilson N. Undetected rheumatic heart disease revealed using portable echocardiography in a population of school students in Tairawhiti, New Zealand. *N Z Med J*. 2012;125(1363):53-64.

28. Paar JA, Berrios NM, Rose JD, et al. Prevalence of rheumatic heart disease in children and young adults in Nicaragua. *Am J Cardiol*. 2010;105(12):1809-1814.

29. Spitzer E, Mercado J, Islas F, et al. Screening for rheumatic heart disease among Peruvian children: a two-stage sampling observational study. *PLoS One*. 2015;10(7):e0133004.

30. Engel ME, Haileamlak A, Zühlke L, et al. Prevalence of rheumatic heart disease in 4720 asymptomatic scholars from South Africa and Ethiopia. *Heart*. 2015;101(17):1389-1394.

31. Bahadur KCM, Sharma D, Shrestha MP, et al. Prevalence of rheumatic and congenital heart disease in schoolchildren of Kathmandu valley in Nepal. *Indian Heart J*. 2003;55(6):615-618.

32. Bryant PA, Robins-Browne R, Carapetis JR, Curtis N. Some of the people, some of the time: susceptibility to acute rheumatic fever. *Circulation*. 2009;119(5):742-753.

33. UNICEF. Nepal. Statistics. http://www.unicef.org/infobycountry/nepal_nepal_statistics.html. Updated December 27, 2013. Accessed April 24, 2015.

34. Agarwal AK, Yunus M, Ahmad J, Khan A. Rheumatic heart disease in India. *J R Soc Health*. 1995;115(5):303-304, 309.

35. Rizvi SF, Khan MA, Kundi A, Marsh DR, Samad A, Pasha O. Status of rheumatic heart disease in rural Pakistan. *Heart*. 2004;90(4):394-399.

36. Sani MU, Karaye KM, Borodo MM. Prevalence and pattern of rheumatic heart disease in the Nigerian savannah: an echocardiographic study. *Cardiovasc J Afr*. 2007;18(5):295-299.

37. Carapetis JR, Wolff DR, Currie BJ. Acute rheumatic fever and rheumatic heart disease in the top end of Australia's Northern Territory. *Med J Aust*. 1996;164(3):146-149.

38. Ozer O, Davutoglu V, Sari I, Akkoyun DC, Sucu M. The spectrum of rheumatic heart disease in the southeastern Anatolia endemic region: results from 1900 patients. *J Heart Valve Dis*. 2009;18(1):68-72.

39. Sliwa K, Carrington M, Mayosi BM, Zigiriadis E, Mvungi R, Stewart S. Incidence and characteristics of newly diagnosed rheumatic heart disease in urban African adults: insights from the heart of Soweto study. *Eur Heart J*. 2010;31(6):719-727.

40. Shrestha NR, Pilgrim T, Karki P, et al. Rheumatic heart disease revisited: patterns of valvular involvement from a consecutive cohort in eastern Nepal. *J Cardiovasc Med (Hagerstown)*. 2012;13(11):755-759.

41. Mirabel M, Fauchier T, Bacquelin R, et al. Echocardiography screening to detect rheumatic heart disease: a cohort study of schoolchildren in French Pacific Islands. *Int J Cardiol*. 2015;188:89-95.

42. Chhetri S, Shrestha NR, Pilgrim T. Pregnancy complicated by heart disease in Nepal. *Heart Asia*. 2014;6(1):26-29.

43. Colquhoun SM, Kado JH, Remenyi B, Wilson NJ, Carapetis JR, Steer AC. Echocardiographic screening in a resource poor setting: borderline rheumatic heart disease could be a normal variant. *Int J Cardiol*. 2014;173(2):284-289.

44. Beaton A, Okello E, Aliku T, et al. Latent rheumatic heart disease: outcomes 2 years after echocardiographic detection. *Pediatr Cardiol*. 2014;35(7):1259-1267.

Invited Commentary

Screening for Rheumatic Heart Disease in Eastern Nepal

Bongani M. Mayosi, DPhil, FCP(SA)

The burden of rheumatic heart disease in developing countries is persistently high. A systematic review[1] of active surveillance studies found that 28.0 per 1000 people are affected with the disease in Southeast Asia, 14.0 per 1000 people in Oceania, and 7.9 per 1000 people in Africa. A previous surveillance study[2] led to estimates that 50 million to 100 million people may be affected with rheumatic heart disease worldwide. Furthermore, a prospective study[3] of symptomatic patients indicated that there are serious gaps in the translation of effective interventions into clinical practice, resulting in suboptimal use of proven interventions, such as antibiotic prophylaxis to prevent acute rheumatic fever and surgical treatment for patients with heart failure. It is therefore not surprising that rheumatic heart disease is a leading cause of premature death and an important economic burden in developing countries where age-standardized death rates may be more than twice those reported in current global estimates.[4]

Related article page 89

The article by Shrestha et al[5] in this issue of *JAMA Cardiology* reports the prevalence and incidence of latent rheumatic heart disease in schoolchildren in rural and urban