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Circulation. 2014;129:1953-1961; originally published online March 12, 2014;
doi: 10.1161/CIRCULATIONAHA.113.003495
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

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Background—Echocardiographic screening for rheumatic heart disease (RHD) is becoming more widespread, but screening studies to date have used different echocardiographic definitions. The World Heart Federation has recently published new criteria for the echocardiographic diagnosis of RHD. We aimed to establish the prevalence of RHD in high-risk Indigenous Australian children using these criteria and to compare the findings with a group of Australian children at low risk for RHD.

Methods and Results—Portable echocardiography was performed on high-risk Indigenous children aged 5 to15 years living in remote communities of northern Australia. A comparison group of low-risk, non-Indigenous children living in urban centers was also screened. Echocardiograms were reported in a standardized, blinded fashion. Of 3946 high-risk children, 34 met World Heart Federation criteria for definite RHD (prevalence, 8.6 per 1000 [95% confidence interval, 6.0–12.0]) and 66 for borderline RHD (prevalence, 16.7 per 1000 [95% confidence interval, 13.0–21.2]). Of 1053 low-risk children, none met the criteria for definite RHD, and 5 met the criteria for borderline RHD. High-risk children were more likely to have definite or borderline RHD than low-risk children (adjusted odds ratio, 5.7 [95% confidence interval, 2.3–14.1]; $P<0.001$).

Conclusions—The prevalence of definite RHD in high-risk Indigenous Australian children approximates what we expected in our population, and no definite RHD was identified in the low-risk group. This study suggests that definite RHD, as defined by the World Heart Federation criteria, is likely to represent true disease. Borderline RHD was identified in children at both low and high risk, highlighting the need for longitudinal studies to evaluate the clinical significance of this finding. **(*Circulation*. 2014;129:1953-1961.)**

Key Words: echocardiography ■ pediatrics ■ rheumatic heart disease ■ mass screening

Rheumatic heart disease (RHD) attributed to acute rheumatic fever (ARF) is the leading cause of cardiac disease in children in developing countries.[1] Poverty and overcrowding are known risk factors for RHD,[2] and the disease has largely disappeared from industrialized countries, with the notable exceptions of the Indigenous populations of Australia, as well as Maori and Pacific Islander populations in New Zealand.

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Over the past decade, there has been increasing interest in echocardiographic screening for RHD, and several population-based surveys of school children have been published.[3–11] The reported prevalence of RHD detected by screening in school-aged children from high-risk populations varies widely, from 5 per 1000[5,10] to >50 per 1000,[6–8] but echocardiographic definitions used in these studies vary, making direct comparisons difficult.[12] Echocardiography has been shown to be extremely sensitive for the detection of valve abnormalities; however, questions have been raised about its specificity, with concerns that echocardiographic screening may be generating high numbers of false-positive results.[12] In the absence of an established gold-standard test for the diagnosis of RHD, and given that publications to date have

Received August 25, 2013; accepted February 7, 2014.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.113.003495**

focused exclusively on children at high risk, it is difficult to assess whether this is indeed the case.

There are 3 major knowledge gaps that lead to concerns that estimates of RHD prevalence arising from echocardiographic screening studies to date may be exaggerated: (1) they have not relied on an internationally accepted standard set of diagnostic criteria, (2) the reference ranges for valvular regurgitation and valve morphology are poorly defined in children, and (3) the subjective nature of interpreting echocardiography may increase the risk of overdiagnosis if the reader is aware that a child comes from a high-risk population (observer bias). The World Heart Federation (WHF) recently published criteria for the echocardiographic diagnosis of RHD,[13] which addresses the first of these concerns. These guidelines are designed for children without a history of ARF, aiming to differentiate mild RHD from normal findings by providing very specific definitions of left-sided valvular abnormalities (Table 1). These criteria have not yet been applied to a screened cohort.

Indigenous Australians (Aboriginal and/or Torres Strait Islander peoples) continue to experience among the highest rates in the world, with an ARF incidence of ≈200 per 100 000 children aged 5 to 14 years[14] and an estimated RHD prevalence of 8.5 per 1000 in this group.[14,15] These figures are based on clinical data from the Northern Territory RHD register, but information is lacking about disease burden in remote Indigenous populations in other parts of Australia. No prospective survey of RHD prevalence has been undertaken in Australia. Because of the high rates of disease documented by existing surveillance mechanisms, this population represents an ideal group for evaluation of the role of echocardiographic screening.

This study aimed to establish the prevalence of RHD in remote Indigenous Australian children at high risk and to compare their echocardiographic findings with a cohort of non-Indigenous children at low risk for RHD living in the same geographic regions. We hypothesized that the application of an accurate and useful set of echocardiographic criteria should mirror previously described RHD epidemiology in this population and, therefore, expected that the WHF criteria would identify a higher proportion of children who were RHD positive in the remote Indigenous cohort, whereas RHD should be virtually absent in children at low risk.

Table 1. World Heart Federation Criteria for the Echocardiographic Diagnosis of RHD in Individuals Aged ≤20 Years[13]

Echocardiographic Criteria for RHD*	
Definite RHD (A, B, C, or D)	
A) Pathologic MR and at least 2 morphologic features of RHD of the MV	
B) MS mean gradient ≥4 mm Hg	
C) Pathological AR and at least 2 morphological features of RHD of the AV	
D) Borderline disease of both the AV and MV	
Borderline RHD (A, B, or C)	
A) At least 2 morphologic features of RHD of the MV without pathologic MR or MS	
B) Pathologic MR	
C) Pathologic AR	
Echocardiographic criteria for pathologic regurgitation (all 4 Doppler criteria must be met)	
Pathologic MR	Pathologic AR
1. Seen in 2 views	1. Seen in 2 views
2. In at least 1 view jet length ≥2 cm†	2. In at least 1 view jet length ≥1 cm†
3. Peak velocity ≥3 m/s for 1 complete envelope	3. Peak velocity ≥3 m/s in early diastole
4. Pansystolic jet in at least 1 envelope	4. Pandiastolic jet in at least 1 envelope
Morphologic features of RHD	
Features in the MV	Features in the AV
1. AMVL thickening ≥3 mm‡	1. Irregular or focal thickening
2. Chordal thickening	2. Coaptation defect
3. Restricted leaflet motion	3. Restricted leaflet motion
4. Excessive leaflet tip motion during systole	4. Prolapse

AMVL indicates anterior mitral valve leaflet; AR, aortic regurgitation; AV, aortic valve; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; and RHD indicates rheumatic heart disease.

*Congenital anomalies must be excluded.

†A regurgitant jet length should be measured from the vena contracta to the last pixel of regurgitant color (blue or red) on nonmagnified (nonzoomed) images.

‡AMVL thickness should be measured during diastole at full excursion. Measurement should be taken at the thickest portion of the leaflet and should be performed on a frame with maximal separation of chordae from the leaflet tissue.

Methods

Setting and Participants

Our study was conducted in northern and central Australia between 2008 and 2010. Approval was obtained from the relevant human research ethics committees in each participating jurisdiction. The high-risk cohort was composed of Aboriginal and Torres Strait Islander children living in remote communities from 4 regions (the Top End of the Northern Territory, Central Australia, far north Queensland, and the Kimberley region of northern Western Australia.) The total Indigenous population in these regions is ≈74 000 (40% to 50% of the total population), with ≈16 000 Indigenous children aged 5 to 14 years old.[16] Thirty-two communities of different sizes were selected (population range, 150–3000 residents) and were distributed across a vast area (>2 000 000 km^2), encompassing both tropical and desert regions. Using standardized Australian measures of socioeconomic disadvantage, which incorporate data on income, education, employment and housing, all of the participating communities had scores in the lowest decile, between 3 and 4 SDs below the Australian average.[17] The average proportion of Indigenous students enrolled in participating remote schools was 94.5%.

The low-risk cohort was selected from 5 schools in relatively affluent suburbs of the tropical Australian cities of Darwin and Cairns; all had standardized measures of socioeconomic advantage above the Australian average, and students of participating schools had median family incomes greater than the national median.[18] More than 90% of students in the selected urban schools were non-Indigenous.

Children were identified by the enrollment record of participating schools and recruited at school or, for those not present at school on screening days, by approaching families. All of the children between the ages of 5 and 15 years were eligible to participate in the study, including children with a known history of ARF/RHD or congenital heart disease. For the purposes of analysis, Indigenous children were subsequently excluded from the low-risk cohort, and non-Indigenous children were excluded from the high-risk cohort. This was done because there is effectively no RHD in the school-aged non-Indigenous Australian population,[14,15,19–21] and our aim was to analyze 2 populations on the basis of a priori categorization of level of risk for RHD. Written informed consent was obtained from parents/guardians, and written assent was also obtained from children ≥13 years. Attempts were made to locate children who were absent from school on the day of screening, and multiple screening days were undertaken in each site to maximize coverage.

Screening Procedure

At each screening visit, we obtained basic demographic information, measured height and weight, and an experienced cardiac sonographer performed a screening echocardiogram using Vivid *e* or Vivid *i* (GE Healthcare, Freiburg, Germany) portable cardiovascular ultrasound machines. A probe with a variable range from 2.5 to 5.0 megahertz was used for all of the studies. Gain settings were optimized by sonographers by turning the color gain settings down completely and gradually increasing until static background noise barely appeared.

Echocardiography Protocol

Screening echocardiograms were performed according to an abbreviated protocol, previously used in Tonga and Fiji,[4,22] that focused on the mitral and aortic valves but would also allow detection of significant congenital lesions. Standard views included parasternal long axis, parasternal short axis, and apical 4- and 5-chamber views, noting valve morphology on cross-sectional 2-dimensional imaging, and the presence and extent of mitral or aortic regurgitation using color flow Doppler. Pulse-wave and continuous-wave Doppler interrogation of regurgitant jets was subsequently undertaken to assess velocity, spectral envelope, and duration.

Sonographers were provided with a list of 5 features indicating possible abnormalities (mitral regurgitation [MR] >1 cm, any aortic regurgitation, thickened anterior or posterior mitral valve leaflets, and suspected congenital anomalies.) The presence of any of these features prompted a more detailed, comprehensive echocardiogram, involving additional views and Doppler interrogation of valves undertaken at the time of screening. All of the echocardiograms were recorded to DVD for offsite reporting. Comprehensive echocardiograms were reviewed by a local cardiologist, and decisions about diagnosis and clinical management, including secondary antibiotic prophylaxis, were at the discretion of these clinicians, independent of the study protocol.

Echocardiogram Reporting Protocol

Screening echocardiograms of children at high and low risk were interspersed on the same DVD, and reporters were blinded as to whether the child came from the high- or low-risk cohort. A pool of 14 cardiologists experienced in the diagnosis and management of RHD reported screening echocardiograms according to our own standardized electronic protocol. Data were entered directly into a Microsoft Access database (Microsoft, Redmond, WA).

Comprehensive echocardiograms were read once by a single expert pediatric cardiologist (B.R.) who was also blinded to the risk status of the child. Where there was a discrepancy in the final diagnosis between the screening and comprehensive echocardiograms, the result from the comprehensive study was accepted.

Echocardiographic Definitions

Cardiologist Assessment of Pathology

After viewing all of the echocardiography frames, cardiologists were asked to state whether they considered there to be pathology, and, if so, whether they thought it was RHD. They were asked to categorize RHD as "definite," "probable," or "possible" (suggested definitions were provided for each category).

2012 WHF Criteria for RHD

Children were ultimately classified as having pathologic valvular regurgitation or morphologic abnormalities, and definite or borderline RHD according to the 2012 WHF criteria for the echocardiographic diagnosis of RHD[13] (Table 1). This was done post hoc by extracting each individual echocardiographic feature, as objectively measured and recorded by cardiologists, and combining features to determine whether WHF definitions were met.

Assessment of Interobserver Agreement

A subset of 398 screening echocardiograms was read twice by different cardiologists (all 14 of the cardiologists were involved in the initial reading, and 3 cardiologists were involved in the second read of each echocardiogram). Given the low prevalence of pathology in the cohort overall (and, therefore, the high likelihood that echocardiograms would be normal), we ensured that 50% (197) of the echocardiograms were from children who subsequently required a comprehensive echocardiogram to increase the likelihood of possible valvular abnormalities. We also ensured that there was representation of echocardiograms from Indigenous and non-Indigenous children (N=322 and N=76, respectively).

Statistical Methods

Statistical analysis was performed using Stata statistical package version 12.1 (Stata Corp, College Station, TX). Sample size was calculated on the basis of Northern Territory register estimates that the point prevalence of RHD in those aged 5 to 14 years was 7.6 per 1000 in Indigenous (high-risk) children and 0.2 per 1000 in non-Indigenous (low-risk) children.[19] A sample size of 4000 children at high risk gave a 95% confidence interval (CI) of 5.1 to 10.7 per 1000 around the point prevalence of 7.6 per 1000, which was considered to be sufficiently precise. Using this sample plus a comparison group of 1000 children at low risk was adequate to detect a difference in prevalence at the 0.05 significance level with a power of 80%.

Categorical variables were compared using the χ^2 or Fisher's exact test where appropriate. Multivariate logistic regression was used to control for confounding factors, including age, sex, and BMI when comparing the proportion of children with RHD in each group. The multirater κ statistic was used to assess interobserver agreement.

Results

A total of 5330 children had a screening echocardiogram (Figure 1). Ninety-three children were excluded because of ineligibility, and an additional 31 Indigenous children from the low-risk urban cohort and 207 non-Indigenous children from the high-risk remote cohort were excluded from the final analysis. The demographic characteristics of 1053 non-Indigenous children at low risk and 3946 Aboriginal and/or Torres Strait Islander children at high risk are presented in Table 2. The height, weight, and BMI of children at high risk were all significantly lower than their low-risk counterparts, despite similar age and sex distributions.

A total of 104 low-risk children (9.9%) and 569 high-risk children (14.4%) had a comprehensive echocardiogram performed. Of these 673 comprehensive studies, 487 (72.4%) were considered to be normal (no evidence of RHD meeting WHF criteria or of other cardiac pathology) after review. Thirteen of 4326 children who did not have a comprehensive study were found to have pathology when their screening echocardiogram was reviewed (11 with minor congenital anomalies and 2 with WHF borderline RHD, category A).

Congenital anomalies were identified in 72 high-risk children (1.8%) and 26 low-risk children (2.5%; Table 3). Most were minor anomalies, with the most common being mitral valve prolapse (0.3%) and bicuspid aortic valve (0.4%). Four high-risk children had both RHD and minor congenital anomalies (2 with small atrial septal defects and 2 with a patent ductus arteriosus).

Echocardiographic Findings

Some degree of MR was detected in 18.6% of low-risk children and 22.1% of high-risk children (P=0.015; Table 4). The majority (17.8% and 18.7%, respectively) were subjectively labeled as having trivial MR in both groups. Aortic regurgitation was more common in high-risk children (4.4%) than low-risk children (1.8%; P<0.001). After excluding significant

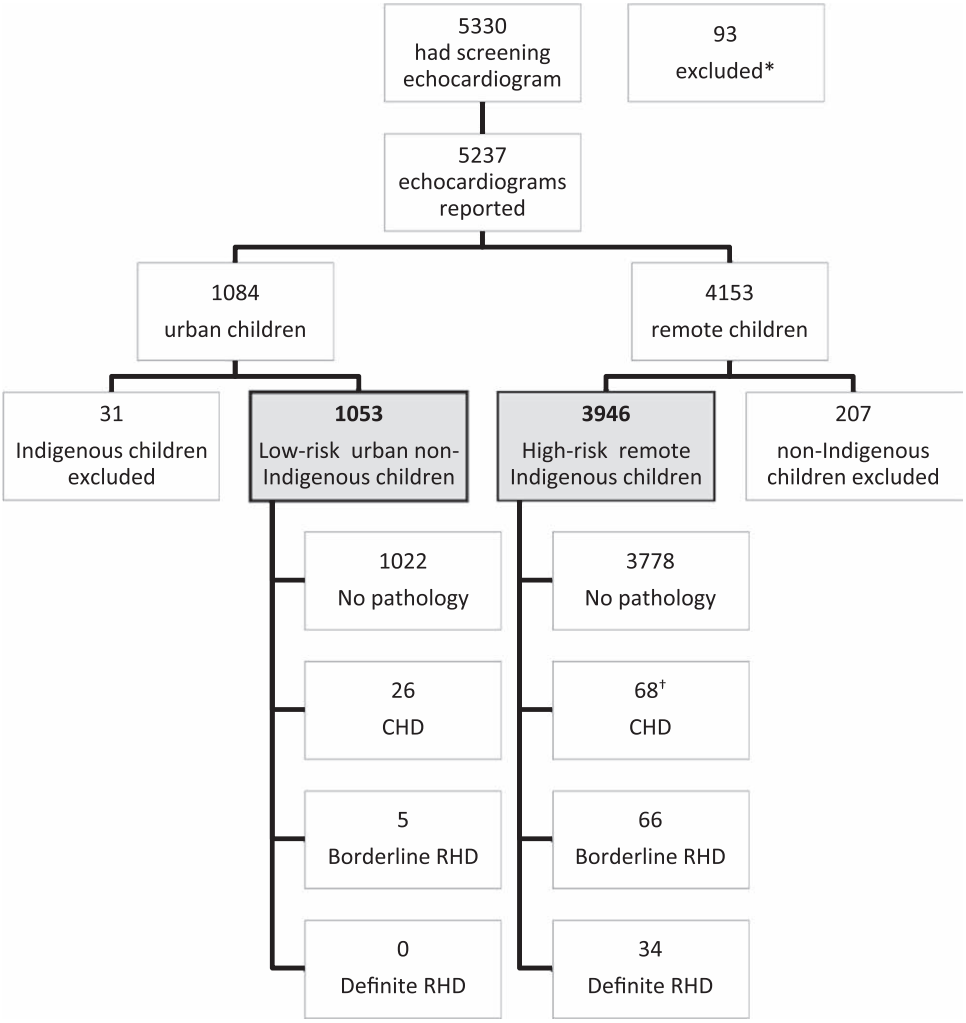

Figure 1. Rheumatic heart disease detected by echocardiographic screening. CHD indicates congenital heart disease; and RHD, rheumatic heart disease. *Exclusions, 67 ineligible because of age; 18, echo quality problem; 7, missing ethnicity; 1, missing consent. †Four additional high-risk children had both CHD (2 atrial septal defects and 2 patent ductus arteriosus) and RHD; they have been categorized as RHD.

congenital pathology, both MR and aortic regurgitation meeting WHF criteria for pathologic regurgitation (defined in Table 1) were more common in high-risk than low-risk children (P=0.001 and P=0.013, respectively). Four children at high risk had both pathologic MR and pathological aortic regurgitation.

One or more morphologic abnormalities of the mitral valve were reported in 2.2% of the low-risk group and 2.9% of the high-risk group (P=0.227). The most common abnormality in both groups was a thickened anterior mitral valve leaflet (defined by the WHF criteria as ≥3 mm at its thickest point, measured in late diastole). Two or more morphologic abnormalities of the mitral valve meeting WHF criteria were reported in 0.2% of low-risk children and 1.2% of high-risk children (P=0.003). Morphologic abnormalities of the aortic valve were seen in 0.6% of the low-risk group and 0.9% of the high-risk group (P=0.36).

Application of WHF Criteria

No low-risk child met the WHF criteria for definite RHD (Table 5) compared with 34 high-risk children (0.9%; P=0.003). Five low-risk children (0.5%) and 66 high-risk children (1.7%) met criteria for borderline RHD (adjusted odds ratio, 3.7 [95% CI, 1.5–9.3]; P<0.005). The odds ratio for a diagnosis of definite or borderline RHD in high-risk compared to low-risk children was 5.7 (95% CI, 2.3–14.1; P<0.001).

The prevalence of definite RHD in high-risk children was 8.6 per 1000 (95% CI, 6.0–12.0 per 1000), and borderline RHD was 16.7 per 1000 (95% CI, 13.0–21.2 per 1000). The prevalence of both definite and borderline RHD increased with age, peaking at 46.9 per 1000 in 12-year-old children (Figure 2), with a prevalence of 17.3 per 1000 children aged 5 to 9 years (95% CI, 12.4–23.4) and 36.8 per 1000 children aged 10 to 14 years (95% CI, 28.2–47.2). There were no significant differences in the proportion of girls among cases of definite RHD (52.9%), borderline RHD (45.5%), or those without RHD (49.2%).

Of the 34 children who met criteria for definite RHD, 27 (79.4%) had isolated mitral valve disease, of whom 3 had mitral stenosis. Eighteen children with definite RHD (52.9%) were new cases (no previous history of ARF or RHD). Of these 18, the severity of RHD (subjectively graded, on the basis of expert review of the comprehensive echocardiogram) was considered to be mild in 10, moderate in 7, and severe in 1 (this child had clinical ARF at the time of screening and was referred immediately to the hospital).

Table 2. Demographic Characteristics of Children Screened

Characteristic	Low Risk (n=1053)		High Risk (n=3946)	
	Number	%	Number	%
Sex				
Male	514	48.8	2006	50.9
Female	539	51.2	1940	49.1
Ethnicity				
Aboriginal Australian	0	0.0	3422	86.7
Torres Strait Islander	0	0.0	307	7.8
Aboriginal Australian and Torres Strait Islander	0	0.0	217	5.5
Caucasian	979	93.0	0	0.0
Other	74	7.0	0	0.0
	Median	IQR	Median	IQR
Age, y	9.4	7.0–11.8	9.3	7.3–11.4
Weight, kg	31.7	24.6–42.7	28.0*	21.8–38.7
Height, cm	138.5	125.5–152.2	133.5*	121.2–147.0
BMI, kg/m^2	16.7	15.3–18.7	15.8*	14.5–18.1

IQR indicates interquartile range.
*P<0.001.

Comparison of Cardiologist Assessment With WHF Criteria

Abnormalities thought to represent RHD by cardiologists were reported in 215 high-risk children (5.5%) and 29 low-risk children (2.8%; P<0.001). Cardiologists identified more than twice as many cases of RHD (n=244) as the WHF criteria (n=105). When compared with the WHF criteria, cardiologist opinion had a positive predictive value of 41.0%. Of the 144 cases assessed by cardiologists as having RHD but who did not fulfill the WHF criteria, >90% had been labeled as "possible RHD" by reporting cardiologists. Two thirds had MR that did not meet WHF criteria for pathologic MR.

Table 3. Congenital Cardiac Anomalies Detected by Screening Echocardiography

Congenital Anomaly	Low Risk (n=1053)		High Risk (n=3946)	
	n	%	n	%
Mitral valve prolapse	9	0.9	7	0.2
Bicuspid aortic valve	6	0.6	16	0.4
Dilated aortic root	6	0.6	10	0.3
Atrial septal defect	1	0.1	5	0.1
Patent ductus arteriosus	2	0.2	12	0.3
Ventricular septal defect	0	0.0	8	0.2
Other CHD*	2	0.2	14	0.4
Total	26	2.5	72	1.8

CHD indicates congenital heart disease.
*This includes 2 postoperative CHD, 4 minor mitral valve anomalies, 1 left atrial accessory tissue, 1 subaortic stenosis, 3 mild pulmonary stenosis, 1 minor aortic valve abnormality, 1 left ventricular hypertrophy, 1 pericardial effusion, and 2 dilated right ventricle.

Table 4. Echocardiographic Findings in Children at Low and High Risk of RHD

Echocardiographic Finding	Low Risk (n=1030)		High Risk (n=3891)		P Value
	n	%	n	%	
MR					
Any MR	192	18.6	861	22.1	0.015
MR 1 cm to <2 cm	35	3.4	136	3.5	0.814
MR ≥2 cm	7	0.7	86	2.2	0.001
WHF pathologic MR*	2	0.2	57	1.5	0.001
AR					
Any AR	18	1.8	171	4.4	<0.001
AR 0.5 cm to <1.0 cm	4	0.4	19	0.5	0.656
AR ≥1.0 cm	3	0.3	68	1.8	<0.001
WHF pathologic AR*	1	0.1	30	0.8	0.013
MV abnormality					
Any MV abnormality	23	2.2	114	2.9	0.227
AMVL thickening ≥3 mm	16	1.6	83	2.1	0.239
Chordal thickening	2	0.2	21	0.5	0.200
Restricted leaflet motion	4	0.4	32	0.8	0.215
Excessive leaflet tip motion	0	0.0	16	0.4	0.032
WHF criteria for abnormal MV	2	0.2	45	1.2	0.003
AV abnormality					
Any AV abnormality	6	0.6	34	0.9	0.355
Irregular or focal thickening	5	0.5	29	0.8	0.371
Coaptation defect	0	0.0	0	0.0	NA
Restricted leaflet motion	0	0.0	1	0.0	1.000
Prolapse	0	0.0	2	0.1	1.000
WHF criteria for abnormal AV	0	0.0	3	0.1	1.000

AMVL indicates anterior mitral valve leaflet; AR, aortic regurgitation; AV, aortic valve; MR, mitral regurgitation; MV, mitral valve; NA, not applicable (P value unable to be calculated because of 0 findings in both groups); and WHF indicates World Heart Federation.
*Pathologic MR and AR are defined in Table 1. Children with congenital pathology other than patent ductus arteriosus or atrial septal defect have been excluded.

Assessment of Interobserver Agreement

For the 398 echocardiograms read in duplicate by different cardiologists, there was moderate agreement (>90%, κ=0.4–0.6) in response to the questions, "Is the mitral/aortic valve normal?" and "Is there significant mitral/aortic regurgitation?" Agreement was lower in response to the questions, "Is there any pathology" (83.4%; κ=0.4) and "Is the pathology RHD?" (83.9%; κ=0.3).

Discussion

This is the first study to simultaneously undertake echocardiographic screening for RHD in a large cohort of children at high and low risk in a blinded fashion. Our rigorous reporting procedures permitted an objective assessment of the performance of clearly defined RHD diagnostic criteria, and we also provided the best available data on normal echocardiographic findings in low-risk children.

Table 5. Rheumatic Heart Disease Cases Broken Down by WHF Category

RHD Category	WHF Definition	Low Risk (n=1053) n	Low Risk (n=1053) %	High Risk (n=3946) n	High Risk (n=3946) %
Definite RHD		0	0.0	34	0.9
Definite RHD (A)	Pathologic MR + abnormal MV	0		26*	
Definite RHD (B)	Mitral stenosis	0		3†	
Definite RHD (C)	Pathologic AR + abnormal AV	0		3	
Definite RHD (D)	Borderline disease of MV and AV	0		2‡	
Borderline RHD		5	0.5	66	1.7
Borderline RHD (A)	2 or more MV morphologic abnormalities	2		16	
Borderline RHD (B)	Pathologic MR	2		27	
Borderline RHD (C)	Pathologic AR	1		23	

AR indicates aortic regurgitation; AV, aortic valve; MR, mitral regurgitation; MV, mitral valve; and WHF, World Heart Federation; Pathologic MR and AR, as well as morphological abnormalities of the MV and AV, are defined in Table 1.

*Two of these children also had pathologic AR.

†Two of these children also met criteria for definite category (A).

‡ Both of these children had pathologic MR and AR.

The prevalence of definite RHD in remote Aboriginal Australian and Torres Strait Islander children was 8.6 per 1000, which approximates previous estimates based on routine surveillance from the Northern Territory RHD register[14,15] and which is comparable to rates of RHD detected by echocardiographic screening in other high-risk populations.[5,10,11,23] No child at low risk in our study met the criteria for definite RHD, and all 34 cases of definite RHD identified by the WHF criteria were also assessed as having definite RHD by reporting cardiologists.

It is difficult to directly compare our rates of definite RHD with other echocardiographic screening surveys, because echocardiographic definitions vary considerably, with most studies using less-stringent criteria than the WHF criteria.[12] Earlier studies used the 2001 World Health Organization definition of pathologic MR [24] (jet length, >1 cm compared with ≥2 cm in the WHF criteria) as a marker for RHD. It is not surprising, therefore, that some studies using these sensitive criteria reported RHD rates in excess of 30 per 1000.[3,4,6]

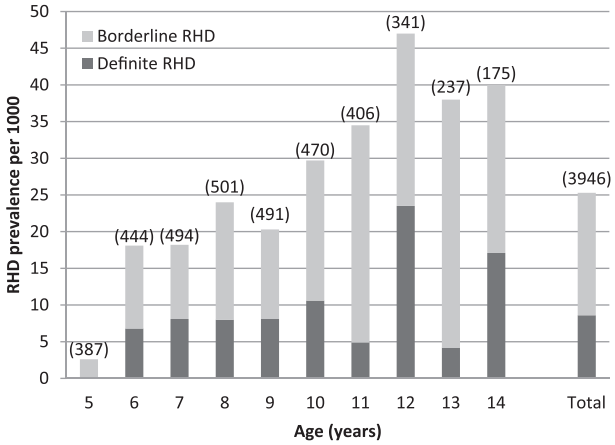

Figure 2. Rheumatic heart disease (RHD) prevalence in high-risk remote Indigenous children by age and World Heart Federation category. (n) indicates number of children screened in each age group. Prevalence of RHD (95% confidence interval), 5–9 years; definite=6.5 per 1000 (3.6–10.7), borderline=10.8 per 1000 (7.0–15.0); 10–14 years, definite=11.7 per 1000 (7.0–18.2), borderline=25.2 per 1000 (18.1–34.0).

In 2006, the National Institutes of Health and World Health Organization published updated consensus guidelines for the diagnosis of RHD[25] that more closely resemble the WHF criteria, because they consider structural as well as functional valvular abnormalities. Three large screening studies have used the National Institutes of Health/World Health Organization criteria. The combined prevalence of definite, probable, and possible RHD was 14.8 per 1000 in Uganda,[10] 48.0 per 1000 in Nicaragua,[5] and 56.5 per 1000 in Maori and Pacific Islander children in New Zealand[7] compared with a combined prevalence of definite and borderline RHD of 25.3 per 1000 (95% CI, 20.7–30.7) in our high-risk population. Possible explanations for such variation include true differences in prevalence (which may be affected by selection bias, eg, in the New Zealand study, an older group of children from the poorest schools was selected), differences in case definitions (the National Institutes of Health/World Health Organization criteria include children with a single morphologic abnormality of the mitral valve as "possible RHD," whereas the WHF criteria do not), and differences in reporting methodologies.

In our study, the echocardiographic finding of borderline RHD was not restricted to children at high risk; the prevalence of borderline RHD was 16.7 per 1000 in our high-risk group compared with 4.7 per 1000 in the low-risk group (adjusted odds ratio, 3.7 [95% CI, 1.5–9.3]; $P<0.005$). The clinical significance of the borderline RHD category in individuals without a past history of rheumatic fever remains unclear. The WHF states that it was, "established to improve the sensitivity of the test at the expense of specificity,"[13] and our data support the assertion by the WHF that a diagnosis of borderline RHD may not necessarily represent true disease. However, the increased likelihood of this finding in our high-risk group suggests that this echocardiographic entity deserves further attention and evaluation. We believe that the echocardiographic

findings in the 5 children at low risk meeting criteria for borderline RHD are more likely to represent the upper range of normal findings (and, hence, false-positive results) than true RHD. We consider a false-positive rate of 0.5% to be acceptable and indeed a reassuring indicator of the criteria's sensitivity. If this estimated false-positive rate of 0.5% from our low-risk cohort were extrapolated to the high-risk group, up to one third of the children at high risk who were identified with borderline RHD may also be false-positive cases. A clear priority in developing accurate echocardiographic screening approaches will be to identify features within the borderline category that make a diagnosis of true RHD more likely.

The natural history of valvular changes consistent with borderline RHD is not known. Three studies have followed children with subclinical RHD (echocardiographic changes in the absence of a pathologic murmur) detected incidentally by screening echocardiogram.[5,9,26] However, different echocardiographic definitions, short follow-up periods, and incomplete information about secondary prophylaxis make it difficult to draw conclusions from their data. We are following up high-risk children with borderline RHD and other mild echocardiographic abnormalities, as well as matched controls with normal echocardiograms.[27] Understanding the natural history of borderline RHD and refining our ability to identify children within this group who have true disease that is likely to progress will allow us to better target treatment to those who need it and reduce unnecessary treatment for those who do not.

To our knowledge, this is the first echocardiographic screening study to simultaneously evaluate children at high and low risk of RHD with reporting cardiologists blinded to risk status. Previous studies have relied on consensus expert opinion to allocate final RHD diagnostic category rather than the compilation of a series of objectively measured data points, as we have done. Although reporting cardiologists in previous studies may have been blinded to clinical findings, all would have been aware that the echocardiograms were of children at high risk for RHD. In our study, the observed discrepancy between the proportion of RHD cases diagnosed by cardiologists compared with those diagnosed by application of the WHF criteria raises 2 possibilities: that the WHF criteria are insufficiently sensitive or that cardiologists experienced in managing RHD in high-risk children may be susceptible to observer bias, preferring to be overinclusive in their diagnosis rather than to risk missing a potential case.

A high rate of false-positive results has important implications for screening programs, both to the individual and his or her family (dealing with the possibility of an incorrect diagnosis of a chronic disease) and to the health system (allocating resources to the further evaluation of potential cases, which may be particularly difficult in developing countries and remote settings).[28] This needs to be balanced against the possibility of false-negative results, with the associated longer-term health consequences of individuals presenting later with severe RHD that could otherwise have been prevented by earlier commencement of secondary prophylaxis. Together with the relatively low rate of interobserver agreement on the presence of pathology or of RHD, these considerations highlight the need for further validation of objective diagnostic criteria and for ensuring that approaches to performing and analyzing screening echocardiograms are standardized.

Concerns have been raised that the WHF criteria may be too complex for immediate application in the field, particularly in resource-poor settings.[23,29–31] Simplified screening protocols have been proposed, such as the single criterion of a mitral regurgitant jet of ≥2 cm seen in any plane.[23] Applied to our high-risk cohort, this criterion would have a sensitivity of 63.0% and a positive predictive value of 73.3% for definite and borderline RHD, with a specificity and negative predictive value of >99%. If only definite RHD is considered, a single MR jet ≥2 cm would detect 91.2% of cases, with a positive predictive value of 36.1% and specificity and negative predictive value >98.5%. There is practical appeal to this approach, particularly if considering the use of minimally trained staff to perform the initial screening echocardiogram, as has been recently piloted in Fiji.[31]

When applied to our data, the sensitivity and specificity of a single MR jet ≥2 cm for detecting definite RHD are high, despite the lower positive predictive value. However, all of the children with isolated morphologic abnormalities of the mitral valve (n=16 in our study), plus all of the children with pathologic aortic regurgitation in the absence of MR (n=26, 3 of whom met criteria for definite RHD), would be missed, resulting in the much lower sensitivity for detecting borderline cases. Although others have suggested that isolated aortic valve disease is a rare manifestation of RHD,[23] this group represented one third of our borderline cases, so a simplified protocol could potentially be expanded to include detection of significant aortic regurgitation, as well as MR. It is imperative to establish the significance of each borderline RHD category before recommending the use of abbreviated echocardiographic protocols.

A technical limitation of this study was that sonographers were asked to optimize contrast and gain settings rather than having these specified. Despite an otherwise standardized protocol, minor variations in image quality were observed by reporting cardiologists.

Another limitation of this study was our sampling method. A school-based approach to screening is practical but potentially excludes those who may be most at risk of disease, children who are not regular school attendees. We did not collect precise information about the number of eligible children in each school or about the number of eligible children not enrolled in school (although this is appears to be negligible when comparing school enrollment data with census data). However, we know that the average attendance for the participating remote schools was 67% and that the total number of children enrolled (all ages and all ethnicities) was 9691, of whom 9000 would be estimated to be Indigenous.[18] We, therefore, estimate that we screened ≈50% of age-eligible Indigenous children in the participating communities.

This self-selection of participants as a result of attending school is particularly relevant in our setting, where school attendance is frequently <70%, and it is likely that the true prevalence of RHD in remote Indigenous children is higher than that ascertained by our study. This is critical information to take into account when evaluating the use of screening, as is the fact that only half of the definite RHD cases identified in our study were new cases. There are many elements

to consider before instigating any screening program,[12] but important principles are that screening is accessible to those at highest risk of disease and that the number of new cases detected and amenable to treatment is sufficient to justify the costs (financial and otherwise) of the screening process.

We conclude that echocardiographic findings meeting the WHF definitions of definite RHD are likely to represent true pathology, and the prevalence of definite RHD in nearly 1% of high-risk remote Indigenous children is what we expected in our population. Caution must be exercised in interpreting findings consistent with borderline RHD, because they are likely to overlap with the upper range of normal findings in children. However, given the significantly higher prevalence of borderline RHD in our high-risk population, this category cannot be ignored, and longitudinal follow-up of these children is important. Although it is not yet possible to advocate for routine echocardiographic screening for RHD, we propose that the WHF criteria be adopted internationally in further echocardiographic screening studies to allow standardization of RHD diagnosis, comparison of RHD prevalence, and recruitment of children with similar echocardiographic findings to follow-up studies.

Acknowledgments

We gratefully acknowledge the work of study staff Colette Davis, Loraine Kelpie, Vijaya Joshi, Yvonne Hodder, Rhona Dawson, and Dr Sally Stokes, together with the study echocardiographers and cardiologists. We also thank the staff and students at the participating schools.

Sources of Funding

This study was funded by the Australian government. Additional funding was received from the Children First Foundation, Kiwanis clubs of Australia (Heartkids), and Cabrini Health. Dr Roberts was supported by an Australian Postgraduate Award from Charles Darwin University. Associate Professor Maguire is supported by a National Health and Medical Research Council Practitioner Fellowship and the Margaret Ross Chair in Indigenous Health.

Disclosures

None.

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CLINICAL PERSPECTIVE

Rheumatic heart disease (RHD) affects ≈20 million people worldwide, and whilst disease burden is highest in developing countries, it remains a significant cause of morbidity and mortality in the Australian Indigenous population. Over the past decade, there has been increasing interest in echocardiographic screening for RHD, in the hope that earlier detection and instigation of secondary prophylaxis will improve patient outcome. However, methodologies and echocardiographic definitions have varied, making comparisons between studies difficult. In 2012, the World Heart Federation published evidence-based guidelines for the echocardiographic diagnosis of RHD, but these criteria have not yet been applied to a screened cohort. Our study is the first to apply these criteria to a large cohort of Indigenous Australian children at high risk for RHD, providing the first cross-sectional prevalence data in our population. In addition, we included a cohort of non-Indigenous children at low risk for RHD, providing detailed information about normal echocardiographic findings in children and allowing some assessment of the performance of the World Heart Federation criteria when applied to these 2 different risk groups in a blinded, standardized fashion. Our results suggest that that children meeting World Heart Federation criteria for definite RHD are likely to have true disease, but that the borderline RHD group is likely to include children with echocardiographic findings in the upper range of normal. Longitudinal follow-up is essential to establish the clinical significance of borderline RHD in particular. We propose that the World Heart Federation criteria be adopted internationally in future echocardiographic screening studies to allow meaningful comparisons between populations and recruitment of children with similar echocardiographic findings to follow-up studies.