Echocardiographic Screening for Rheumatic Heart Disease in High and Low Risk Australian Children

Running title: Roberts et al.; Echocardiographic screening for RHD in Australia

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Abstract

**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 (WHF) 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 to 15 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 WHF criteria for Definite RHD (prevalence 8.6 per 1000; 95% CI 6.0-12.0) and 66 for Borderline RHD (prevalence 16.7 per 1000; 95% CI 13.0-21.2). Of 1053 low-risk children, none met criteria for Definite RHD, and 5 met 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% CI 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 low risk children. This study suggests that Definite RHD, as defined by the WHF criteria, is likely to represent true disease. Borderline RHD was identified in both low- and high-risk children, highlighting the need for longitudinal studies to evaluate the clinical significance of this finding.

**Key words:** rheumatic heart disease, echocardiography, pediatrics, screening
Background

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

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. The reported prevalence of RHD detected by screening in school-aged children from high-risk populations varies widely, from 5 per 1000 to over 50 per 1000, but echocardiographic definitions used in these studies vary, making direct comparisons difficult. 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. In the absence of an established gold standard test for the diagnosis of RHD, and given that publications to date have focused exclusively on high-risk children, it is difficult to assess whether this is indeed the case.

There are three 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 ‘normal 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 over-diagnosis 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.
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 amongst the highest rates in the world, with an ARF incidence of around 200 per
100,000 children aged 5-14 years,14 and an estimated RHD prevalence of 8.5 per 1,000 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 high-risk remote Indigenous Australian
children, 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 RHD-positive children in the remote Indigenous cohort,
while RHD should be virtually absent in low-risk children.

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 comprised Aboriginal and Torres Strait Islander children living in remote communities from four 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 about 74,000 (40-50% of the total population), with approximately 16,000 Indigenous children aged 5-14 years old (Australian Bureau of Statistics; www.abs.gov.au). Thirty-two communities of different sizes were selected (population range 150 - 3000 residents), and were distributed across a vast area (>2 million km²), encompassing both tropical and desert regions. Using standardized Australian measures of socioeconomic disadvantage which incorporate data on income, education, employment and housing, all participating communities had scores in the lowest decile, between 3 and 4 standard deviations below the Australian average (http://www.abs.gov.au/websitedbs/censushome.nsf/home/seifa). The average proportion of Indigenous students enrolled in participating remote schools was 94.5%.

The low-risk cohort was selected from five 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 (Australian Curriculum, Assessments and Reporting Authority; www.myschool.edu.au). Over 90% of students in the selected urban schools were non-Indigenous.

Children were identified by the enrolment record of participating schools and recruited at school or, for those not present at school on screening days, by approaching families. All 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\textsuperscript{14-18} and our aim was to analyze two populations based on \textit{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 $\geq$13 years. Attempts were made to locate children who were absent from school on the day of screening, and multiple screening days in each site were undertaken 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 \textsuperscript{e}TM or Vivid \textsuperscript{i}TM (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 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,\textsuperscript{4,19} 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 four- and five-chamber views, noting valve morphology on cross-sectional two-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 five features indicating possible abnormalities
(mitral regurgitation >1cm, 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 echocardiograms were recorded
to DVD for off-site 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 high-risk and low-risk children 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.

Comprehensive echocardiograms were read once by a single expert pediatric cardiologist
(BR) 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**

(i) Cardiologist assessment of pathology
After viewing all echocardiography frames, cardiologists were asked to state whether they considered there to be pathology or not, 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).

(ii) 2012 World Heart Federation criteria for RHD

Children were ultimately classified as having pathological valvular regurgitation or morphological abnormalities, and Definite or Borderline RHD according to the 2012 WHF criteria for the echocardiographic diagnosis of RHD\textsuperscript{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 inter-observer agreement

A subset of 398 screening echocardiograms was read twice by different cardiologists (all 14 cardiologists were involved in the initial reading, and three 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 (322 and 76, respectively).

Statistical methods

Statistical analysis was performed using Stata\textsuperscript{TM} statistical package version 12.1 (StataCorp, Texas, USA). Sample size was calculated based on Northern Territory register estimates that the point prevalence of rheumatic heart disease in those aged 5-14 years was 7.6 per 1000 in
Indigenous (high risk) children, and 0.2 per 1000 in non-Indigenous (low risk) children. A sample size of 4000 high risk children gave a 95% confidence interval (CI) of 5.1-10.7 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 low risk children 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 chi-squared test or Fisher’s exact test where appropriate. Multivariate logistic regression was used to control for confounding factors including age, sex and body mass index (BMI) when comparing the proportion of children with RHD in each group. The multi-rater kappa statistic was used to assess inter-observer agreement.

Results

A total of 5330 children had a screening echocardiogram (Figure 1). Ninety-three children were excluded due to 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 low-risk non-Indigenous children and 3946 high-risk Aboriginal and/or Torres Strait Islander children are presented in Table 2. The height, weight and BMI of high-risk children were all significantly lower than their low-risk counterparts, despite similar age and gender distributions.

One hundred and four 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 two with WHF Borderline RHD, category A).

Congenital anomalies were identified in 72 (1.8%) high-risk children and 26 (2.5%) low-risk children (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 (two with small atrial septal defects, and two with a patent ductus arteriosus).

**Echocardiographic findings (Table 4)**

Some degree of mitral regurgitation (MR) was detected in 18.6% of low-risk children and 22.1% of high-risk children (p=0.015). The majority (17.8% and 18.7% respectively) was subjectively labeled as ‘trivial MR’ in both groups. Aortic regurgitation (AR) was more common in high-risk children (4.4%) than low-risk children (1.8%, p<0.001). After excluding significant congenital pathology, both MR and AR meeting WHF criteria for pathological regurgitation (defined in Table 1) were more common in high-risk than low-risk children (p=0.001, p=0.013 respectively). Four high-risk children had both pathological MR and pathological AR.

One or more morphological 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 ≥3mm at its thickest point, measured in late diastole). Two or more morphological 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). Morphological 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 children met the WHF criteria for Definite RHD (Table 5), compared with 34 high-
risk children (0.9%; p=0.003). Five (0.5%) low-risk children and 66 (1.7%) high-risk children met criteria for Borderline RHD (adjusted OR 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 8.6/1000 (95% CI 6.0-12.0/1000) and Borderline RHD was 16.7/1000 (95% CI 13.0-21.2/1000). The prevalence of both Definite and Borderline RHD increased with age, peaking at 46.9/1000 in 12 year olds (Figure 2), with a prevalence of 17.3 per 1000 children aged 5-9 years (95% CI 12.4-23.4), and 36.8 per 1000 children aged 10-14 years (95% CI 28.2-47.2). There were no significant differences in the proportion of females between 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, based on expert review of the comprehensive echocardiogram) was considered to be mild in 10, moderate in 7 and severe in one (this child had clinical ARF at the time of screening and was referred immediately to hospital).

**Comparison of cardiologist assessment with WHF criteria**

Abnormalities thought to represent RHD by cardiologists were reported in 215 (5.5%) high-risk children and 29 (2.8%) low-risk children (p<0.001). Cardiologists identified over 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, over 90% had been labeled
as ‘possible RHD’ by reporting cardiologists. Two thirds had MR which did not meet WHF criteria for pathological MR.

Assessment of inter-observer agreement

For the 398 echocardiograms read in duplicate by different cardiologists, there was moderate agreement (>90%, kappa 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%, kappa 0.4), and ‘Is the pathology RHD?’ (83.9%, kappa 0.3).

Discussion

This is the first study to simultaneously undertake echocardiographic screening for RHD in a large cohort of high-risk and low-risk children 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.

The prevalence of Definite RHD in remote Aboriginal Australian and Torres Strait Islander children was 8.6/1000, which approximates previous estimates based on routine surveillance from the Northern Territory RHD register, and is comparable to rates of RHD detected by echocardiographic screening in other high-risk populations. No low-risk child 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. Earlier studies used the 2001 World Health Organization (WHO) definition of pathological mitral regurgitation (jet length >1cm, compared with ≥2cm 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 1000.13

In 2006, the National Institutes of Health (NIH) and WHO published updated consensus guidelines for the diagnosis of RHD which more closely resemble the WHF criteria, as they consider structural as well functional valvular abnormalities. Three large screening studies have used the NIH/WHO 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; for example, in the New Zealand study, an older group of children from the poorest schools was selected), differences in case definitions (the NIH/WHO criteria will include children with a single morphological abnormality of the mitral valve as ‘Possible RHD’, whereas the WHF criteria will not), and differences in reporting methodologies.

In our study, the echocardiographic finding of Borderline RHD was not restricted to high-risk children; 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 OR 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 WHF’s assertion 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 five low-risk children 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 high-risk children 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 which 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 pathological murmur) detected incidentally by screening echocardiogram. 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, plus matched controls with normal echocardiograms. 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 high- and low-risk children 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. Whilst 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 to those diagnosed by application of the WHF criteria raises two 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 over-inclusive 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 their family (dealing with the possibility of an incorrect diagnosis of a chronic disease), and the health system (allocating resources to the further evaluation of potential cases, which may be particularly difficult in developing countries and remote settings). 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 which could otherwise have been prevented by earlier commencement of secondary prophylaxis. Together with the relatively low rate of inter-observer 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. Simplified screening protocols have been proposed, such as the single criterion of a mitral regurgitant jet of ≥2cm seen in any plane. Applied to our high-risk cohort, this criterion would have a sensitivity of 63.0%, and a positive predictive value (PPV) of 73.3% for Definite and Borderline RHD, with a
specificity and negative predictive value (NPV) of >99%. If only Definite RHD is considered, a single MR jet ≥2cm would detect 91.2% of cases, with a PPV of 36.1% and specificity and NPV >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.28

When applied to our data, the sensitivity and specificity of a single MR jet ≥2cm for detecting Definite RHD is high, despite the lower PPV. However, all children with isolated morphological abnormalities of the mitral valve (n=16 in our study), plus all children with pathological aortic regurgitation in the absence of mitral regurgitation (n=26, 3 of whom met criteria for Definite RHD), would be missed, resulting in the much lower sensitivity for detecting Borderline cases. Whilst others have suggested that isolated aortic valve disease is a rare manifestation of RHD,20 this group represented one third of our Borderline cases, so a simplified protocol could potentially be expanded to include detection of significant aortic as well as mitral regurgitation. It is imperative to establish the significance of each Borderline RHD category prior to 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 enrolment 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, all ethnicities) was 9691, of whom 9000 would be estimated to be Indigenous (www.myschool.edu.au). We therefore estimate that we screened around 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 below 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 utility 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 prior to instigating any screening program, 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.

Conclusions
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 as 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.

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**Conflict of Interest Disclosures:** None.

**References:**


Table 1. World Heart Federation criteria for the echocardiographic diagnosis of RHD in individuals aged ≤20 years.13

**Echocardiographic criteria for RHD**

**Definite RHD (either A, B, C or D):**
A) Pathological MR and at least two morphological features of RHD of the MV
B) MS mean gradient ≥ 4 mmHg
C) Pathological AR and at least two morphological features of RHD of the AV
D) Borderline disease of both the AV and MV

**Borderline RHD (either A, B or C):**
A) At least two morphological features of RHD of the MV without pathological MR or MS
B) Pathological MR
C) Pathological AR

**Echocardiographic criteria for pathological regurgitation**
(all four Doppler criteria must be met)

<table>
<thead>
<tr>
<th>Pathological MR</th>
<th>Pathological AR</th>
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<tbody>
<tr>
<td>1. Seen in two views</td>
<td>1. Seen in two views</td>
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<tr>
<td>2. In at least one view jet length ≥ 2 cm†</td>
<td>2. In at least one view jet length ≥ 1 cm†</td>
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<tr>
<td>3. Peak velocity ≥ 3m/sec for one complete envelope</td>
<td>3. Peak velocity ≥ 3m/sec in early diastole</td>
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<tr>
<td>4. Pan-systolic jet in at least one envelope</td>
<td>4. Pan-diastolic jet in at least one envelope</td>
</tr>
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**Morphological features of RHD**

<table>
<thead>
<tr>
<th>Features in the MV</th>
<th>Features in the AV</th>
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<tbody>
<tr>
<td>1. AMVL thickening ≥ 3mm‡</td>
<td>1. Irregular or focal thickening</td>
</tr>
<tr>
<td>2. Chordal thickening</td>
<td>2. Coaptation defect</td>
</tr>
<tr>
<td>3. Restricted leaflet motion</td>
<td>3. Restricted leaflet motion</td>
</tr>
<tr>
<td>4. Excessive leaflet tip motion during systole</td>
<td>4. Prolapse</td>
</tr>
</tbody>
</table>

*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 non-magnified (non-zoomed) 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. RHD- rheumatic heart disease; MR- mitral regurgitation; MV- mitral valve; MS-mitral stenosis; AR- aortic regurgitation; AV- aortic valve; AMVL- anterior mitral valve leaflet.
Table 2. Demographic characteristics of children screened.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low risk (n=1053)</th>
<th></th>
<th>High risk (n=3946)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
<td></td>
<td>Number (%)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>514 (48.8%)</td>
<td>2006 (50.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>539 (51.2%)</td>
<td>1940 (49.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aboriginal Australian</td>
<td>0 (0.0%)</td>
<td>3422 (86.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torres Strait Islander</td>
<td>0 (0.0%)</td>
<td>307 (7.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aboriginal Australian &amp; Torres Strait Islander</td>
<td>0 (0.0%)</td>
<td>217 (5.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>979 (93.0%)</td>
<td>0 (0.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>74 (7.0%)</td>
<td>0 (0.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong> (years)</td>
<td>9.4 (7.0-11.8)</td>
<td>9.3 (7.3-11.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weight</strong> (kg)</td>
<td>31.7 (24.6-42.7)</td>
<td>28.0* (21.8-38.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Height</strong> (cm)</td>
<td>138.5 (125.5-152.2)</td>
<td>133.5* (121.2-147.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BMI</strong> (kg/m2)</td>
<td>16.7 (15.3-18.7)</td>
<td>15.8* (14.5-18.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IQR- inter-quartile range. BMI- body mass index. *p<0.001

Table 3. Congenital cardiac anomalies detected by screening echocardiography.

<table>
<thead>
<tr>
<th>Congenital anomaly</th>
<th>Low risk (n=1053)</th>
<th></th>
<th>High risk (n=3946)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
<td></td>
<td>Number (%)</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>9 (0.9%)</td>
<td>7 (0.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>6 (0.6%)</td>
<td>16 (0.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated aortic root</td>
<td>6 (0.6%)</td>
<td>10 (0.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>1 (0.1%)</td>
<td>5 (0.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>2 (0.2%)</td>
<td>12 (0.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>0 (0.0%)</td>
<td>8 (0.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other CHD*</td>
<td>2 (0.2%)</td>
<td>14 (0.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>26 (2.5%)</td>
<td>72 (1.8%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CHD- congenital heart disease. *Includes 2 post-operative 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, 2 dilated right ventricle.
Table 4. Echocardiographic findings in high-risk and low risk-children.

<table>
<thead>
<tr>
<th>Echocardiographic finding</th>
<th>Low risk (n=1030)</th>
<th>High risk (n=3891)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mitral regurgitation (MR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any MR</td>
<td>192 (18.6%)</td>
<td>861 (22.1%)</td>
<td>p=0.015</td>
</tr>
<tr>
<td>MR 1cm to &lt;2cm</td>
<td>35 (3.4%)</td>
<td>136 (3.5%)</td>
<td>p=0.814</td>
</tr>
<tr>
<td>MR ≥ 2cm</td>
<td>7 (0.7%)</td>
<td>86 (2.2%)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>WHF pathological MR†</td>
<td>2 (0.2%)</td>
<td>57 (1.5%)</td>
<td>p=0.001</td>
</tr>
<tr>
<td><strong>Aortic regurgitation (AR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AR</td>
<td>18 (1.8%)</td>
<td>171 (4.4%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>AR 0.5cm to &lt;1cm</td>
<td>4 (0.4%)</td>
<td>19 (0.5%)</td>
<td>p=0.656</td>
</tr>
<tr>
<td>AR ≥ 1cm</td>
<td>3 (0.3%)</td>
<td>68 (1.8%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>WHF pathological AR†</td>
<td>1 (0.1%)</td>
<td>30 (0.8%)</td>
<td>p=0.013</td>
</tr>
<tr>
<td><strong>Mitral Valve (MV) abnormality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any MV abnormality</td>
<td>23 (2.2%)</td>
<td>114 (2.9%)</td>
<td>p=0.227</td>
</tr>
<tr>
<td>AMVL thickening ≥3mm</td>
<td>16 (1.6%)</td>
<td>83 (2.1%)</td>
<td>p=0.239</td>
</tr>
<tr>
<td>Chordal thickening</td>
<td>2 (0.2%)</td>
<td>21 (0.5%)</td>
<td>p=0.200</td>
</tr>
<tr>
<td>Restricted leaflet motion</td>
<td>4 (0.4%)</td>
<td>32 (0.8%)</td>
<td>p=0.215</td>
</tr>
<tr>
<td>Excessive leaflet tip motion</td>
<td>0 (0.0%)</td>
<td>16 (0.4%)</td>
<td>p=0.032</td>
</tr>
<tr>
<td>WHF criteria for abnormal MV</td>
<td>2 (0.2%)</td>
<td>45 (1.2%)</td>
<td>p=0.003</td>
</tr>
<tr>
<td><strong>Aortic valve (AV) abnormality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AV abnormality</td>
<td>6 (0.6%)</td>
<td>34 (0.9%)</td>
<td>p=0.355</td>
</tr>
<tr>
<td>Irregular or focal thickening</td>
<td>5 (0.5%)</td>
<td>29 (0.8%)</td>
<td>p=0.371</td>
</tr>
<tr>
<td>Coaptation defect</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Restricted leaflet motion</td>
<td>0 (0.0%)</td>
<td>1 (0.0%)</td>
<td>p=1.000</td>
</tr>
<tr>
<td>Prolapse</td>
<td>0 (0.0%)</td>
<td>2 (0.1%)</td>
<td>p=1.000</td>
</tr>
<tr>
<td>WHF criteria for abnormal AV</td>
<td>0 (0.0%)</td>
<td>3 (0.1%)</td>
<td>p=1.000</td>
</tr>
</tbody>
</table>

WHF- World Heart Federation; AMVL- anterior mitral valve leaflet. N/A- not applicable (p value unable to be calculated due to zero findings in both groups). †Pathological MR and AR defined in Table 1. Children with congenital pathology other than patent ductus arteriosus or atrial septal defect have been excluded.
Table 5. Rheumatic heart disease cases broken down by WHF category.

<table>
<thead>
<tr>
<th>RHD Category</th>
<th>WHF Definition</th>
<th>Low risk (n= 1053)</th>
<th>High risk (n= 3946)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite RHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite RHD (A)</td>
<td>Pathological MR + abnormal MV</td>
<td>0 (0.0%)</td>
<td>26*</td>
</tr>
<tr>
<td>Definite RHD (B)</td>
<td>Mitral stenosis</td>
<td>0 (0.0%)</td>
<td>3†</td>
</tr>
<tr>
<td>Definite RHD (C)</td>
<td>Pathological AR + abnormal AV</td>
<td>0 (0.0%)</td>
<td>3‡</td>
</tr>
<tr>
<td>Definite RHD (D)</td>
<td>Borderline disease of MV and AV</td>
<td>0 (0.0%)</td>
<td>2‡</td>
</tr>
<tr>
<td>Borderline RHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borderline RHD (A)</td>
<td>≥2 MV morphological abnormalities</td>
<td>5 (0.5%)</td>
<td>66 (1.7%)</td>
</tr>
<tr>
<td>Borderline RHD (B)</td>
<td>Pathological MR</td>
<td>2 (0.2%)</td>
<td>16</td>
</tr>
<tr>
<td>Borderline RHD (C)</td>
<td>Pathological AR</td>
<td>1 (0.1%)</td>
<td>23</td>
</tr>
</tbody>
</table>

*Two of these children also had pathological AR. †Two of these children also met criteria for Definite category (A). ‡Both of these children had pathological MR and AR. MR- mitral regurgitation; MV- mitral valve; AR- aortic regurgitation; AV- aortic valve. Pathological MR and AR, and morphological abnormalities of the MV and AV defined in Table 1.

Figure Legends:

Figure 1. Rheumatic heart disease detected by echocardiographic screening. RHD- rheumatic heart disease; CHD- congenital heart disease. *Exclusions: 67 ineligible due to age, 18 echo quality problem, 7 missing ethnicity, 1 missing consent. †4 additional high-risk children had both CHD (2 atrial septal defects, 2 patent ductus arteriosus) and RHD; they have been categorized as RHD.

Figure 2. Rheumatic heart disease prevalence in high-risk Indigenous children by age and WHF category. (n)= number of children screened in each age group. Prevalence of RHD (95% CI): 5-9 years, Definite = 6.5/1000 (3.6-10.7), Borderline = 10.8/1000 (7.0-15.0); 10-14 years, Definite = 11.7/1000 (7.0-18.2), Borderline = 25.2/1000 (18.1-34.0).
Figure 1

- 5330 had screening echocardiogram
- 93 excluded*

5237 echocardiograms reported

1084 urban children

- 31 Indigenous children excluded
- 1053 Low-risk urban non-Indigenous children
  - 1022 No pathology
  - 26 CHD
  - 5 Borderline RHD
  - 0 Definite RHD

4153 remote children

3946 High-risk remote Indigenous children

- 3778 No pathology
- 68† CHD
- 66 Borderline RHD
- 34 Definite RHD

207 non-Indigenous children excluded
Echocardiographic Screening for Rheumatic Heart Disease in High and Low Risk Australian Children
Kathryn Roberts, Graeme Maguire, Alex Brown, David Atkinson, Bo Reményi, Gavin Wheaton, Andrew Kelly, Raman Krishna Kumar, Jiunn-Yih Su and Jonathan R. Carapetis

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