Echocardiography for latent rheumatic heart disease in first degree relatives of children with acute rheumatic fever: Implications for active case finding in family members

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ABSTRACT
Background: Individuals with Acute Rheumatic Fever (ARF) often report a family history of ARF or Rheumatic Heart Disease (RHD) however the degree of familial susceptibility to RHD is poorly defined. This study aimed to determine RHD prevalence among first degree relatives of ARF patients using echocardiography.

Methods: Children with ARF were recruited from Auckland, New Zealand. Parents and siblings ≤ 4 years were offered echocardiography. Echocardiograms were reported according to World Heart Federation 2012 criteria. RHD prevalence in first degree relatives was compared to previously established population rates in the region.

Findings: In total, 70 index cases with ARF were recruited. Echocardiography was performed in 94 parents and 132 siblings. There were 3 siblings with definite RHD and 9 with borderline RHD. There were 4 parents with definite RHD. Overall prevalence of RHD (definite and borderline) in siblings was 90/1,000 (95% CI 87/1,000 – 93/1,000) compared to 36/1,000 (95% CI 30 – 42/1,000) in New Zealand children from high ARF incidence populations (p 0.001). Prevalence of definite RHD in parents was 42/1,000 (95% CI 7 – 87/1,000) compared to 22/1,000 (95% CI 9 – 36/1,000) in adults from a high ARF incidence New Zealand population (p 0.249).

Interpretation: RHD prevalence in siblings and parents of ARF cases is significantly greater than in comparable background populations. The contribution of hereditary versus environmental risk factors remains uncertain. We recommend targeted echocardiographic case-finding among siblings and parents of ARF/RHD cases in order to detect previously unrecognized latent RHD.

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1. Introduction

Acute rheumatic fever (ARF) and its sequela chronic rheumatic heart disease (RHD) are important global health problems, accounting for approximately 300–350,000 deaths annually and affecting around 33 million people [1]. Globally, the majority of adults presenting with RHD do not have a documented history of ARF and present instead with features of established valvular heart disease [2].

Echocardiographic screening enables RHD to be detected before the onset of clinical signs and symptoms, and has been undertaken in many high prevalence ARF/RHD populations around the globe [3], including New Zealand [4–6], to describe RHD burden. However, the utility of screening echocardiography in RHD control programmes remains the subject of ongoing debate in high-burden populations [7,8] Fig. 1.

A component of genetic susceptibility or heritability to ARF and RHD has been suspected for almost a century, based on reports of families with multiple affected members [9–11] and studies demonstrating increased risk of ARF in children born to parents with RHD compared to children of unaffected parents [12]. A recent systematic
review and meta-analysis reported a concordance risk for ARF of 44% in monozygotic twins and 12% in dizygotic twins, with estimated overall heritability of 60% [13]. It has also been estimated that up to 6% of any population may have a degree of underlying susceptibility to ARF [14,15]. However the sharp reduction in ARF incidence in most high-income countries in the 20th century, and the strong association between environmental risk factors, particularly household crowding, and ARF [16,17] indicate that environmental factors also contribute to ARF susceptibility. Family members of those with ARF or RHD may be at increased risk of RHD compared to the general population, due to the combination of genetic susceptibility and shared environmental predisposing factors.

To date, the prevalence of RHD in relatives of ARF patients is poorly described. Only one previous published study has used echocardiography to evaluate familial RHD risk, reporting increased prevalence of Deﬁnite RHD in siblings of children with latent RHD compared to siblings of controls. [18]

In New Zealand, there are high rates of ARF and RHD among indigenous Māori and Paciﬁc peoples [5,19]. The prevalence of deﬁnite RHD in schoolchildren from high incidence ARF populations in New Zealand is estimated to be around 1% using widely accepted 2012 WHF criteria for echocardiographic diagnosis of RHD [6,20]. Among young adults of Paciﬁc ethnicity living in Auckland, the prevalence of deﬁnite RHD is around 2% [21]. Despite these high local rates of ARF and RHD, and previously described genetic and environmental risks, there are major gaps in knowledge regarding RHD disease burden in New Zealand family members. Furthermore, the clinical approach to family members of individuals with ARF/RHD is not speciﬁcally addressed in current New Zealand ARF/RHD management guidelines or in other international clinical practice guidelines [22,23].

This study aimed to determine the prevalence of latent RHD in ﬁrst degree relatives of children with ARF. We hypothesised that RHD prevalence would be higher in siblings and parents of ARF cases than RHD prevalence in the background population.

2. Materials and methods

2.1. Study setting

This study was conducted in Auckland, New Zealand, where there is a high incidence of ARF/RHD almost exclusively affecting Māori and Paciﬁc peoples, associated with high levels of socio-economic deprivation and household crowding [5,6,21].

2.2. Participant selection and enrolment

Between January 2014 and December 2016, all families of children under 15 years of age with ARF (diagnosed as per New Zealand guidelines) [22] at the three public hospitals in the Auckland region were
approached for participation in the study. First degree relatives, including biological parents and siblings, including half-siblings, were deemed eligible. Non-biologic, non-first degree relatives (e.g. cousins, adopted family members, step-parents) were excluded as were children under four years of age. Individuals who were not New Zealand residents were also deemed ineligible, due to inability to ensure appropriate clinical follow-up of echocardiogram findings. Informed consent was obtained from participants. Parental consent was obtained for participants under 16 years, in addition to written consent for children between 10 and 16 years.

A standardised questionnaire regarding family demographics and composition was administered. Past history and family history of ARF/RHD were documented, along with history of non-rheumatic cardiac conditions. Electronic medical records were reviewed to clarify the diagnoses for participants disclosing a past history of ARF/RHD or other cardiac conditions.

2.5. Rheumatic heart disease classification

For participants under 20 years of age, echocardiograms were classified as Definite RHD or Borderline RHD according to WHF Diagnostic Criteria for RHD [20], Normal or Other Abnormal. For participants over 20 years of age, echocardiograms were classified as Definite RHD, Normal or Other Abnormal, acknowledging that the Borderline RHD category in the WHF criteria applies only to persons under 20 years of age [20].

2.6. Participant management and follow-up

Those under 20 years with definite RHD were offered benzathine penicillin prophylaxis and those with borderline RHD were recommended enhanced surveillance for sore throats and follow-up echocardiography, in keeping with global best-practice recommendations at the time the study was conducted [23]. Those diagnosed with non-RHD cardiac abnormalities were counselled and referred for cardiology review as appropriate.

2.7. Determination of background population RHD prevalence

Comparative data were previously established by population-based echocardiographic studies using the same techniques for children [6] and young adults [21] in similar high prevalence ARF/RHD regions in New Zealand. The previously established prevalence of definite and borderline RHD in children is 36 per 1000 (95% CI 30–42 per 1000) [6] and in young adults of Pacific ethnicity aged less than 40 years is 22 per 1000 (95% CI 9–36 per 1000) [21].

2.8. Statistical methods

Prevalence of RHD in siblings was calculated by the sum of the sibling RHD cases detected by echocardiography, plus those with clinically diagnosed RHD, expressed as a proportion of those siblings scanned, i.e. siblings not participating were not included in the denominator. The sibling prevalence of RHD was compared to the background population prevalence.

Prevalence of RHD in parents was calculated by the sum of the echocardiographic RHD cases plus those with clinically diagnosed RHD, expressed as a proportion of those parents scanned, i.e. parents not participating were not included in the denominator. The parent prevalence of RHD was compared to the background population prevalence.

Categorical data are expressed as proportions. Relative risks were calculated to determine prevalence of RHD among different groups. To compare the prevalence of RHD between siblings (sample study) and New Zealand children and between those with definite RHD and borderline RHD, a chi-square ($\chi^2$) test of independence (equality of proportions) was used. Significance was set at $p < 0.05$ for all analyses. Statistical Analysis System (SAS) Version 9.4 from SAS Institute Inc., Cary, NC, USA was used for data analysis.

2.9. Ethics

Ethics approval was obtained from the New Zealand Health and Disability Ethics Committee (13/STH/189/AM04) and locality approval obtained from the research offices of each participating hospital.

2.10. STROBE statement

This study was conducted and reported according to STROBE guidelines for observational studies.

2.11. Role of the funding source

This study was funded by the Health Research Council of New Zealand ([Ref. 13]/965). The funding source had no role in study design, conduct analysis or interpretation of results. All authors had full access to the data and accept responsibility to submit for publication.

3. Results

3.1. Demographics of index cases and family members

There were 70 children (index cases of ARF) and families who participated in the study. The median age of index cases was 11 years (range 4–15 years). Forty patients (57%) were male. The majority of
children with ARF were of Pacific ethnicity (55/70, 79%) and 15/70 (21%) were Maori.

There were 134 eligible parents and 187 eligible siblings aged 4 years or older. The median number of eligible siblings per index case was 2 (range 0–9).

There were 132/187 (71%) of eligible siblings and 94/134 (70%) of eligible parents who underwent echocardiography (Table 1). The median age of participating siblings was 37 years (range 22–61 years, IQR 33–43). The median age of participating siblings was 10 years (range 4–23 years, IQR 7–13). 57/133 (43%) of enrolled siblings were male and 38/96 (40%) of parents were male.

A family history of ARF/RHD in one or more biologic relatives was found in 18/70 (26%) of index cases.

3.2. Clinical features of index cases and family members

Index cases: All 70 ARF patients were first episodes of ARF and there were no recurrent episodes. There were 34 patients (48%) with mild carditis and 24 (34%) had moderate or severe carditis as defined by New Zealand guidelines [22]. In this cohort, 12 of 70 patients (17%) underwent cardiac surgery for severe carditis or persisting severe RHD within 12 months following their ARF diagnosis. Only 12 patients (17%) had ARF without carditis. Chorea occurred in six patients (9%).

Family members: One sibling had a clinical history of ARF with known chronic RHD and did not undergo a screening echocardiogram but is included in prevalence data. Among parents, three had a medically confirmed history of ARF or RHD. One parent had known clinically diagnosed RHD confirmed by recent clinical echocardiogram, and is included in prevalence data. One parent had a documented history of ARF with a normal echocardiogram conducted as part of prior routine clinical care, and the third parent had a confirmed prior history of ARF with a normal echocardiogram conducted as part of this study.

3.3. Rheumatic heart disease prevalence in siblings and parents

Of the 132 siblings who underwent echocardiography, two siblings were found to have definite RHD (both cases of moderate severity) and nine had borderline RHD detected by screening. One additional sibling had an established diagnosis of moderately severe RHD prior to participation in the study. In two families, two siblings were found to have borderline RHD. Siblings with RHD detected by echocardiography had a median age of 11 years (range 5–17 years). The prevalence of total RHD (definite and borderline) in siblings was 90 per 1000 (95% CI 45–143 per 1000) compared to 36 per 1000 (95% CI 30–42 per 1000) background population children (p 0.001) (Table 2).

Of the 94 parents who underwent echocardiography, three had definite RHD (2 mild, 1 moderate severity). One additional parent with clinically diagnosed RHD was included in prevalence data. The overall prevalence of definite RHD in parents was 43 per 1000 (95% CI 7–87 per 1000) compared to 22 per 1000 (95% CI 9–36 per 1000) background population adults (p 0.249) (Table 3).

Following echocardiography, there were 16 families with two first-degree family members with RHD and two families with three affected first-degree family members.

The relative risk of any latent RHD for siblings compared to the background population was 2.52 (p 0.01) (Table 4). The relative risk of definite RHD for parents compared to the background population was 1.94 (p 0.255) (Table 4). The relative risk of RHD for siblings compared to the background population if the index case required cardiac surgery was 4.78 (p 0.003) (Table 5).

3.4. Non-rheumatic echocardiographic abnormalities

Three siblings had non-rheumatic abnormalities detected by echocardiography: two had minor congenital anomalies of the mitral valve and one had a dilated aortic root.

There were 10 parents with non-rheumatic abnormalities detected by echocardiography: two congenital valvular abnormalities (one mitral, one aortic), three with dilated ascending aorta, two left ventricular hypertrophy (one mild, one moderate), two with aortic valve sclerosis (one with aortic stenosis) and one regional wall motion abnormality.

4. Discussion

This study found that RHD prevalence (definite and borderline) among siblings of children with ARF was 2.5 times the background population prevalence (9% compared to 3.5%). Restated, siblings and parents of ARF patients are themselves at increased risk of latent RHD. Of note, the relative risk of RHD in siblings was markedly elevated (4.8, see Table 5) if the index ARF case in the family had also undergone RHD surgery, suggesting the potential for a gradient in familial RHD risk. Whilst Definite RHD prevalence in biologic parents

Table 1
Demographic data of siblings and parents who underwent echocardiography.

| Age (years) | Siblings (n = 133) | Parents (n = 96) |
|------------|------------------|-----------------|
| Median     | 10               | 37              |
| Range      | 4–23             | 22–61           |
| Sex        |                  |                 |
| Male       | 57 (43%)         | 38 (40%)        |
| Female     | 76 (57%)         | 58 (60%)        |
| Ethnicity  |                  |                 |
| NZ Maori   | 26 (20%)         | 14 (15%)        |
| Pacific    | 107 (80%)        | 81 (84%)        |
| NZ European|                 | 1 (1%)          |
| Previously known ARF/RHD | 1 | 2 |

Table 2
Prevalence of rheumatic heart disease in siblings vs. background population children.

|                | Borderline RHD | Definite RHD | Total RHD (Borderline + Definite) |
|----------------|---------------|--------------|----------------------------------|
| Siblings       | 9/133         | 68 per 1000  | 3/133 23 per 1000 95% CI 8–64 per 1000 |
| NZ children (6) | 90/3634       | 25 per 1000  | 40/3634 11 per 1000 95% CI 8–15 per 1000 |
| p-value        | 0.002         | 0.218        | 0.001                               |

Table 3
Prevalence of rheumatic heart disease in parents vs. background adult population.

|                | Definite RHD |
|----------------|--------------|
| Parents        | 4/96 42 per 1000 95% CI 7–87 per 1000 |
| NZ adults (21) | 10/465 22 per 1000 95% CI 9–36 per 1000 |
| p-value        | 0.249        |
of children with ARF was nearly twice the background population rate (4% compared to 2.3%), this did not reach statistical significance.

The one previously published study from Uganda using echocardiography to evaluate familial RHD risk had important differences in methodology [18]. Index cases with RHD were identified via echocardiographic studies, in contrast to the children in our study who were recruited following a clinical diagnosis of ARF. The relative risk of definite RHD for siblings of cases with any latent RHD (definite or borderline) was 4.6, when compared to siblings of controls with normal echocardiograms. The concordant finding of these two studies confirms a familial risk of RHD. The current study found that sibling risk of RHD increases with increasing severity of cardiac involvement in the index case, similar to the Ugandan study where siblings of children with definite RHD had a relative risk of definite RHD of 5.3 [18,26].

Table 4

| Relative risk of rheumatic heart disease for siblings and parents compared to New Zealand children and adults. |
|--------------------------------------------------|-----------------|-----------------|
| Relative risk (95% confidence interval) p value | RHD in sibling | Relative risk (95% confidence interval) p value |
|--------------------------------------------------|-----------------|-----------------|
| Siblings                                         |                 |                 |
| All RHD                                          | 2.52 (1.43–4.44) | 0.001           |
| Definite RHD                                     | 2.05 (0.64–6.54) | 0.226           |
| Borderline RHD                                   | 2.73 (1.41–5.30) | 0.003           |
| Parents                                          |                 |                 |
| Definite RHD                                     | 1.94 (0.62–6.05) | 0.255           |

Table 5

| Relative risk of rheumatic heart disease for siblings with other factors. |
|--------------------------------------------------|-----------------|-----------------|
| RHD in sibling | Relative risk (95% confidence interval) p value | RHD in sibling | Relative risk (95% confidence interval) p value |
|--------------------------------------------------|-----------------|-----------------|
| If reported family history of ARF/ RHD            | 1.10 (0.32–3.80) | 0.884           |
| If moderate/severe carditis in index case         | 1.83 (0.62–5.36) | 0.270           |
| If RHD surgery in index case                      | 4.78 (1.69–13.51) | 0.003           |

Reported family history may not be always be reliable and interestingly we found that a family history of ARF/RHD on the study questionnaire was not associated with increased relative risk of RHD. Recall bias and prior unrecognized episodes of ARF in family members may have contributed to this observation. Several families in our study had multiple affected first degree relatives, in keeping with findings from Uganda [18]. This scenario presents a strong mandate for active case finding among family members and may also inform prioritization of echocardiography in resource-limited settings. Family history may also assist clinicians and individuals to make decisions regarding initiation of benzathine penicillin secondary prophylaxis when individuals with suspected ARF do not meet full diagnostic criteria.

Siblings <20 years of age diagnosed with definite RHD were recommended to commence benzathine penicillin secondary prophylaxis as per guidelines [22], based on the rationale that benzathine penicillin secondary prophylaxis prevents recurrences of ARF and worsening of RHD. New Zealand has a proven record of high adherence to benzathine penicillin secondary prophylaxis for individuals with RHD detected by echocardiography [28]. We shared the uncertainty of the diagnosis of borderline RHD with the families and recommended enhanced surveillance with interval follow up echocardiography and education regarding the importance of primary prevention [23]. Some families still chose to embark on secondary prevention usually influenced by the diagnosis of ARF in the index case or other family members with RHD.

Our study did not address the wider issue of population screening for RHD, nor the detail of which subsets of RHD should be offered secondary prophylaxis.

There is also currently a lack of international consensus regarding the appropriateness (or otherwise) of commencing adults with newly diagnosed and previously unrecognized RHD on benzathine penicillin secondary prophylaxis. However, there are other benefits of making a new diagnosis in adulthood including referral to cardiology services, potentially also improving pregnancy outcomes for women with RHD in their childbearing years.

Non-rheumatic cardiac abnormalities were detected in 2% of siblings and 10% of parents. We have previously emphasised that not all valvular heart disease found by echocardiographic screening in children is rheumatic [5]. The high prevalence of non-rheumatic abnormalities in adults is in keeping with previous New Zealand echocardiographic screening studies in young adults of Maori and Pacific ethnicity [21,29,30]. It must be anticipated that a number of non-rheumatic abnormalities will be found when echocardiographic screening is undertaken, some of which require physician follow-up.

New Zealand is in a unique position globally as a high income country with a high incidence of ARF/RHD. New Zealand has a history of significant efforts in RHD control with primary prevention efforts via intensive management of sore throats in schools in high-ARF incidence areas and previous experience with echocardiographic screening for RHD undertaken in schools in high-ARF incidence areas.

First degree relatives within the same household share common environmental exposures and are likely exposed to the same strains of streptococcus over time. In addition to family Group A streptococcal contact management as already occurs with throat swabbing in New Zealand, echocardiographic screening of family members offers a more comprehensive risk management strategy when a household member is diagnosed with ARF.

There is ongoing uncertainty regarding the natural history and clinical significance of RHD detected by echocardiography. Findings from a randomised trial of benzathine penicillin in latent RHD currently underway in Uganda are expected to further inform future global approaches to the clinical management of latent RHD detected by echocardiography [26].

The study exemplifies the concept of enhanced case detection for high risk persons, as distinct from whole population screening for
RHD. The high participation rate demonstrates the acceptability of echocardiography to families affected by ARF/RHD. This study is just the second study to determine the familial susceptibility of ARF/RHD using echocardiographic methodology [18].

This study was not designed to determine whether increased familial risk of RHD was due to genetic or environmental factors and involved a relatively small number of ARF patients and family members. There is uncertainty associated with the limited sample size. Although a high proportion of eligible family members underwent echocardiography, it remains uncertain whether family members who did not undergo echocardiography would have had a higher or lower chance of having RHD than those who had echocardiograms.

Echocardiography of first degree relatives of individuals with ARF detects 2.3 times the RHD prevalence of the background population, although contribution of heritability, environmental and epigenetic factors cannot be differentiated. Where feasible, active case detection for RHD using echocardiography should be offered to family members after a new diagnosis of ARF or RHD.

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Data sharing statement
The study protocol and participant materials may be made available upon email request to the corresponding author. De-identified data may be made available upon email request to the corresponding author within a formal data sharing agreement, subject to all of the following: (1) agreement by Maori and Pacific advisors to the study, particularly regarding matters pertaining to indigenous data sovereignty, (2) ethical approval by the New Zealand Health and Disability Ethics Committee (13/STH/189/AM04), (3) conduct and dissemination of additional analyses to be undertaken with involvement of senior investigators NW and RW, together with Maori and Pacific advisors and (4) commitment to not publish or share any potentially identifiable information.

Declaration of Competing Interest
The authors have no financial or personal conflicts of interest to declare.

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References
[1] Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, et al. Global, regional, and national burden of rheumatic heart disease, 1990–2015. N Engl J Med 2017;377:713–22.
[2] Zuhlike L, Engel ME, Karthikeyan G, Ranganjan S, Mackie P, Cupido B, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). Eur Heart J 2015;36:1115–22 a.