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Focused cardiac ultrasound screening for rheumatic heart disease by briefly trained health workers: a study of diagnostic accuracy

Daniel Engelman, Joseph H Kado, Bo Reményi, Samantha M Colquhoun, Jonathan R Carapetis, Susan Donath, Nigel J Wilson, Andrew C Steer

Summary

Background Echocardiographic screening for rheumatic heart disease (RHD) can identify individuals with subclinical disease who could benefit from antibiotic prophylaxis. However, most settings have inadequate resources to implement conventional echocardiography and require a feasible, accurate screening method. We aimed to investigate the accuracy of screening by non-expert operators using focused cardiac ultrasound (FoCUS).

Methods In this prospective study of diagnostic accuracy, we recruited schoolchildren aged 5 to 15 years in Fiji to undergo two blinded tests. The index test was a FoCUS assessment of mitral and aortic regurgitation, performed by nurses after an 8-week training programme. The reference standard was the diagnosis of RHD by a paediatric cardiologist, based on a standard echocardiogram performed by a skilled echocardiographer. The primary outcome was the accuracy of the index test with use of the most sensitive criteria (any regurgitation).

Findings We included 2004 children in the study. The index tests were done between September, 2012, and September, 2013, by seven nurses in eight schools in Fiji. The diagnostic accuracy of the screening test (area under receiver operator characteristic curve) was 0.89 (95% CI 0.83–0.94). When the primary cut-off point (any regurgitation) was used for analysis, sensitivity was 84·2% (72·1–92·5) and specificity was 85·6% (83·9–87·1). The sensitivity of individual nurses ranged from 66·7% to 100% and specificity 74·0% to 93·7%.

Interpretation Screening by briefly trained nurses using FoCUS was accurate for the diagnosis of RHD. Refinements to training and screening test methods should be studied in a range of settings, and in parallel with investigations of the long-term clinical and cost-effectiveness of screening for RHD.

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Introduction Rheumatic heart disease (RHD) is an important cause of global morbidity and mortality. Patients typically present late in the illness, and there is a high risk of death in the first years after diagnosis. Screening can detect people who might benefit from secondary antibiotic prophylaxis, and is recommended by WHO in high-prevalence areas; however, there is a lack of evidence to inform implementation.

Population screening requires a test that is safe, accurate, and readily available. Echocardiography is safe and much more accurate for diagnosing RHD than is clinical evaluation. However, the shortage of echocardiographers and cardiologists to perform and interpret echocardiograms is a major barrier to their use and hampers scale-up of screening to the population level. Task shifting screening to non-expert health workers could overcome the human resource constraints. In this approach, nurses who have completed a short training course use focused cardiac ultrasound (FoCUS) to screen for valvular regurgitation, and refer positive cases for diagnostic assessment, including standard echocardiography.

In Fiji, there are too few physicians to perform echocardiographic screening, but the country does have a capable nursing workforce and a nurse-led school health programme. Therefore, we sought to assess whether task shifting FoCUS to existing school-health nurses is a feasible strategy for implementation of population screening for RHD. We have shown in a pilot study that the training of nurses in ultrasound-based RHD screening was feasible. We have also reported in another study that nurses who had undertaken an 8-week training course could acquire FoCUS images of appropriate quality and accurately measure regurgitation. Here, we aimed to investigate the accuracy of FoCUS screening tests done by non-experts, using a range of cutoff criteria.

Methods

Study design and setting

In this prospective investigation of the accuracy of a new test, the index test was FoCUS for RHD, performed by nurses who had completed a defined training programme, using a simplified protocol and portable
Research in context

Evidence before this study
A search of PubMed and Embase between Jan 1, 1990, and Dec 31, 2011, using search terms “non-expert”, “nurse”, “community health worker”, “education”, “echocardiography”, “ultrasound”, and “rheumatic heart disease”, and discussion with colleagues yielded no relevant publications. We repeated the search in December, 2015. We found two studies: both trained and assessed two nurses who used hand-held ultrasound for screening. Three additional feasibility studies were found.

Added value of this study
This study is large and is consistent with guidelines for studies of diagnostic accuracy. The design included training a large group of health workers and unsupervised screening at eight sites over 12 months, which may be more representative of a real-world scenario than other studies. The training programme and test protocols were highly defined and could be replicated in other settings. Our results show that the screening test was accurate. Additionally, these data clarify the influence of various criteria and cut-off points on test sensitivity and specificity. Our results also highlight the issue of variation in accuracy between operators.

Implications of all available evidence
Screening by non-expert operators, using simplified imaging protocols, has been shown to be accurate across all studies. Further studies and refinements of test methods should be explored.

Procedures
In June and July, 2012, school-health nurses in Fiji, who had only a basic understanding of cardiac anatomy and physiology and no previous imaging experience, were trained to screen for RHD using FocUS. Training included 1 week of classroom-based workshops and 7 weeks of practical training, as reported elsewhere.7 The evaluation of the screening test was conducted in eight primary schools in the Central, Northern, and Western administrative divisions of Fiji (figure 1). Children underwent two tests: a FocUS performed by a nurse, and a standard echocardiogram by an echocardiographer. Tests were done in different rooms, so that the nurse and echocardiographer were not aware of the other’s findings. We aimed to have both tests take place on the same day.

Nurses followed a simplified 12-step protocol, assessing the presence of mitral regurgitation or aortic regurgitation on colour Doppler imaging in the parasternal long axis, parasternal short axis, and apical views, and if present, measuring the longest visible jet (appendix). To attempt to avoid the measurement of benign closing volumes, we asked nurses to measure regurgitation only if it had been seen in two or more frames. Nurses made assessments at the time of examination and clinical information was not available to them. All images and loops were saved. Nurses used the M-Turbo portable ultrasound machine (SonoSite Inc, Bothell, WA, USA), chosen for acceptable colour Doppler imaging and relative affordability, therefore representing the type of machine that could be practical to procure and use in resource-limited and remote settings.

The echocardiographer was highly skilled in RHD imaging, and performed a directed echocardiogram, including parasternal long axis, parasternal short axis, and apical views on all children, and continued to an extended echocardiogram, including continuous-wave Doppler and M-mode imaging if any of the following abnormalities were seen: mitral regurgitation ≥1·5 cm; aortic regurgitation ≥0·5 cm; mitral or aortic stenosis; morphological features of RHD as described in the 2012 World Heart Federation (WHF) criteria;18 or any other pathology. The echocardiographer used a Vivid e ultrasound machine (GE Healthcare, Freiburg, Germany), which has been used in other screening studies.19,20 Standard echocardiograms were reported by a paediatric cardiologist, who was unaware of the nurses’ assessment or any clinical information. Diagnosis was in accordance with WHF criteria,18 with categories of normal, borderline RHD, definite RHD, and congenital abnormalities. The severity of RHD was based on a grading of valvular regurgitation and/or stenosis.18,22 If there was diagnostic uncertainty, a second cardiologist reported the echocardiogram. In the case of an inconsistent diagnosis between the first and second cardiologist, the report of a third cardiologist was used. We entered data into a REDCap electronic database hosted at the Murdoch Childrens Research Institute in Melbourne, Australia.23 Children with abnormal echocardiograms were referred to specialist centres for diagnostic assessment and management.

Participants
Seven nurses participated: two from each of the three administrative Divisions and one additional nurse from Central Division in case of dropout. We included schools that would allow each nurse to screen within their local Division and do approximately equal numbers of tests (figure 1). Research staff explained study procedures to students, parents, and teachers at the participating schools and we provided information sheets in Fijian and
English. All children aged from 5 to 15 years who attended the selected schools were eligible to participate. Parents gave written consent for their children to participate, and we obtained assent from children aged 10 years or older. Participating nurses gave written informed consent.

Statistical analysis
The primary analysis was the accuracy of the index test for the diagnosis of any RHD (including definite and borderline disease). We also calculated test accuracy for definite RHD. We used the area under the receiver operator characteristic curve (AUC ROC) for the longest mitral or aortic regurgitation jet measured in any view to calculate overall diagnostic accuracy.

The evaluation of criteria for screen-positivity compared the accuracy of the index test at different clinically relevant jet length cut-off points. The primary analysis used cut-off points from the ROC curve for the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positivity were then compared, including the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positivity were then compared, including the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positivity were then compared, including the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positivity were then compared, including the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positivity were then compared, including the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positivity were then compared, including the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positivity were then compared, including the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positivity were then compared, including the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positivity were then compared, including the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positivity were then compared, including the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positivity were then compared, including the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positivity were then compared, including the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positivity were then compared, including the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positivity were then compared, including the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positivity were then compared, including the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positivity were then compared, including the longest mitral or aortic regurgitation jet measured in any view. Other exploratory combinations of criteria for screen positiv...
Between Sept 11, 2012, and Sept 12, 2013, we recruited 2023 children from eight schools in Fiji. We excluded children who had only had one test or if their reference echocardiogram was not interpretable, resulting in a final cohort of 2004 children included in analysis (figure 2).

Of the investigations for included children, five were reviewed by a second reporter and three were referred to a third reporter. There were no missing data. Nurses assessed between 236 and 339 children each. Because of the unavailability of the echocardiographer, only 66% of paired tests were done on the same day and 94% within 28 days. A sensitivity analysis of participants with tests on the same day showed that testing on different days did not significantly affect reported results (data not shown). There were no adverse events.

Mean age of enrolled children was 10·0 years (range 5·1–15·7, table 1). 51·4% were girls and 60·7% were iTaukei (indigenous Fijian). On the cardiologist’s report of the echocardiographer studies, 501 (25%) participants had regurgitation, 433 (21·6%) had mitral regurgitation, 41 (2·0%) had aortic regurgitation, and 27 (1·3%) had both. There were 57 cases of RHD, with an overall prevalence of 28·4 per 1000 children (95% CI 21·4–36·3).

Results

Table 1: Participant characteristics and prevalence of rheumatic heart disease

Table 2: Cardiologist diagnosis from reference standard echocardiogram

Table 3: Accuracy of nurse-performed FoCUS for screening of RHD
### Table 4: Accuracy of screening test criteria

<table>
<thead>
<tr>
<th>Jet length (cm) and multiple views</th>
<th>Any RHD (n=57)</th>
<th>Definite RHD (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>MR &gt;0, 2 views or AR=0</td>
<td>46</td>
<td>80.7</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>78.9</td>
</tr>
<tr>
<td>MR &gt;1, 2 views or AR&gt;0.5</td>
<td>44</td>
<td>77.2</td>
</tr>
<tr>
<td>MR &gt;1, 3 views or AR&gt;1</td>
<td>44</td>
<td>77.2</td>
</tr>
<tr>
<td>MR &gt;1, 4 views or AR&gt;2</td>
<td>44</td>
<td>77.2</td>
</tr>
<tr>
<td>MR &gt;2, 5 views or AR&gt;2.5</td>
<td>44</td>
<td>77.2</td>
</tr>
<tr>
<td>MR &gt;3, 6 views or AR&gt;3</td>
<td>44</td>
<td>77.2</td>
</tr>
</tbody>
</table>

### Longest regurgitation jet (cm)

<table>
<thead>
<tr>
<th>MR or AR (primary analysis)</th>
<th>Any RHD (n=57)</th>
<th>Definite RHD (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR &gt;0.5 or AR</td>
<td>48</td>
<td>84.2</td>
</tr>
<tr>
<td>MR &gt;1 or AR &gt;1</td>
<td>47</td>
<td>82.5</td>
</tr>
<tr>
<td>MR &gt;1.5 or AR &gt;1.5</td>
<td>44</td>
<td>77.2</td>
</tr>
<tr>
<td>MR &gt;2 or AR &gt;2</td>
<td>28</td>
<td>49.1</td>
</tr>
</tbody>
</table>

22–0.36-7), including 14 cases of definite RHD (7–0.1000 children) and 43 cases of borderline RHD (21–4 per 1000 children, table 1). Six cases (10–5%) were isolated to the aortic valve (table 2). Of definite RHD cases, two (14–3%) were severe, six (42–9%) were moderate, and six (42–9%) were mild. There were 26 congenital cases (prevalence 12.9 per 1000 children); all were mild or clinically insignificant (table 2).

The nurse operators reported 329 participants (16–4%) with regurgitation (306–15–3%) with mitral regurgitation, 26 [1–3%] with aortic regurgitation, and three [0–1%] with both). Regurgitation was not identified by nurses in nine of the 57 RHD cases reported by cardiologists (ie, false negatives). Conversely, nurses identified 281 cases of regurgitation that were not diagnosed as RHD by cardiologists (table 3). The diagnostic accuracy of the index test (AUC ROC, plotting the longest mitral or aortic regurgitation jet, appendix) was 0.89 (95% CI 0.83–0.94). Maximum sensitivity at the primary cut-off point (mitral or aortic regurgitation >0 cm) was 84–2%
(95% CI 72·1–92·5), which corresponded to a specificity of 85·6% (83·9–87·1). Sensitivity and specificity for definite RHD were 85·7% and 84·1%, respectively. The sensitivity of criteria was increased by incorporating aortic regurgitation measurements, whereas specificity was increased by increasing regurgitation cut-off lengths and by requiring mitral regurgitation to be seen in multiple views (table 4).

Of the seven nurses, one had a much lower accuracy than the others, with six of the nine false negatives screened by this operator, whereas other nurses had either one or none. When the primary cut-off point (mitral or aortic regurgitation >0 cm) was used for analysis, the sensitivity of individual nurses ranged from 66·7% to 100% and specificity 74·0% to 93·7% (table 5). As the least accurate nurse may have skewed the evaluation of the optimum criteria, we repeated analyses with this nurse excluded. In this scenario, sensitivity and specificity were 92·3% and 85·6%, respectively, for any regurgitation (appendix), and the AUC ROC was 0·93 (appendix).

Discussion

Our study showed that a FoCUS screening test performed by nurses who had completed a brief, structured training programme was accurate for the diagnosis of RHD. The sensitivity and specify of the test were high. Although sensitivity (84% at the primary cut-off point) was below the 95% estimate used to calculate sample size, this level of accuracy might be acceptable for screening in some contexts. Refinements to training and screening test procedures could lead to further improvements in accuracy.

Analysis of individual nurses’ performances showed variation in the quality of images and measurement of regurgitation by the seven nurses.15 Although some variation between operators is to be expected, these data suggest that training protocols require further refinement. Specifically, future training should require operators to demonstrate competency before they begin screening. In this study, we deliberately excluded such “hurdle” assessments or ongoing training, so that we could evaluate a highly-defined programme. By contrast, a real-world screening programme would require quality assurance protocols, continued professional development, and supervision.7 We can hypothesise that, through training refinements, quality assurance and the benefits of experience, programmatic test accuracy may approach or even exceed the level of accuracy of the best performing individual operators reported in this study.

The results of test accuracy using different criteria and cut-off points do not conclusively identify the best strategy, but factors that contribute to accuracy are evident. Mitral regurgitation length is the main determinant of the accuracy of the test, whereas the aortic regurgitation cut-off point has only a small effect. Our results suggest the optimum mitral regurgitation jet length would be around 1–1·5 cm. Sensitivity reduces slightly at 1·5 cm (although the highest diagnostic OR is observed at this cut-off, because of increased specificity) and is unacceptably low at a cut-off point of 2 cm. The referral of all patients with mitral regurgitation >0 cm would be most sensitive. Although the requirement for mitral regurgitation to be seen in two views improved the specificity of the test, it had the undesirable effect of a loss of sensitivity.

We noted that 10% of participants with RHD had isolated aortic pathology, reinforcing our view that screening should include assessment for aortic regurgitation. Use of a different cut-off point for mitral and aortic regurgitation appears preferable. Since aortic regurgitation far less

<table>
<thead>
<tr>
<th>Participants screened (n)</th>
<th>Prevalence of any RHD (per 1000)</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TP</td>
<td>FP</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
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<td>4</td>
<td>8</td>
<td>78</td>
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<tr>
<td>5</td>
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<td>34</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>37</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>281</td>
</tr>
</tbody>
</table>

Positive test cut-off point: any regurgitation (>0 cm) of either mitral or aortic valve. Any RHD=definite or borderline rheumatic heart disease. TP=true positive. FP=false positive. FN=false negative. TN=true negative. PPV=positive predictive value. NPV=negative predictive value. DOR=diagnostic odds ratio. *DOR could not be calculated because of zero values, therefore approximated DOR shown.

Table 5: Accuracy of screening for rheumatic heart disease by individual nurses
commonly represents normal echocardiographic variation, and that there were very few cases of aortic regurgitation <1 cm, suggests that the best approach might be to refer all children who have any degree of aortic regurgitation.

Three other studies have considered criteria for an abbreviated RHD screening test. Ploutz and colleagues noted that a combination of mitral regurgitation ≥2 cm or any aortic regurgitation to be the most accurate of the criteria they evaluated for handheld ultrasound. In another study that used handheld ultrasound devices in a “spiked” cohort (that is, a sample that included known cases of RHD), Mirabel and colleagues concluded that a combination of mitral regurgitation ≥2 cm or any atrial regurgitation were the best criteria to use, although a shorter mitral regurgitation cut-off was noted to be more sensitive. The same researchers had previously proposed a cut-off point of mitral regurgitation ≥2 cm, based on a retrospective analysis. Ultimately, cut-off points for screening are always a trade-off between sensitivity and specificity, and as such the policy for individual country programmes should be based on the tolerance of false-negative cases and the capacity of the health system.

An important consideration for the feasibility of screening programmes is the recall rate: i.e., the proportion of cases referred for further evaluation due to an abnormal screening test, in this case related to the prevalence of regurgitation and the test-positive predictive value (PPV). In our study, regurgitation was detected in 16% (nurse FoCUS) to 25% (standard portable machines) of low-risk, healthy populations of children ranges widely from 2-5% to 45%, partly due to methodological differences and the inclusion of closing volumes. The recall or referral rate and PPV reported in previous screening studies has also varied. In Uganda, 2-9% had an abnormality on screening, resulting in a PPV of 55%; in Mozambique, 5-7% had suspicious mitral or aortic regurgitation, with a PPV of 53%; and in New Caledonia, 8-5% had any abnormality, and a PPV of 11-3%. Of note, these three studies were done before 2012 and used different diagnostic criteria than those used in this study. Further, it is possible that children with minor abnormalities were detected by the screening cardiologists but not referred, which seems to be the case in Mozambique, where a subsequent analysis of the same data reported that 9-6% had mitral regurgitation, resulting in a PPV of 7-2%, which is similar to the findings from our study.

Extrapolation of our results to a population level suggests that 1642 of every 10 000 children screened would be referred for diagnostic assessment, of whom 239 would receive a diagnosis of RHD (approximately 25% definite and 75% borderline) and 44 would have their diagnosis missed. A recall rate of 16% is not excessive for a disease prevalence of 2-8%, and does not differ greatly from the 12% recall rate for first time mammography. However, to assess the recalled group would require a large number of skilled workers, which would not be feasible in many settings. To our knowledge, New Caledonia, Tonga, and Samoa are the only countries to have implemented public-health screening programmes for RHD using echocardiography. All have populations of less than 300 000 people and the most populous of these, New Caledonia, has a substantially greater physician workforce capacity than do most settings with a high prevalence of RHD.

Further innovation in RHD screening may result in greater accuracy, reduced resource requirements, or both. Screening with handheld ultrasonography is one such innovation, and is highly accurate when used by experienced cardiologists. Two recent studies have assessed non-expert operators. Although the methods varied from our study, the accuracy results were, likewise, encouraging. Mirabel and colleagues reported 77–84% sensitivity and 91–92% specificity for two nurses in New Caledonia, and Ploutz and colleagues reported 74% sensitivity and 79% specificity for two nurses with some echocardiography experience in Uganda. Compared with standard portable machines, handheld machines are less expensive and more portable; however, current models have short battery life, limited Doppler capabilities, are prone to overheating, and the recall rate of handheld screening may be higher (24% in Uganda). Although we have used regurgitation as a risk marker for disease, this approach has inherent limitations. For example, differentiation of closing volumes and benign mitral regurgitation from true disease, without additional valve morphology criteria remains a challenge to the accuracy of RHD screening. We tried to exclude closing volumes by asking nurses to ignore regurgitation seen in only a single frame; however, some closing volumes were likely still coded as regurgitation. Specificity might be improved by adopting a more subjective approach, in which operators do not refer jets with a benign appearance. Screening for regurgitation will also miss some cases of congenital heart disease and mitral stenosis, which could be important in areas with high prevalence of juvenile mitral stenosis. From our experience, identification of these lesions or the morphological changes of RHD require advanced skills that cannot be expected of briefly trained operators, but further investigation is warranted.

Our study has some limitations. Despite our intentions, many children did not undergo both tests on the same day. However, we believe the interval between tests was not clinically relevant and did not affect the results. The absence of a true gold standard for RHD diagnosis is a limitation for comparisons of accuracy. The WHF criteria represent important progress; however, some challenges remain in the differentiation of mild disease from the upper limits of normal. For practical reasons and cost, one cardiologist reported most of the studies. Our results are representative of our study population, our training

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and screening methods, the ultrasound equipment used, and the participating nurses, and, therefore, might not be generalisable to other settings. However, these limitations are balanced by our rigorous methods, consistent with the STARD guidelines, a well-defined training programme, and a group of non-expert operators trained for RHD screening that was larger than that in the other studies we reviewed.

There are a number of pertinent issues that affect the effectiveness of screening as a control strategy. A strong health system is required to manage detected patients, including delivery of secondary prophylaxis. Further, the direct costs and opportunity costs of a screening programme should not be underestimated, and data from this and other screening studies will inform cost-effectiveness models. Finally, the prognosis of borderline and subclinical RHD has not been established, and, therefore, the benefits of detecting and treating these cases remains unclear. However, there is a pressing need to improve global RHD control, and the rigorous investigation of early case detection, including practical screening methodologies, should take place in parallel with these other evaluations.

Contributors
ACS, JHK, and SMC conceived the study, which was designed with DE, BR and JRC. ACS, DE, JHK, and BR designed and delivered the training programme. DE, SD, and ACS designed the statistical methods and data analysis plan. BR and NJW reported the ultrasounds. DE performed the statistical analysis and was the primary author of the manuscript. All authors contributed to the writing of the manuscript, and read and approved the final version.

Declaration of interests
We declare no competing interests.

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