RESEARCH

# Is calcaneal broadband ultrasound attenuation a valid index of dual-energy x-ray absorptiometry-derived bone mass in children?

**B. K. Weeks,**
**R. Hirsch,**
**R. C. Nogueira,**
**B. R. Beck**

*Menzies Health Institute Queensland, Griffith University, Gold Coast, Australia*

## Objectives

The aim of the current study was to assess whether calcaneal broadband ultrasound attenuation (BUA) can predict whole body and regional dual-energy x-ray absorptiometry (DXA)-derived bone mass in healthy, Australian children and adolescents at different stages of maturity.

## Methods

A total of 389 boys and girls across a wide age range (four to 18 years) volunteered to participate. The estimated age of peak height velocity (APHV) was used to classify children into pre-, peri-, and post-APHV groups. BUA was measured at the non-dominant heel with quantitative ultrasonometry (QUS) (Lunar Achilles Insight, GE), while bone mineral density (BMD) and bone mineral content (BMC) were examined at the femoral neck, lumbar spine and whole body (DXA, XR-800, Norland). Associations between BUA and DXA-derived measures were examined with Pearson correlations and linear regression. Participants were additionally ranked in quartiles for QUS and DXA measures in order to determine agreement in rankings.

## Results

For the whole sample, BUA predicted 29% of the study population variance in whole body BMC and BMD, 23% to 24% of the study population variance in lumbar spine BMC and BMD, and 21% to 24% of the variance in femoral neck BMC and BMD ($p < 0.001$). BUA predictions were strongest for the most mature participants (pre-APHV $R^2 = 0.03$ to 0.19; peri-APHV $R^2 = 0.05$ to 0.17; post-APHV $R^2 = 0.18$ to 0.28) and marginally stronger for girls ($R^2 = 0.25$-0.32, $p < 0.001$) than for boys ($R^2 = 0.21$-0.27, $p < 0.001$). Agreement in quartile rankings between QUS and DXA measures of bone mass was generally poor (27.3% to 38.2%).

## Conclusion

Calcaneal BUA has a weak to moderate relationship with DXA measurements of bone mass in children, and has a tendency to misclassify children on the basis of quartile rankings.

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## Article focus

- Quantitative ultrasonometry (QUS) is a quick, inexpensive and highly portable alternative measure of bone health to radiation-based dual-energy x-ray absorptiometry (DXA). However, the association between QUS and DXA measures for children across the age span has not been well established.
- Our aim was to examine the associations between QUS-derived calcaneal broadband ultrasound attenuation (BUA) and regional DXA measures of bone across the maturational stages of childhood.

B. K. Weeks, PhD, Senior Lecturer,
R. Hirsch, BPhty (Hons), BExSc, Physiotherapist,
R. C. Nogueira, PhD, Research Scientist,
B. R. Beck, PhD, Professor, School of Allied Health Sciences, Menzies Health Institute Queensland, Griffith University, Gold Coast, Australia.

Correspondence should be sent to B. K. Weeks at b.weeks@griffith.edu.au

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## Key messages

- Only weak positive associations exist between DXA-based bone mass measures and QUS-derived BUA in children.
- Positive associations between bone mass and BUA are strongest for the most physically mature children.

## Strengths and limitations

- Our study made use of a relatively large cohort of 389 children across a broad age range (four to 18 years), which facilitated the examination of bone mass associations across the stages of physical maturity.
- We examined associations between absolute measures of bone mass and quality rather than applying diagnostic criteria, thus the clinical utility of our findings is indirect.

## Introduction

The benchmark regarding the estimation of bone mass is radiation-based dual-energy x-ray absorptiometry (DXA) from which bone mineral density (BMD) is derived. Whilst DXA-derived BMD remains the clinical measurement for bone mass estimation and diagnosis of osteoporosis, it is limited in a number of ways, not least in its ability to address bone microarchitecture. The use of DXA is also hampered by its relatively high cost, poor accessibility, and radiation exposure, which limit its application in large paediatric trials, particularly those conducted in schools or other community locales. Furthermore, DXA measures of BMD are inherently biased by the size of the patient,[1] and can therefore be problematic for use in growing children.

In contrast, broadband ultrasound attenuation (BUA) measured with quantitative ultrasonometry (QUS) is a quick, inexpensive, radiation-free and highly portable alternative measure of bone health, and is therefore commonly used in paediatric studies.[2,3] BUA is not, however, a direct measure of bone mass, and therefore its validity as a surrogate measure for BMD is sometimes questioned. Speed of sound, also determined by QUS, has been shown to misclassify children into BMD categories on the basis of Z-scores (i.e. comparison to normative reference value based on age and gender).[4] Stiffness index is a composite measure that can be reported from QUS as it is derived from BUA and speed of sound (SOS)[5] measures. A recent investigation of Chinese children demonstrated strong positive associations between stiffness index and whole body bone mass.[6] Furthermore, a change in calcaneal BUA with growth has been shown to correlate with changes in BMD at the femoral neck and lumbar spine in children.[7] Of the three common QUS measures, BUA best reflects changes in bone mass during growth, and holds the strongest association with DXA measures of bone mass in children.[8-10] Nonetheless, data on the direct association of BUA with bone mass at clinically important regions are not available for children across a broad age range.

The World Health Organization highlights two important features of bone integrity that characterise osteoporosis in their definition – that is, "low bone mass" and "microarchitectual deterioration" that, together, contribute to an increased risk of a low-impact fracture.[11] Data from histomorphometry studies suggest that BUA reflects microarchitectural parameters, such as trabecular separation and connectivity.[12] Furthermore, cadaveric research shows that QUS measures predict *in vitro* failure loads of the proximal femur as strongly as femoral neck and lumbar spine BMD.[13] Prospective studies of older men and women indicate that BUA is a good predictor of the risk of fracture.[14,15] Nevertheless, there remains a gap in current knowledge as a position statement for the use of QUS in children is yet to be published by the International Society for Clinical Densitometry.[16] The practicalities around testing bone health status in large paediatric research trials make QUS a very attractive option. However, researchers must be confident that QUS measures are valid predictors of bone health before they can be used as a surrogate measure for DXA.

The aim of the study, therefore, was to examine the associations between QUS-derived calcaneal BUA and regional DXA measures of bone across the various stages of growth, from young children to adolescents. We hypothesised that positive associations would be observed between calcaneal BUA and DXA measures of femoral neck, lumbar spine and whole body bone mass, and associations would be similarly strong across each maturational stage. The findings will provide BUA data for healthy Australian children across the range of age groups and maturity stages, and will therefore be a source of important information on the use of QUS as a surrogate for DXA measures in paediatric research.

## Patients and Methods

**Ethics statement.** Approval to conduct the study was granted by the Griffith University Human Research Ethics Committee (#PES/09/05/HREC, #PES/09/09/HREC, and #PES/25/11/HREC). Written informed consent was obtained from each participant and their parent/guardian. All research activities were in accordance with the Declaration of Helsinki.[17]

**Study design.** A cross-sectional study was undertaken in order to evaluate whole body and regional parameters of bone strength of children with DXA-derived bone mass and QUS-derived calcaneal BUA.

**Subjects and selection.** Healthy girls and boys from local Gold Coast schools and the surrounding community volunteered to participate. Recruitment was undertaken via community advertisements (i.e. posters and flyers) and notices at local schools. Children were eligible for inclusion if they were apparently healthy, fully mobile, gave their consent to participate, and had the consent of their parents. Children were ineligible if they were taking medications known to affect bone, were recovering from a

**Table I.** Participant characteristics including maturity, body composition, and bone measures for the whole cohort (n = 389)

| Measure | Mean (SD) | Range |
|---|---|---|
| Age (yrs) | 11.9 (3.2) | 4.3 to 18.2 |
| Weight (kg) | 43.8 (15.8) | 16.4 to 113.5 |
| Standing height (m) | 1.51 (0.18) | 1.05 to 1.88 |
| Sitting height (m) | 0.81 (0.11) | 0.40 to 1.17 |
| Body mass index (kg/m$^2$) | 18.7 (3.4) | 13.1 to 37.6 |
| Lean mass (kg) | 30.3 (11.9) | 8.8 to 77.6 |
| Fat mass (kg) | 13.7 (8.4) | 3.3 to 44.2 |
| APHV (years) | 13.0 (1.1) | 10.9 to 16.1 |
| BUA (dB/MHz) | 76.5 (15.9) | 44.8 to 134.4 |
| Femoral neck BMC (g) | 3.66 (1.09) | 1.68 to 8.41 |
| Femoral neck BMD (g/cm$^2$) | 0.82 (0.17) | 0.16 to 1.43 |
| Lumbar spine BMC (g) | 28.3 (12.6) | 9.1 to 77.0 |
| Lumbar spine BMD (g/cm$^2$) | 0.75 (0.19) | 0.46 to 1.34 |
| Whole body BMC (g) | 1833 (631) | 722 to 4272 |
| Whole body BMD (g/cm$^2$) | 0.77 (0.13) | 0.53 to 1.27 |

APHV, age of peak height velocity; BMC, bone mineral content; BMD, bone mineral density; BUA, broadband ultrasound attenuation; SD, standard deviation

limb injury or fracture in the past six months, or if their parents declined to consent.

**Approach.** Sitting and standing height (stretch-stature method) were measured to the nearest millimetre using a portable stadiometer (HART Sport and Leisure, Brisbane, Queensland, Australia) and a 50 cm flat stool. Weight was measured to the nearest 0.1 kg using a portable digital scale (Soehnle, Hamburg, Germany) with output blinded from the participant. Body mass index (BMI, kg/m$^2$) was calculated using measures of height and weight per the accepted formula (BMI = weight/height$^2$). Maturity was estimated by calculating the age of peak height velocity (APHV) with validated gender-specific algorithms incorporating height, sitting height, weight, and age.[18]

Whole body lean and fat mass and regional bone mineral content (BMC, g) and bone mineral density (BMD, g/cm$^2$) for the whole body, non-dominant femoral neck, and lumbar spine, fat and lean mass were obtained using DXA (Norland XR-800, Norland Cooper Surgical, Trumbull, Connecticut). Short-term measurement precision for repeated DXA measures (with repositioning) in our lab is 0.9%, 1.1%, 0.4%, 0.8% and 2.3% for whole body, femoral neck, lumbar spine, lean and fat mass, respectively (data not available).

BUA (dB/MHz) of the non-dominant heel was examined using a calcaneal ultrasonometer (Lunar Achilles Insight, GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom). The non-dominant heel was identified for each participant based on their preferred side for kicking a soccer ball or football.[19] Short-term measurement precision with repositioning was 2.5%.

**Statistical analysis.** Relationships between calcaneal BUA and regional BMC and BMD measures were examined using Pearson correlations and linear regression for the whole cohort in addition to gender-specific groupings. Covariates of age and gender were considered by including those variables in multiple regression analyses. Participants were classified by skeletal maturity on the basis of the number of years from APHV as pre- (< -1 year), peri- (-1 year to 1 year), or post-APHV (> +1 year) in order to examine associations at each maturational stage. Within each maturity group, participants were additionally ranked in quartiles based on BUA, femoral neck BMC, femoral neck BMD, lumbar spine BMC, and lumbar spine BMD in order to determine agreement in quartile classifications for QUS and DXA measures. Thus, an ideal result for exact agreement between quartiles would be 100%, where all participants are classified into the same quartile group for both measures. The Fisher's exact test was used to examine differences in classification agreement between maturity groups. All statistical procedures were undertaken using SPSS version 22.0 (IBM, Chicago, Illinois). Statistical significance was determined at a p-value of ≤ 0.05.

## Results

A total of 389 children and adolescents (age 11.9 years, SD 3.2, range 4.3 to 18.2) including 206 boys and 183 girls volunteered to participate in the study (Table I). A total of 188 children were classified as pre-APHV (age 10.4 years, SD 1.2, range 4.9 to 13.1), 89 were peri-APHV (age 13.2 years, SD 1.1, range 10.6 to 15.4), and 112 were post-APHV (age 14.9 years, SD 1.8, range 12.8 to 18.2).

For the whole cohort, calcaneal BUA showed moderate positive associations with BMC and BMD at the femoral neck (r = 0.47-0.49, p = 0.001) (Fig. 1a), lumbar spine (r = 0.49 to 0.50, p = 0.001) (Fig. 1b), and whole body (r = 0.54 to 0.56, p = 0.001) (Fig. 1c). BUA predicted 21.3% to 24.4% of the variance in femoral neck BMC and BMD measures, 23.5% to 23.8% of the variance in lumbar spine BMD and BMC measures, and 29.1% of the variance in whole body BMC and BMD measures (p ≤ 0.05). Age showed strong positive associations with all BMC and BMD measures (r = 0.74 to 0.86, p < 0.001), such that when age was considered in the regression models, BUA explained only a further 2.2% to 4.1% of the variance in DXA measures.

BUA bone mass associations were somewhat stronger for girls than for boys with 25.1%, 27.0%, and 31.8% of variance accounting for femoral neck, lumbar spine, and whole body bone mass in girls, respectively, compared with 24.8%, 21.2%, and 27.2% in boys (p ≤ 0.05). Stronger associations were observed between BUA and DXA measures for participants in more advanced stages of maturity compared with those who were less mature (Table II) at the femoral neck and the lumbar spine. When gender was included in maturity-stratified regression analyses, BUA remained a weak, yet statistically significant, predictor of DXA measures of bone mass at each stage, accounting for an additional 9.4% to 30.4% of the variance in those measures (p ≤ 0.05).

The exact agreement (%) between quartile classifications based on calcaneal BUA and DXA measures of bone mass was relatively poor, ranging between 27.3% and 42.7%. (Table III). No differences were observed in classification agreement between maturity groups.

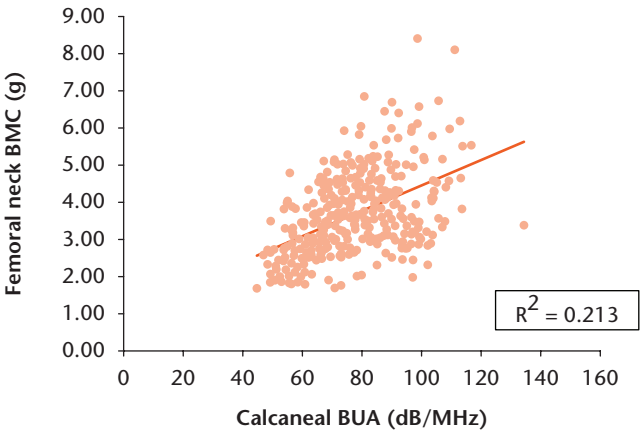


Fig. 1a

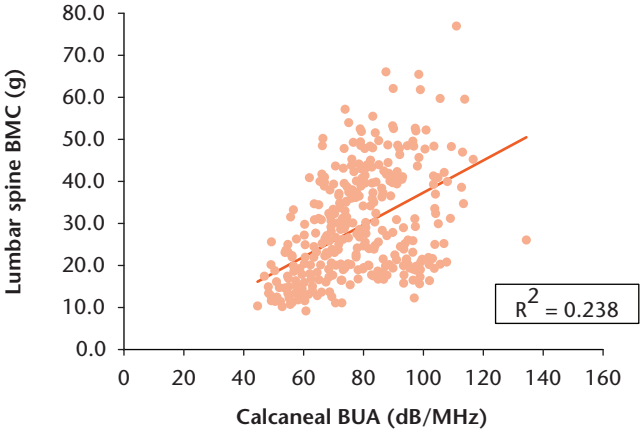


Fig. 1b

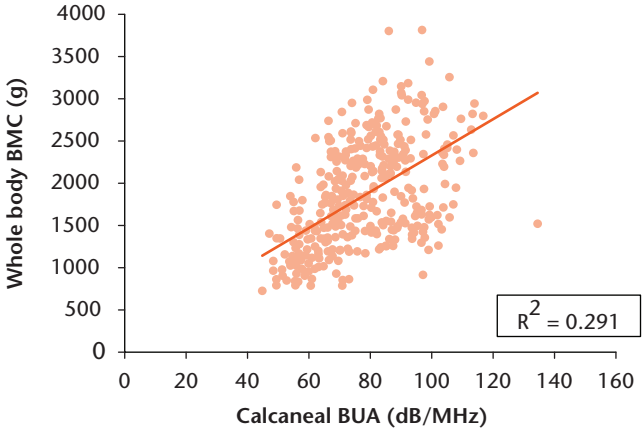


Fig. 1c

Calcaneal broadband ultrasound attenuation (BUA) predictions of a) femoral neck bone mineral content (BMC), b) lumbar spine BMC, and c) whole body BMC for the whole cohort (n = 389).

## Discussion

The aim of this study was to determine the ability of QUS measured BUA, a quick, safe and portable measure of bone integrity to predict radiation-based DXA estimates of bone mass. If the relationship were found to be strong, QUS measures would be particularly attractive for use in paediatric studies. In a sample of children across a broad age range, we observed moderate positive associations between calcaneal BUA and DXA-derived bone mass that were of similar strength in boys and girls. A strengthening of associations between calcaneal BUA and DXA-derived bone mass was observed with an advancing maturational stage. The ability of BUA to predict DXA-derived estimates of bone mass was also moderate, such that the agreement between quartiles of calcaneal BUA and femoral neck BMD and BMC was relatively low. There are a number of reasons, aside from the fundamental difference in technology that may explain the low measurement congruence, that are primarily associated with the different measurement site. The calcaneus is comprised of a lower proportion of cortical bone, and is subject to a very different loading milieu to that of the proximal femur. Furthermore, measurement precision is typically lower for BUA than DXA-derived BMD or BMC.[20]

Our data support the findings of two other large paediatric studies comparing calcaneal QUS and DXA measures of bone.[6,7] Alwis et al[8] examined the associations between BUA and SOS and DXA-derived bone mass at the hip and spine in a large cohort of Swedish children, and while both QUS measures held significant associations with DXA, BUA exhibited the strongest relationships (r = 0.64 to 0.75). In a Chinese cohort of children between five and 19 years of age, calcaneal BUA exhibited weak positive associations with DXA-derived whole body BMC and BMD (r = 0.16 to 0.38).[6] Others have observed associations between BUA and DXA-derived lumbar spine BMD of up to r = 0.83[21] and whole body BMD of r = 0.73 to 0.76,[8,22] which are stronger than the associations we observed in the current study (lumbar spine BMD, up to r = 0.45; and whole body BMD, up to r = 0.53).

The fact that significant associations between QUS and regional DXA measurements were observed in this study, and indeed in previous reports, does not imply diagnostic validity for osteoporosis. Previous studies[23,24] have observed, as have we, that while there are positive correlations, when participants are categorised into quartiles

**Table II.** Significant associations between BUA and bone mass measures at the femoral neck, lumbar spine, and whole body across each level of maturity

| Measure | Pre-APHV(n = 188) | | | Peri-APHV (n = 89) | | | Post-APHV (n = 112) | | |
|---|---|---|---|---|---|---|---|---|---|
| | β | $R^2$ | SEE | β | $R^2$ | SEE | β | $R^2$ | SEE |
| Femoral neck BMC | 6.33 | 0.046 | 16.1 | 5.61 | 0.099 | 11.7 | 5.63 | 0.210 | 11.0 |
| Femoral neck BMD | 26.71 | 0.025 | 16.2 | 19.52 | 0.046 | 12.1 | 35.25 | 0.191 | 11.2 |
| Lumbar spine BMC | 1.00 | 0.063 | 15.9 | 0.50 | 0.089 | 11.8 | 0.59 | 0.182 | 11.2 |
| Lumbar spine BMD | 38.33 | 0.033 | 16.2 | 44.28 | 0.168 | 11.3 | 40.69 | 0.200 | 11.1 |
| Whole body BMC | 0.03 | 0.190 | 14.8 | 0.01 | 0.107 | 11.7 | 0.02 | 0.256 | 10.7 |
| Whole body BMD | 92.03 | 0.128 | 15.3 | 56.60 | 0.158 | 11.3 | 69.86 | 0.281 | 10.5 |

APHV, age of peak height velocity; BMC, bone mineral content; BMD, bone mineral density; SEE, standard error of the estimate; β, beta coefficient of equation.

**Table III.** Exact agreement (%) in quartile cross-classification between calcaneal BUA and DXA measures at the femoral neck and lumbar spine for each maturity level

| Measure (%, n) | Pre-APHV | Peri-APHV | Post-APHV |
|---|---|---|---|
| Femoral neck BMC | *37.6* (71/188) | *37.5* (33/89) | *38.2* (42/112) |
| Femoral neck BMD | *34.9* (66/188) | *27.3* (24/89) | *38.2* (42/112) |
| Lumbar spine BMC | *39.4* (74/188) | *42.7* (38/89) | *32.1* (36/112) |
| Lumbar spine BMD | *35.6* (67/188) | *42.7* (38/89) | *36.6* (41/112) |

APHV, age of peak height velocity; BMC, bone mineral content; BMD, bone mineral density

based on calcaneal BUA and regional BMD, substantial misclassification is observed,[23] a finding that also holds true for radial SOS and BMD measures.[24] Similarly, disagreement between DXA and QUS is observed when z-scores are applied to determine 'normal' measures (z-score > -2.0 SD) from 'abnormal' measures (z-score ≤ -2.0 SD).[4] Moreover, a recent systematic review on the diagnostic accuracy of QUS for the assessment of paediatric osteoporosis concluded that although research design quality of included studies was high, there was insufficient evidence to support the diagnostic value of QUS.[25] It is therefore unsurprising that our data showed a similar discord between QUS and DXA classifications on the basis of quartiles. As others contend that QUS has potential as a pre-screening tool for the assessment of osteoporosis that may reduce the requirement for use of DXA scans,[26] it appears that further research is required to establish its clinical use.

Several limitations of this study warrant acknowledgement. Firstly, with many different types of DXA and QUS scanners available, our data may not be generalisable across any devices other than the Norland XR-800 and the Lunar Achilles Insight. Secondly, as we examined relationships between DXA and QUS measures based on absolute measures of bone mass and quality, rather than diagnostic criteria, our data may not have direct clinical use. Our intention was not to test the diagnostic capability of QUS against DXA, for which there are as yet no robust clinical criteria, but rather to establish if collecting paediatric QUS data is a reasonable approach when DXA measures are not suitable or feasible. Thirdly, there is a large degree of measurement error in calcaneal QUS measures for very small or very young children, which may account for the weaker predictive ability of BUA in our pre-APHV participants. Finally, we recognise that estimates of somatic growth based on anthropometric measures may not provide a perfect representation of skeletal maturity (for which radiographs are required) and therefore the observed relationships at each stage of maturity may not be fully representative of true skeletal status. Moreover, the algorithms to estimate APHV in the current study have not been validated for children younger than eight years. Nevertheless, we used APHV only to stratify children into three maturity stages and did not examine it as a continuous variable in comparisons or correlations.

In conclusion, we found that calcaneal BUA is moderately related to DXA-derived bone mass at clinically important sites in girls and boys, and most strongly related to BMD in post-APHV children than in peri- and pre-APHV children. BUA from QUS demonstrates relatively poor agreement with classification quartiles of bone mass from densitometry. DXA-based BMC and BMD remain the benchmark estimates of paediatric bone mass for diagnostic purposes.

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**Author Contribution**
- B. K. Weeks: Study design, Data collection, Data analyses and interpretation, and Manuscript preparation
- R. Hirsch: Data collection, Data processing, and Manuscript review
- R. C. Nogueira: Data collection, Data processing, and Manuscript review
- B. R. Beck: Study design, Data analysis and interpretation, and Manuscript review

**ICMJE COI Statement**
- B. R. Beck is a co-director of The Bone Clinic, Brisbane, Australia, a health service providing support for individuals with osteoporosis. Quantitative ultrasonometry is not used at, nor are children ever clients of, the clinic.