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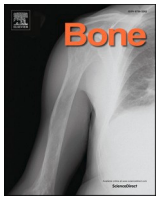

Full Length Article

Is the skull responsive to bone mineralisation stimuli in children?

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ABSTRACT

Background: Whole-body-less-head (WBLH) is the recommended skeletal region of interest (ROI) for dual-energy X-ray absorptiometry (DXA) assessment of bone mineral density (BMD) in children. Historically it has been suggested that the skull is less responsive than the rest of the skeleton to stimuli that affect BMD but there are few published data to support this notion. We compared the associations of BMD with anthropometric, body composition, diet, and activity variables across various ROI.

Methods: Children from the Southampton Women's Survey (SWS) mother-offspring cohort participated at age 6–7 years, including measurement of height, weight, and whole-body and lumbar spine (LS) BMD by DXA (Hologic Discovery). Physical activity was assessed by accelerometry (Actiheart) and diet by interviewer-led questionnaire. BMD was measured in the following skeletal ROI: whole-body, skull, WBLH and lower limbs (all derived from the whole-body scan) and LS.

Results: 1218 children participated. Height z-score, weight z-score, lean mass and milk intake were associated with skull BMD, but associations were weaker than observed for other ROI; for example, the association between lean mass and skull BMD was β (95% CI) 0.11 (0.08, 0.14) SD/kg, compared with 0.32 (0.30, 0.34), 0.38 (0.37, 0.40) and 0.23 (0.21, 0.25) SD/kg for whole body, WBLH and lumbar spine, respectively. Relationships with whole-body BMD were attenuated compared with WBLH.

Conclusion: Associations between skull BMD and anthropometry, body composition and dietary variables were weaker than for other DXA sites. These findings support, and importantly provide a quantitative basis for, the recommendation that the skull should be excluded from whole-body DXA analyses in children.

1. Introduction

Dual-energy X-ray absorptiometry (DXA) is the gold standard for assessment of bone mineral density (BMD). In children, the sites recommended by the International Society for Clinical Densitometry (ISCD) for DXA assessment are whole-body-less-head (WBLH) and lumbar spine [1,2]. The usually stated rationale for exclusion of the head from the whole-body scan is that the contribution of the skull to whole body bone mineral content (BMC) and BMD is high, particularly in young children [3,4]. Furthermore, the relative contribution of the skull to whole-body BMC and BMD reduces over the course of childhood, and thus, exclusion of the head allows more accurate comparison of serial scans. However, it has not been established that WBLH BMD is superior to whole-body BMD in fracture prediction [1]. The flat bones of the skull have a unique macro- and microarchitecture [5], and it has also been suggested that the skull is less responsive that other skeletal sites to stimuli that affect BMD [1]. However, we have identified very few published data to support this statement [4,6–8]. We therefore assessed in a prospective mother-offspring cohort study whether the associations between anthropometric, body composition and lifestyle factors and BMD differed by skeletal site and, in particular, whether these were weaker for the skull compared to other ROI and between whole-body and WBLH.

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2. Materials and methods

2.1. The Southampton Women's Survey

The Southampton Women's Survey is a prospective pre-conception mother-offspring cohort study. Details of the study have been previously published [9]. Briefly, 12,583 women aged 20–34 years living in the city of Southampton, UK were recruited into the study between 1998 and 2002. 3158 of these women delivered a liveborn infant during the course of the study.

The SWS was conducted according to the guidelines laid down in the Declaration of Helsinki, and the Southampton and South West Hampshire Research Ethics Committee approved all procedures (06/Q1702/104). Written informed consent was obtained from all participants and by a parent or guardian with parental responsibility on behalf of their children.

2.2. 6–7 year follow-up visit

1342 children attended a follow-up visit at 6–7 years of age. Height was measured with a Leicester height measurer (Seca Ltd, Birmingham, UK) to the nearest 0.1 cm with the head placed in the Frankfurt plane. Weight was measured in light clothing to the nearest 0.1 kg using electronic scales (Seca Ltd, Birmingham, UK). Standard deviations scores (SDS) for height and weight adjusting for age and sex were calculated using the British 1990 reference data [10].

BMD was assessed by DXA using a Hologic Discovery Instrument (Hologic Inc., Bedford, MA, USA). Scans were obtained of the whole-body and lumbar spine. Whole-body scans were segmented into regions of interest (ROI), which are automatically placed by the scanning technology, but were reviewed by a trained densitometry technician and adjusted as necessary. The skull ROI was defined by a horizontal line between the mandible and shoulders. This therefore does contain part of the upper cervical spine. WBLH scans excluded the skull ROI from the remainder of the skeleton included in the whole-body scan. The leg ROI was defined by a line passing diagonally downwards through the femoral neck to below the pubis. All scan images were reviewed by two researchers and any scans with excess movement or artefact were excluded. Positioning and content of the ROI were also reviewed to ensure the ROI contained the correct anatomical regions. The DXA instrument underwent daily calibration using a spine phantom. The experimental coefficient of variation for this instrument when a spine phantom was repeatedly scanned in the same position 16 times, in a single session with no repositioning, was 0.68%.

Fracture history was determined by parent interview. Diet over the preceding three months was assessed using an interviewer-administered 80-item food frequency questionnaire (FFQ) completed by the parent/guardian. Daily volumes, types and amounts of milks were recorded as well as any sugar added to food. A prudent diet score (dietary quality score) was calculated for each child, as described previously [11,12]. The dietary quality scores were standardised to a normally distributed variable with a mean of zero and standard deviation of one. Higher scores represented better dietary quality and a dietary pattern consistent with dietary recommendations characterised by frequent consumption of fruit, vegetables, and fish.

Habitual physical activity was assessed in a subset of children using an Actiheart combined accelerometer and heart rate monitor (Cambridge Neurotechnology Ltd, Cambridge, UK). The device was worn on the chest, connected to the skin by two ECG electrodes, continuously for 7 days except during bathing and swimming. Pre-defined cut-points were used for the accelerometry data to determine the average number of minutes per day spent in sedentary, light, moderate, vigorous and very vigorous physical activity [13]. Moderate, vigorous, and very vigorous physical activity were combined to give the variable moderate-vigorous physical activity (MVPA).

2.3. Statistical analysis

To enable comparison of beta coefficients across skeletal ROI, only children that had useable scans reporting BMD at all ROI (whole-body, WBLH, lumbar spine, skull, and lower limbs) were included in the analysis. All outcomes were assessed for normality using visual inspection. Comparison between boys and girls were performed using *t*-tests, Mann-Whitney *U* tests and χ^2 tests for normally distributed continuous variables, non-normally distributed continuous variables, and categorical variables, respectively. Owing to differences between boys and girls, BMD, fat mass, lean mass and physical activity were adjusted for age and sex using linear regression. BMD measurements at each skeletal ROI were converted to a standard deviation score (z-score), such that the distribution had a mean of zero and standard deviation of one. Linear regression was used to assess the relationships between the anthropometric, body composition and lifestyle characteristics and BMD at each site, yielding a beta coefficient reported as SD difference in BMD per unit of predictor. All data were analysed using Stata 16.0 (Statacorp, Texas, USA).

3. Results

1342 children attended the 6–7-year follow-up visit. 1218 (90.8%) children had useable whole-body, WBLH and lumbar spine scans and were therefore included in the analysis. Details of these children are shown in Table 1. The boys had higher BMD than the girls at all sites except the lumbar spine (Table 1).

Associations between anthropometric, body composition, physical activity and diet and BMD at the five ROI are shown in Fig. 1 and Table 2. Height z-score, weight z-score, lean mass and milk intake were associated with skull BMD, but these associations were weaker than observed for the other ROI (Fig. 1). For example, the β (95% CI) between lean mass and skull BMD was 0.11 (0.08, 0.14) SD/kg, compared with 0.32 (0.30, 0.34), 0.38 (0.37, 0.40) and 0.23 (0.21, 0.25) SD/kg for whole-body, WBLH and lumbar spine, respectively. The associations with whole-body BMD were attenuated compared to WBLH BMD (Fig. 1).

Fracture history was available for 487 children, of which 11.9% of the boys and 9.8% of the girls had a history of one or more fractures. There was weak evidence for an inverse association between whole body BMD (β (95% CI) −0.16 (−0.45, 0.12) SD/kg) or WBLH BMD (−0.13 (−0.42, 0.15) SD/kg) and fracture history, with similar findings at the skull (−0.16 (−0.44, 0.12) SD/kg), lumbar spine (−0.13 (−0.41, 0.15) SD/kg) and lower limb sites (−0.11 (−0.39, 0.18) SD/kg).

Table 1
Characteristics of the study participants.

	Boys	Girls	p
N	617	601	
Age (years)	6.82 (0.31)	6.82 (0.34)	0.72
Height (cm)	122.1 (5.2)	121.3 (5.5)	0.01
Height z-score	0.16 (0.95)	0.13 (1.01)	0.65
Weight (kg)	24.1 (3.7)	24.3 (4.5)	0.41
Weight z-score	0.20 (1.01)	0.25 (1.03)	0.47
Whole body BMD (g/cm^2)	0.738 (0.051)	0.716 (0.053)	<0.0001
Whole body less head BMD (g/cm^2)	0.603 (0.047)	0.595 (0.050)	0.002
Skull BMD (g/cm^2)	1.229 (0.116)	1.188 (0.112)	<0.0001
Lumbar spine BMD (g/cm^2)	0.535 (0.058)	0.550 (0.060)	<0.0001
Lower limb BMD (g/cm^2)	0.696 (0.063)	0.683 (0.067)	0.006
Total lean mass (kg)	17.1 (2.1)	15.9 (2.2)	<0.0001
Fat mass (kg), median (IQR)	5.1 (4.2, 6.2)	6.4 (5.2, 8.0)	<0.0001
Moderate-vigorous physical activity (hours/day)	1.83 (0.61)	1.51 (0.50)	<0.0001
Daily milk intake (pints/day), median (IQR)	0.50 (0.35, 0.75)	0.50 (0.25, 0.65)	0.002
Prudent diet score (SD)	−0.02 (1.05)	0.01 (0.94)	0.62

Shown as mean (SD) unless otherwise stated. p represents the difference between boys and girls.

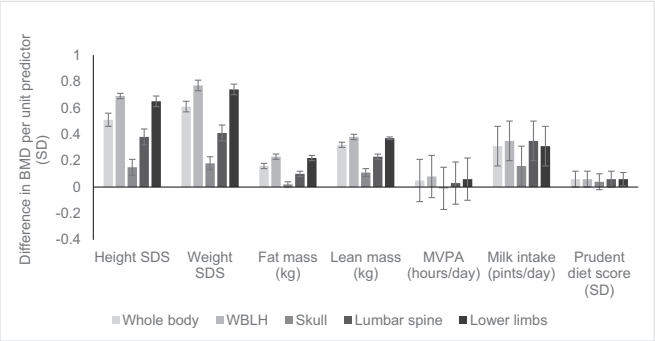

Fig. 1. Associations between anthropometric, body composition and lifestyle factors and bone mineral density at five skeletal regions of interest.
Bars represent the beta (SD difference in bone mineral density (BMD) per unit predictor) and whiskers the 95% CI.
MVPA, moderate vigorous physical activity; SDS, standard deviation score; WBLH, whole-body-less-head.

Table 2
Associations between anthropometric, body composition and lifestyle factors and bone mineral density at five skeletal regions of interest.

	n	Whole-body	Whole-body-less-head	Skull	Lumbar spine	Lower limbs
Height z-score (SD)	1207	0.51 (0.46, 0.56)	0.69 (0.62, 0.71)	0.15 (0.10, 0.21)	0.38 (0.33, 0.44)	0.65 (0.60, 0.69)
Weight z-score (SD)	1206	0.61 (0.56, 0.65)	0.77 (0.74, 0.81)	0.18 (0.13, 0.24)	0.41 (0.37, 0.47)	0.74 (0.70, 0.78)
Whole body fat mass (kg)	1204	0.16 (0.14, 0.18)	0.23 (0.21, 0.25)	0.02 (−0.01, 0.04)	0.10 (0.08, 0.12)	0.22 (0.20, 0.24)
Whole body lean mass (kg)	1203	0.32 (0.30, 0.34)	0.38 (0.37, 0.40)	0.11 (0.08, 0.14)	0.23 (0.21, 0.25)	0.37 (0.35, 0.38)
MVPA (hours/day)	524	0.05 (−0.11, 0.21)	0.08 (−0.07, 0.24)	−0.01 (−0.16, 0.15)	0.03 (−0.12, 0.19)	0.06 (−0.09, 0.22)
Milk intake (pints/day)	1214	0.31 (0.16, 0.46)	0.35 (0.20, 0.50)	0.16 (0.01, 0.31)	0.35 (0.20, 0.50)	0.31 (0.16, 0.46)
Prudent diet score (SD)	1215	0.06 (0.00, 0.12)	0.06 (0.00, 0.12)	0.04 (−0.02, 0.10)	0.06 (0.01, 0.12)	0.06 (0.00, 0.11)

Shown as beta (SD difference in BMD per unit of predictor), 95% CI.

4. Discussion

In children, WBLH rather than whole-body DXA scan is recommended [1]. Our findings support the statement in the International Society of Clinical Densitometry (ISCD) Paediatric Official Positions that the skull is less responsive to stimuli associated with bone mineralisation at other skeletal sites [1], which we have previously been able to identify few data to support. Skull BMD was associated with some anthropometric, body composition and dietary factors, but the associations were weaker than at other ROI.

Similarly to Taylor et al., we found that height and weight were more strongly associated with WBLH than whole-body BMD [3]. This was also consistent with associations with other factors examined, apart from prudent diet score, which was equally associated with whole body and WBLH BMD. Physical activity was not associated with BMD in this cohort. Zouch et al. observed that whole body and lumbar spine BMD but not head BMD increased over a 3 year period in adolescent footballers compared to controls [7] and Courtiex et al. reported lower head but similar whole body BMD in children participating in competitive gymnastics compared to controls [6]. These studies included children participating in high intensity training programmes rather than a population cohort as in our study. Together, these findings all support the use of WBLH scans in clinical research as potential effects on whole-body BMD might be attenuated by a more limited impact on skull mineralisation.

Although there was some evidence of lower BMD amongst children with a history of fracture compared to those without, the associations were uncertain given that the 95% confidence interval bounded zero. Other studies have reported lower BMD in children with fracture compared to non-fracturing controls [14,15]. The difference in findings might reflect the power of our study given fracture history was not available for all participants, and in this study we assessed historical rather than contemporary fractures. Changes to lifestyle factors following a fracture might have improved BMD since the time of fracture. Additionally, we were not able to confirm reported fractures through review of historic radiological examinations. Furthermore, over-reporting of soft tissue injuries as a fracture by caregivers is recognised [16] and would likely reduce the chance of finding a difference between the groups. We are therefore unable to establish differential patterns of WBLH BMD compared to whole-body BMD in fracture associations.

The strength of this study is in the detailed phenotyping of the children enabling relationships between a number of anthropometric, lifestyle and dietary factors and BMD to be considered. However, there are a number of limitations. First, extrapolation of our findings to clinical care should be taken with caution as our participants were part of a healthy cohort study. Nonetheless, our findings are consistent with that of King et al., who demonstrated that boys with Duchenne muscular dystrophy had preservation of skull BMD with age despite a loss in BMD at other skeletal sites [4], suggesting that the skull is also less responsive to changes in physical activity and medical intervention in that disease model. Second, we were unable to obtain physical activity monitoring on all the children therefore reducing the power of that analysis. Some children removed the physical activity monitors, and we did not systematically record this. However, we accounted for non-wear time in the analysis of the accelerometer output. Third, most children included in this analysis were of White ethnicity, reflecting the local population from which the mothers were recruited.

In summary, we have demonstrated that associations with anthropometric, body composition and lifestyle factors and skull BMD are weaker than the associations with mineralisation at other skeletal sites. As would be expected when considering this observation, associations with whole-body BMD were also weaker than WBLH BMD. These findings support, and importantly provide a quantitative basis for, the recommendation that the skull should be excluded from whole-body DXA analyses in children.

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CRediT authorship contribution statement

Rebecca J. Moon: Conceptualization, Formal analysis, Writing – original draft, Visualization. **Stefania D'Angelo:** Formal analysis, Data curation, Writing – review & editing, Visualization. **Sarah R. Crozier:** Formal analysis, Data curation, Writing – review & editing. **Keith M. Godfrey:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Justin H. Davies:** Conceptualization, Writing – review & editing, Supervision. **Cyrus Cooper:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Nicholas C. Harvey:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

CC reports personal fees from ABBH, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier and Takeda, outside the submitted work. NCH reports personal fees, consultancy, lecture fees and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, Servier, Shire, Consilient Healthcare and Internis Pharma, outside the submitted work. KMG has received reimbursement for speaking at conferences sponsored by companies selling nutritional products, and is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec, BenevolentAI Bio Ltd and Danone. JHD has received travel bursaries from Novo Nordisk, SANDOZ and Pfizer unrelated to this work. RJM, SD and SRC declare no potential conflicts of interest.

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