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**AMALGAMATED REFERENCE DATA FOR SIZE-ADJUSTED BONE  
DENSITOMETRY MEASUREMENTS IN 3598 CHILDREN AND YOUNG ADULTS  
– THE ALPHABET STUDY**

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## 1 **Abstract**

2 The increasing use of dual energy X-ray absorptiometry (DXA) in children has led to the  
3 need for robust reference data for interpretation of scans in daily clinical practice. Such data  
4 need to be representative of the population being studied and be ‘future-proofed’ to software  
5 and hardware upgrades. The aim was to combine all available paediatric DXA reference data  
6 from seven UK centres to create reference curves adjusted for age, sex, ethnicity and body  
7 size to enable clinical application, using in-vivo cross calibration and making data back- and  
8 forward- compatible.

9 Seven UK sites collected data on GE-Lunar or Hologic Scanners between 1996 and 2012.  
10 Males and females aged 4 to 20 years were recruited (n=3598). The split by ethnic group  
11 was: White Caucasian 2887; South Asian 385; Black Afro-Caribbean 286; mixed heritage 40.  
12 Scans of the total body and lumbar spine (L1-L4) were obtained. The European Spine  
13 Phantom was used to cross-calibrate the 7 centres and 11 scanners. Reference curves were  
14 produced for L1-L4 bone mineral apparent density (BMAD) and total body less head (TBLH)  
15 and L1-L4 areal bone mineral density (aBMD) for GE Lunar Prodigy and iDXA (sex-and  
16 ethnic-specific) and for Hologic (sex-specific). Regression equations for TBLH BMC were  
17 produced using stepwise linear regression. Scans of 100 children were randomly selected to  
18 test backwards and forwards compatibility of software versions, up to version 15.0 for GE  
19 Lunar, and Apex 4.1 for Hologic.

20 For the first time, sex and ethnic- specific reference curves for lumbar spine BMAD, aBMD  
21 and TBLH aBMD are provided for both GE-Lunar and Hologic scanners. These curves will  
22 facilitate interpretation of DXA data in children using methods recommended in ISCD  
23 guidelines. The databases have been created to allow future updates and analysis when more

24 definitive evidence for the best method of fracture prediction in children is agreed.

25

26 **Keywords: DXA; paediatric; BMD; BMC; reference; lean mass**

27

## 28 **Introduction**

29 The increasing availability and use of dual energy X-ray absorptiometry (DXA) technology  
30 in children has brought to the fore the need for robust reference data for all DXA  
31 manufacturers. Although manufacturer reference databases are available, they are often not  
32 population based nor representative of the individual population being studied (1). Such  
33 databases may also have wide variability due to small numbers, with limited power to model  
34 rapid skeletal changes during different phases of growth. A further limitation for their use in  
35 daily practice is the widespread use of multiple generations of hardware and acquisition and  
36 analysis software that may distort the output. There is a need to enable transition between  
37 them when monitoring skeletal health in individual patients or undertaking longitudinal  
38 research studies.

39 In 2013 the International Society for Clinical Densitometry (ISCD) updated their 2007  
40 Pediatric Bone Densitometry Guidelines for bone assessment in children (1-3). The  
41 committee concluded that DXA is the preferred method for assessment of areal bone mineral  
42 content (BMC) and density (aBMD) and that estimating aBMD should be part of the overall  
43 assessment for children at elevated risk of a clinically significant fracture (1-3).

44 Measurements of total body less head (TBLH) and/ or posterior-anterior lumbar spine aBMD  
45 or BMC are recommended; in conjunction with a history of clinically significant fractures,  
46 these can be used to indicate the diagnosis of osteoporosis in children and adolescents (1-3).

47 In children with short stature or growth delay, the measurements should be size-corrected  
48 using appropriate methods (4-7). The guidelines also acknowledge that adjustment for soft-  
49 tissue measurements may be useful in children with malnutrition or in those with muscle and/  
50 or skeletal deficits, as has been shown previously (8-11). Despite these guidelines, there are  
51 still inconsistencies in the management of children with low BMD and bone fragility around

52 the world. The lack of robust reference data in a format that permits the diagnostic  
53 application of ISCD recommendations is a source of inconsistency. .  
54 The primary aim of the current study was to combine all available paediatric DXA reference  
55 data from seven UK centres to create age-, sex-, ethnic- and size-corrected reference curves  
56 for use in clinical practice and prediction equations for the assessment of the muscle and bone  
57 relationship, and a database which is in-vivo cross calibrated and back- and forward-  
58 compatible.

59

## 60 **Methods**

### 61 *Subjects*

62 Three thousand five hundred and ninety eight healthy, community dwelling children aged 4  
63 to 20 years were recruited from 7 UK centres (Birmingham, Leeds, London, Glasgow,  
64 Sheffield, Middlesbrough, Manchester) using centre-specific protocols, from 1996 to  
65 2012(**Supplementary Table 1**). Participants were a self-selected convenience sample from  
66 across each study region, recruited through advertisement in local schools and colleges,  
67 general practice surgeries and youth groups. Children of White Caucasian, South-Asian and  
68 Black Afro-Caribbean /African descent were included in the study, depending on centre-  
69 specific inclusion and exclusion criteria. Ethnicity was defined by participants' self-reporting  
70 both parents being of identical ethnic origin; where this was not the case, data were excluded.  
71 All centres recruited healthy children without known metabolic bone disease, confirmed  
72 through centre-specific screening questionnaires (**Supplementary Table 1**); abnormal results  
73 were followed-up and excluded if metabolic bone disease was suspected. Children were  
74 included who had had one or more moderate or high trauma fractures (12). At all centres,  
75 local research Ethics Committees approved the studies. All research was carried out in  
76 accordance with the Declaration of Helsinki.

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*Anthropometric measurements*

Height and weight were measured according to centre specific protocols and body mass index (BMI) calculated as weight/height<sup>2</sup> (kg/m<sup>2</sup>). To describe the population at each centre, height, weight and BMI measurements were transformed to standard deviation scores (Z-Scores) using the 1990 British growth reference data (13-15).

*Scan acquisition*

Children were scanned at each centre on either a GE Lunar™ DPX-L, Prodigy or iDXA scanner (GE Medical Systems, Madison, Wisconsin, US) in Birmingham, Leeds, London, Glasgow, Sheffield, Middlesbrough or on a QDR Discovery Hologic™ scanner (Hologic, Bedford, MA, US) in Manchester. Total body, lumbar spine and proximal femur scans were obtained; since the femur is not currently a recommended site according to the current ISCD guidelines (2) only total body and lumbar spine are reported. Standard operating procedures were followed in each centre. All scans were analysed centrally in Birmingham by two Clinical Scientists and were scored for quality of scan acquisition and analysis. DPX-L scans were analysed using software version 4.6c, Prodigy and iDXA scans using Encore version 15.0 (Basic and Enhanced) and Hologic scans using Apex 4.1. Spine bone mineral apparent density (BMAD) was calculated using an adapted method of Carter et al. (g/cm<sup>3</sup>) (4, 16, 17).

$$\text{Lumbar spine BMAD (g/cm}^3\text{)} = \frac{(BMC_1 + BMC_2 + BMC_3 + BMC_4)}{(V_1 + V_2 + V_3 + V_4)}$$

Where V<sub>n</sub> is the volume of the n<sup>th</sup> individual vertebra = AP<sub>n</sub><sup>1.5</sup> (AP<sub>n</sub> = Projected vertebral area of the n<sup>th</sup> vertebra)

BMC<sub>n</sub> is the bone mineral content of the n<sup>th</sup> vertebrae

101 Prediction equations were generated for GE Lunar (Prodigy, iDXA) and Hologic (Discovery)  
102 for predicted total body less head bone mineral content (TBLH-BMC) by linear regression  
103 analysis of log transformed, lean mass, fat mass, height and age (9, 18).

104

105 *Centre cross-calibration:*

106 The European Spine Phantom (ESP) was used to cross-calibrate bone measurements at 7  
107 centres and 11 scanners. (19, 20). The phantom was measured once at each centre 10 times  
108 without repositioning. For practical purposes this process was not repeated and therefore we  
109 relied on local monitoring of scanner operation to verify machine stability. Birmingham was  
110 used as the reference centre and all sites cross-calibrated to these measurements.

111 Additional measurements were taken on the iDXA and Hologic scanners using the Leeds  
112 Paediatric Spine Phantom, developed by The University of Leeds (in-house).

113

114 *In-vivo cross calibration:*

115 *In-vivo* cross calibration was performed in Birmingham, firstly for DPX-L to Prodigy in  
116 healthy children (n=105) and then for Prodigy to iDXA in children undergoing scans for  
117 clinical purposes (n=70) . Both studies were approved by South Birmingham Ethics  
118 Committees. Cross-calibration equations were produced using linear regression analysis of  
119 absolute values. Machine differences were tested using paired t-test and machine bias with  
120 Bland and Altman (**Supplementary table 2**). The equations were used to transform data from  
121 the other GE-Lunar centres to Birmingham for lumbar spine DPX-L to Prodigy Basic and  
122 iDXA; and for total body DPX-L to Prodigy basic, Prodigy enhanced and iDXA <sup>1</sup>. *In-vivo*  
123 cross-calibration was not performed between Hologic and GE-scanners for bone or soft tissue  
124 measurements.

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<sup>a</sup> Prodigy Enhanced is an option only available for total body scans.

125

126 *Back- and forward compatibility*

127 Scans of 100 children were selected from each of the GE Lunar and Hologic databases to  
128 create equations for back- and forwards-compatibility of the reference curves. Within each  
129 cohort of 100 children, 20 children per age-band (5-7, 8-10, 11-13, 14-16, 17-19 years) were  
130 selected at random (10 male, 10 female) from each of the manufacturer specific datasets.  
131 Total body and lumbar spine scans were analysed on software versions: GE-Lunar 10, 11, 13,  
132 14, 15; Hologic 12.4, Apex 2.4, 3.1, 4.1. This sub-set of scans remains available for analysis  
133 for future software versions.

134

135 *Statistical analysis*

136 The Lambda-Mu-Sigma (LMS) method was used to produce age reference curves for Lumbar  
137 Spine BMAD, L1-L4 aBMD and TBLH BMD. The LMS curves were generated using the  
138 method described by Cole and Green (21) (LMSchartmaker Pro version 2.54 © 1997-2011  
139 Medical Research Council, UK). In brief, reference centile curves describe the distribution of  
140 the dependent variable as it varies with the independent predictor covariate, here being age.  
141 The curves are fitted using the parametric approach of the penalised log likelihood method as  
142 cubic splines by non-linear regression. The degree of smoothing required for the curves is  
143 expressed in terms of the equivalent degrees of freedom (edf) (21). The resulting model for  
144 the dependent variable, generated from the raw data, is summarised by three parameters,  
145 namely: L the Box-Cox power transformation needed to remove any skewness from the  
146 distribution, M the median, and S the coefficient of variation. The LMS models were fitted  
147 using the “Loop” analysis function in the software, setting the maximum edf’s for the cubic

148 splines at 3, 6 and 3 and the minimum edf's at 0,1 and 1, for L, M and S respectively. The  
149 reference model choice was guided by the Schwarz Bayesian Criterion and visual inspection  
150 of the curves, resulting in a parsimonious model. Goodness of fit was investigated using the  
151 detrended Q-Q plots and ensuring the Q-test statistic was less than 2 (22-24). Standardized  
152 residuals were tested for normality and the distribution of subjects within the expected  
153 centiles was calculated.

154 Figures 1-3 and Supplemental Figures 3-5 highlight the age-related mean with the 5<sup>th</sup> and 95<sup>th</sup>  
155 confidence intervals with each sex and ethnic group fitted separately. Standard deviation  
156 scores (Z-scores) are calculated from the LMS parameters using the equation;

$$157 \quad Z = \left( \left( \frac{y}{M} \right)^L - 1 \right) / L * S$$

158 *Z = Z- score, y = measured value, M = estimated mean, L = skewness, S = distribution*

159 The need for ethnic specific curves was tested using a one-sided t-test of the Z-scores  
160 calculated from the gender specific white data. Where, a significant difference from zero was  
161 observed, ethnic specific curves were generated. The goodness of fit of the curves is  
162 described by comparing expected versus observed Z -score centile distributions in  
163 **Supplemental Tables 7a-j.**

164 Regression equations for TBLH-BMC were produced using stepwise linear regression;  
165 covariates in the initial model were log-transformed total body lean, total body fat, height and  
166 age, only significant covariates were used. Residual plots were inspected for normality to  
167 check for skewness and bias in the prediction models.

## 168 **Results**

169 A total of 3598 scans from children and young adults aged 4 to 20 years-old were included in  
170 this study (1820 female, 1778 male). The split by ethnic group was: White Caucasian 2887;

171 South Asian 385; Black African/ Afro Caribbean 286 and 40 mixed heritage. One hundred  
172 and one subjects were excluded (61 extreme body size [either height, weight or BMI SDS < -  
173 3.5 or > 3.5SD]; 40 mixed heritage), leaving a total of 3497 subjects for the generation of  
174 reference data (Table 1). Descriptive data by centre are shown in Table 2. There were small,  
175 significant centre differences in height, weight and BMI SDS. Subjects were generally taller,  
176 heavier with greater BMI than the 1990 UK-reference population (13-15).

177

### 178 *Manufacturer differences*

179 Phantom cross calibration: Using the ESP and with Birmingham as the reference centre there  
180 were no significant differences between all 11 scanners in phantom BMC and aBMD  
181 (including Hologic). In contrast, BA was more variable between the centres but the only  
182 significant difference was observed between the Hologic scanner and all GE scanners  
183 ( $p=0.010$ ) (Supplemental Figure 1).

184 We explored these differences further using the Leeds Paediatric Spine Phantom scanned on  
185 a Hologic Discovery and GE-Lunar iDXA scanners. There were no significant differences in  
186 aBMD however BMC and BA were significantly different between the two ( $p<0.001$ ), with  
187 Hologic giving increasingly higher values compared to the iDXA with increasing BMC and  
188 BA. Therefore, transformation equations were produced. However, when we applied these to  
189 the *in-vivo* data there were still systematic differences between the Hologic and GE-Lunar  
190 datasets. Consequently, we could not combine different manufacturer scan data and thus  
191 needed to generate brand-specific reference data for use in clinical practice.

192 In-vivo cross-calibration: *In-vivo* cross-calibration data were only available for the GE-Lunar  
193 scanners (25, 26). The strong linear relationships between scanners from a single  
194 manufacturer enabled successful transformation of the *in-vivo* reference datasets collected  
195 from three generations of GE-Lunar scanners. Once successfully transformed, the Bland

196 Altman tests showed no residual bias. Consequently, this allowed the pooling of all the GE-  
197 Lunar data.

198

199 *Software differences – backwards and forwards compatibility*

200

201 For GE Lunar, there were no differences in any parameter measured using the basic analysis  
202 from version 10 onwards (Prodigy). Version 14.0 included an enhanced total body analysis  
203 to try and make Prodigy total body results comparable with the newly introduced iDXA.

204 Whilst there were no differences between the basic analysis, it is not surprising that there  
205 were differences between the basic and enhanced total body analyses for all measured  
206 parameters (aBMD, BMC, BA, lean and fat) (**Supplemental Figure 2**).

207 For Hologic there were no differences between software versions 12.4 through Apex 4.1. It is  
208 important to note that this is only true if the same analysis option is used; for this study  
209 NHANES BCA was selected throughout.

210

211 *Reference curve generation (Figures 1-3, Supplementary data S3-5)*

212 Because of the known differences in development between boys and girls their data were  
213 separately analysed for BMAD , aBMD and TBLH-BMC.

214

215 *Size-adjusted lumbar spine (Supplemental tables 4a-c)*

216 Small, but significant differences were found for BMAD between White and Asian, and  
217 White and Black children, (Figure 1). In girls, the mean difference in Z-score, calculated  
218 using White as the referent group, was 0.25 (0.88),  $p < 0.0001$  and 0.62 (1.18)  $p < 0.0001$  for  
219 South Asian and Black Caribbean girls respectively (Supplemental Table 7a-b). In boys, the  
220 mean difference in Z-score, again calculated using White as referent group, was 0.24 (0.96),

221  $p=0.001$  and  $0.46$  ( $0.98$ )  $p<0.0001$  for South Asian and Black Caribbean's respectively  
222 (Supplemental Table 7a-b). When Z-scores were recalculated using ethnic-specific LMS data  
223 they were no longer significantly different from 0. LMS data were therefore generated for  
224 each ethnic group separately.

225 Figure 3 shows inter-scanner curve comparisons for males and females separately. Despite  
226 cross-calibrating the Hologic BMC and BA values to GE Lunar using the ESP, highly  
227 significant differences between the scanners remained confirming the differences described  
228 earlier. The result of these differences was that calculated BMAD was lower from the  
229 Hologic scanner. We explored whether this was due aBMD, BMC or BA. BMC and aBMD  
230 were not different but BA was greater in Hologic. Using log-log transformation, (27) the  
231 relationship between BA and BMC differed between scanners: for Prodigy, iDXA and DPX-  
232 L this was  $BA^{1.7}$  (expected  $BA^{1.5}$  (4)), whereas for the QDR Discovery it was  $BA^{1.9}$ .

233

#### 234 *Lumbar spine and total body less head areal BMD (Supplemental Tables S5-6)*

235 In contrast to the BMAD findings there were no significant differences in South Asian  
236 children when compared to the white group. Differences remained for black compared to  
237 white girls (lumbar spine  $0.69$  ( $1.14$ )  $p<0.001$ ; TBLH  $1.04$  ( $1.08$ ),  $p<0.0001$ ) and boys  
238 (lumbar spine  $0.56$  ( $0.97$ )  $p<0.0001$ ; TBLH  $0.93$  ( $1.06$ ),  $p<0.0001$ ) (Supplemental Tables  
239 S7d,e, 7e, h). We therefore combined the data for White and South Asian children, and re-  
240 checked the distribution of Z-scores to check for normality and to ensure differences were not  
241 significantly different from 0, they were not confirming the appropriateness of combining  
242 data.

243

#### 244 *Total body less head BMC (Tables 3-6)*

245 ANOVA was performed with TBLH-BMC as the dependent variable and lean body mass, fat  
246 body mass, height, age, gender and ethnicity as co-variates or factors in the model.  
247 Significant effects were noted for all covariates and factors. Total body lean mass was the  
248 greatest predictor of TBLH-BMC, closely followed by total body fat mass, age and height.  
249 Significant interactions were noted for all covariates between genders and ethnic groups  
250 ( $p < 0.001$ ). Girls had greater TBLH-BMC than males for the same lean mass, fat mass, height  
251 and age. For the same gender, Afro-Caribbean children had greater TBLH-BMC for the same  
252 covariate values (data not shown). Consequently, using stepwise linear regression analysis  
253 with parsimonious variable selection of the log-transformed parameters, individual predictor  
254 models were generated for each manufacturer, each ethnic group and each gender (Table 3a-  
255 d). Individual Z-scores can be produced from by inputting age, height, lean and fat mass in to  
256 the prediction equation. The predicted value can then be used to calculate the Z-score by  
257 using the following equation:

$$Z - score = \frac{\text{Measured value} - \text{Predicted value}}{\text{Predicted value} \times SEE}$$

## 261 **Discussion**

262 For the first time, DXA measurements in children and young adults aged 4-20 years  
263 combining data collected across multiple generations of GE-Lunar and Hologic DXA  
264 scanners and software have been collated. Reference data are presented using some of the  
265 recently recommended methods by ISCD for clinical use. We provide reference curves for  
266 age- and size-adjusted lumbar spine and total body bone densitometry up to the age of 20  
267 years. We also give prediction equations for size- and body composition-adjusted TBLH-  
268 BMC measurements. These data enable calculation of sex-specific Z-scores for three ethnic

269 groups from 4 years-of-age through to the children switching to adult transition services.  
270 Looking ahead, our random dataset of 100 healthy children provides forwards compatibility  
271 of software, which allows us testing of future software updates.

272

### 273 *Scanner differences*

274 The strong linear relationships between the in-vivo cross-calibration of the reference datasets  
275 enabled pooling of all of the GE-Lunar scanners after applying machine specific (i.e. Prodigy,  
276 i-DXA) in-vivo transformation equations (**Supplementary Table 2a-b**). Unfortunately, only  
277 data from *in-vitro* phantoms were available for cross-calibration between the two scanner  
278 manufacturers. The observed BA differences were due to varying projectional errors of the  
279 fan-beam (Hologic) versus narrow-fan (GE-Lunar) technology. Since the phantom consists  
280 of an anthropomorphic spine set in a fixed position it cannot account for differences in body  
281 thickness or spine depth which introduces significant errors in measurement when scanning  
282 *in-vivo*. For this reason we were unable to cross-calibrate Hologic to GE-Lunar data. Our  
283 findings confirm the inappropriate nature of using phantoms to cross-calibrate between  
284 hardware with different properties, i.e. pencil → narrow-fan → fan beam (28,29).

285

### 286 *Software differences*

287 The data presented here are for the latest software version of each manufacturer; Encore 15.0  
288 (GE Lunar) and Apex 4.1 (Hologic). With simple transformations it is possible to interpret  
289 the DXA results using any version of software going back to GE Lunar Encore 10.0 and  
290 Hologic 12.4. Our findings confirm that for both manufacturers it is necessary to always use  
291 software specific reference data. It should be noted that for both, it is essential to ensure that  
292 when comparing results from different software versions the same analysis options are  
293 selected. For GE-Lunar this means selecting enhanced or basic analysis, and for Hologic

294 Apex software the NHANES BCA analysis should be switched on (30). For older, pre-Apex  
295 versions of Hologic, the ‘auto whole body analysis’ should be used.

296

297 *Reference data and their use in fracture prediction*

298 Our study presents age- (TBLH-aBMD, spine aBMD) and size-adjusted data for bone  
299 densitometric variables (BMAD, TBLH-BMC) previously shown to best predict fractures in  
300 healthy or chronically ill children (31); these also represent some of the methods currently  
301 recommended by ISCD (1, 2). In over 450 children with chronic disease the diagnostic odds  
302 ratio for predicting vertebral fractures was 9.3 (5.3-14.9) for lumbar spine BMAD; for  
303 predicting long bone fractures the odds ratio was 6.5 (4.1-10.2) for TBLH-BMC for lean  
304 mass (31). BMAD has also been shown to be the best size-adjustment method for prediction  
305 of fractures in healthy children (32). Current understanding is that when interpreting  
306 paediatric bone density results it is preferable to use a size-adjustment method, such as  
307 BMAD or a height-adjusted Z-score(1), however a firm consensus regarding the most  
308 appropriate size-adjustment technique has yet to be established and for this reason the use of  
309 age-adjusted aBMD is still recommended by ISCD (2). Unlike previous studies, some of  
310 which are described below, that present reference data from a single manufacturer and using  
311 one software version (7, 16, 33, 34 ) the data presented here can easily be applied to different  
312 software versions and manufacturers. If necessary, data can be regenerated using newer size-  
313 adjustment methodology.

314 The Bone Mineral Density Childhood Study (BMDCS) multi-center study generated robust  
315 US-population-derived reference data for Hologic scanners (software version 12.3 for  
316 baseline and Apex 2.1 for follow-up scans) from over 10 000 measurements in over 2000  
317 individuals of TBLH and lumbar spine BMC and aBMD measurements in 5 to 20-year olds  
318 (6, 6). Size-adjusted prediction equations using height for age Z-scores were also generated

319 and verified using an independent dataset. No data have yet been published to show whether  
320 this method of adjustment significantly improves fracture prediction. Reference data were  
321 also generated from the NHANES study; to date only LMS data for total body composition  
322 have been published (33). It should be noted that both the NHANES and the BMDCS studies  
323 generate Hologic reference data and are from much larger population samples than the UK  
324 database presented here.

325 In contrast to the current study, NHANES data have been cross-calibrated from Hologic to  
326 GE-Lunar. Data generated on Hologic 4500 scanners (software version Apex 3.0) were cross  
327 calibrated to GE Lunar iDXA values (Software version 14.0) (29, 34). However, despite  
328 being the largest published database (approximately 20 000 measurements), only data for  
329 total body measurements were presented. Since reductions in TBLH-BMC only predict long  
330 bone and not vertebral fracture risk (31), isolated total body data may have limited clinical  
331 use. Another possible limitation of the NHANES reference database translation to GE  
332 measurements is that pragmatic cross-calibration was performed using data from a native  
333 Chinese population and then applied to transform a much larger dataset of a North American  
334 US population (34).

335

### 336 *Limitations*

337 There are several limitations to this study. The previously discussed differences in phantom  
338 measurements between the scanners due to projection error and table height differences  
339 (Figure 3) and subsequent lack of in-vivo data for cross-calibration meant that we were  
340 unable to create a single combined dataset, applicable to both manufacturers' scanners. The  
341 data were all collected in UK centres, but are applicable for use worldwide provided the same  
342 software and scan protocols are used. Caution should be applied when using the data in

343 populations in which there may be differences in growth rates or body habitus and robust  
344 testing should be employed. In our study the sample size for the South Asian and Afro-  
345 Carribean populations were considerably smaller than the White population and recruited  
346 mostly from one centre and as such we cannot be certain that this is fully representative of the  
347 population. We cannot rule out recruitment bias in any of the centres but as can be seen from  
348 **Supplementary Table 1** protocols and sampling strategies were broadly the same.  
349 Although we cannot confirm that the differences between GE Lunar and Hologic reference  
350 data were not due to population differences, it is likely that the differences are due to  
351 differences in scanner technology. We believe the cross-calibration procedure is as robust as  
352 it can be, since collecting repeated measurements on scanners across the country is neither  
353 ethical nor feasible. Because only one centre collected Hologic data, in one ethnic group,  
354 there are fewer subjects and the Hologic dataset did not include different ethnic groups.  
355 Despite this, we have made this Hologic dataset robust to software updates and increased the  
356 utility of the data previously published in 2007 (16). Finally, we have focussed on testing  
357 the data based on bone measurements only, clearly repeating this work for body composition  
358 would be an advantage (29, 34).

359

### 360 *Conclusion*

361 In conclusion, we present backwards- and forward- compatible ethnic- and sex specific  
362 reference data for size-adjusted bone density in children and young adults, generated from  
363 measurements in over 3500 individuals using GE and Hologic scanners. These data have  
364 been produced using methods included in the most recent ISCD guidelines and for the first  
365 time present curves for lumbar spine BMAD and prediction equations for TBLH-BMC taking  
366 into account lean mass and body size, together with age-and gender- specific curves for

367 lumbar spine and TBLH aBMD. This reference database data has been specifically designed  
368 to allow future updates and analysis when more definitive evidence for the best method of  
369 fracture prediction in children is agreed.

370

371

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391

392 Authors' roles: Current study design: NJC, KW, NJS, NJB; Study conduct: NJC Data  
393 collection: All authors and the ALPHABET study team. Data analysis: NJC Data  
394 interpretation: NJC, KW Drafting manuscript: NJC, KW. Revising manuscript content: All  
395 authors. Approving final version of manuscript: All authors; Data integrity of manuscript:  
396 NJC

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494 **Figure legends**

495 **Figure 1** Comparison of GE Lunar iDXA™ lumbar spine BMAD LMS reference curves  
496 between the three different ethnic groups. (A) BMAD ( $\text{g}/\text{cm}^3$ ) for girls; (B) BMAD ( $\text{g}/\text{cm}^3$ )  
497 for boys. Solid black line represents the mean for White Caucasian Children ( $\pm 95\%$   
498 Confidence interval -dotted black line). Dark grey dashed line represents the mean for Black  
499 Afro-Caribbean Children; Dashed light grey line represents the mean for South Asian  
500 Children.

501

502 **Figure 2** Comparison of lumbar spine BMAD LMS reference curves between males and  
503 females (A) GE Lunar iDXA; (B) Hologic Discovery. Solid black line represents males  
504 (mean  $\pm 95\%$  Confidence interval). Dashed line represents females (mean  $\pm 95\%$  Confidence  
505 interval).

506

507 **Figure 3** Comparison of lumbar spine BMAD LMS reference curves between manufacturers,  
508 GE Lunar iDXA™ compared to Transformed Hologic Discovery (Hologic data transformed  
509 using cross calibration equations generated from the European Spine Phantom). (A) Females;  
510 (B) Males. Solid black line represents GE Lunar iDXA™ (mean  $\pm 95\%$  Confidence interval).  
511 Dashed line represents Hologic Discovery (mean  $\pm 95\%$  Confidence interval).

512

513 TABLES

514 **Table 1** Distribution of subjects used for the generation of reference data

<b>GE Lunar Prodigy</b>	2547	Male	1245	White Caucasian	925
				South Asian	192
				Black Afro Caribbean	128
		Female	1302	White Caucasian	970
				South Asian	184
				Black Afro Caribbean	148
<b>GE Lunar iDXA</b> (including transformed Prodigy)	2910	Male	1411	White Caucasian	1091
				South Asian	192
				Black Afro Caribbean	128
		Female	1499	White Caucasian	1167
				South Asian	184
				Black Afro Caribbean	148
<b>Hologic Discovery</b>	587	Male	325	White Caucasian	325
		Female	262	White Caucasian	262

515

516

517 **Table 2** Patient anthropometric data. Mean (SD)

Centre	Number	Mean (SD) Height Z-score	Mean (SD) Weight Z-score	Mean (SD) BMI Z-score
Birmingham	935	0.20 (1.09)	0.45 (1.24)	0.46 (1.25)
Middlesbrough	390	0.35 (0.97)	0.41 (0.96)	0.31 (1.00)
Leeds	171	0.34 (1.00)	0.42 (1.10)	0.31 (1.11)
Glasgow	212	0.15 (1.02)	0.34 (1.07)	0.36 (1.02)
London	372	0.11 (1.03)	0.29 (1.10)	0.27 (1.12)
Sheffield	830	0.40 (1.05)	0.59 (1.11)	0.51 (1.15)
Manchester	587	0.30 (0.96)	0.47 (1.01)	0.41 (1.03)
TOTAL	3497	0.28 (1.03)	0.46 (1.11)	0.42 (1.14)
Centre Differences (p value)		<0.001	0.001	0.003

518

519 Using a one-sided t-test all Z-scores were significantly ( $p < 0.0001$ ) greater than zero. Centre  
520 differences were compared using ANOVA.

521

**Table 3a** Prediction Equations for Total body less head bone mineral content (TBLH-BMC (g)) for lean mass (g), fat mass (g), height (cm) and age (1decimal place) for the GE Lunar Prodigy™- Software version Encore 15.0.

		GE Prodigy	r <sup>2</sup>	SEE
Girls	White Caucasian	$TBLH-BMC = 3.77 \times 10^{-4} \times LEAN^{0.845} \times FAT^{0.130} \times Height^{0.928} \times Age^{0.179}$	0.966	0.0988
	South Asian	$TBLH-BMC = 2.24 \times 10^{-4} \times LEAN^{0.603} \times FAT^{0.122} \times Height^{1.535} \times Age^{0.216}$	0.970	0.0935
	Black Afro-Caribbean	$TBLH-BMC = 1.02 \times 10^{-3} \times LEAN^{0.941} \times FAT^{0.100} \times Height^{0.543} \times Age^{0.311}$	0.967	0.1002
Boys	White Caucasian	$TBLH-BMC = 2.93 \times 10^{-4} \times LEAN^{0.939} \times FAT^{0.073} \times Height^{0.930} \times Age^{0.079}$	0.972	0.0976
	South Asian	$TBLH-BMC = 1.47 \times 10^{-4} \times LEAN^{0.978} \times FAT^{0.060} \times Height^{1.060}$	0.978	0.0932
	Black Afro-Caribbean	$TBLH-BMC = 1.94 \times 10^{-3} \times LEAN^{0.983} \times FAT^{0.048} \times Height^{1.018}$	0.973	0.0883

Total body less head BMC = TBLH-BMC; Total body lean mass = LEAN; Total body fat mass = FAT; SEE = Standard error estimate

Z-Score = (Measure Value – Predicted Value) / (Predicted Value x SEE)

**Table 3b** Prediction Equations for Total body less head bone mineral content (TBLH-BMC (g)) for lean mass (g), fat mass (g), height (cm) and age (1dp) for the GE Lunar Prodigy™ using the ENHANCED analysis mode - Software version Encore 15.0.

		GE Prodigy-Enhanced	r <sup>2</sup>	SEE
Girls	White Caucasian	$TBLH-BMC = 4.24 \times 10^{-3} \times LEAN^{0.682} \times FAT^{0.079} \times Height^{0.905} \times Age^{0.122}$	0.967	0.0818
	South Asian	$TBLH-BMC = 6.04 \times 10^{-3} \times LEAN^{0.511} \times FAT^{0.106} \times Height^{1.110} \times Age^{0.185}$	0.937	0.0809
	Black Afro-Caribbean	$TBLH-BMC = 9.01 \times 10^{-3} \times LEAN^{0.744} \times FAT^{0.103} \times Height^{0.545} \times Age^{0.234}$	0.961	0.0910
Boys	White Caucasian	$TBLH-BMC = 1.47 \times 10^{-3} \times LEAN^{0.813} \times FAT^{0.055} \times Height^{0.949}$	0.974	0.0839
	South Asian	$TBLH-BMC = 5.06 \times 10^{-3} \times LEAN^{0.883} \times FAT^{0.044} \times Height^{0.586}$	0.979	0.0775
	Black Afro-Caribbean	$TBLH-BMC = 3.81 \times 10^{-3} \times LEAN^{0.856} \times FAT^{0.047} \times Height^{0.692}$	0.974	0.0735

Total body less head BMC = TBLH-BMC; Total body lean mass = LEAN; Total body fat mass = FAT; SEE = Standard error estimate

Z-Score = (Measure Value – Predicted Value) / (Predicted Value x SEE)

**Table 3c** Prediction Equations for Total body less head bone mineral content (TBLH-BMC (g)) for lean mass (g), fat mass (g), height (cm) and age (1dp) for the GE Lunar iDXA™ - Software version Encore 15.0.

		GE Lunar iDXA	r <sup>2</sup>	SEE
Girls	White Caucasian	$TBLH-BMC = 1.85 \times 10^{-3} \times LEAN^{0.736} \times FAT^{0.077} \times Height^{0.950} \times Age^{0.135}$	0.965	0.0843
	South Asian	$TBLH-BMC = 2.58 \times 10^{-3} \times LEAN^{0.538} \times FAT^{0.110} \times Height^{1.210} \times Age^{0.192}$	0.967	0.0836
	Black Afro-Caribbean	$TBLH-BMC = 4.27 \times 10^{-3} \times LEAN^{0.787} \times FAT^{0.105} \times Height^{0.594} \times Age^{0.239}$	0.962	0.0931
Boys	White Caucasian	$TBLH-BMC = 5.88 \times 10^{-4} \times LEAN^{0.827} \times FAT^{0.055} \times Height^{1.095}$	0.974	0.0849
	South Asian	$TBLH-BMC = 2.01 \times 10^{-3} \times LEAN^{0.906} \times FAT^{0.047} \times Height^{0.708}$	0.980	0.0798
	Black Afro-Caribbean	$TBLH-BMC = 1.78 \times 10^{-3} \times LEAN^{0.887} \times FAT^{0.051} \times Height^{0.765}$	0.975	0.0754

Total body less head BMC = TBLH-BMC; Total body lean mass = LEAN; Total body fat mass = FAT; SEE = Standard error estimate

Z-Score = (Measure Value – Predicted Value) / (Predicted Value x SEE)

**Table 3d** Prediction Equations for Total body less head bone mineral content (TBLH-BMC (g)) for lean mass (g), fat mass (g), height (cm) and age (1dp) for the Hologic Discovery – Software version Apex 4.1.

		Hologic Discovery	r <sup>2</sup>	SEE
Girls	White Caucasian	$TBLH-BMC = 1.20 \times 10^{-2} \times LEAN^{0.704} \times Height^{0.717} \times Age^{0.235}$	0.954	0.0871
Boys	White Caucasian	$TBLH-BMC = 4.77 \times 10^{-3} \times LEAN^{1.041} \times FAT^{-0.046} \times Height^{0.398}$	0.960	0.0962

Total body less head BMC = TBLH-BMC; Total body lean mass = LEAN; Total body fat mass = FAT; SEE = Standard error estimate

Z-Score = (Measure Value – Predicted Value) / (Predicted Value x SEE)

