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Reference values for bone mineral density in healthy Mexican children and adolescents

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ABSTRACT

Introduction: Clinical assessment of bone health by Dual-Energy X-ray Absorptiometry (DXA) in the paediatric population requires robust reference values. The International Society for Clinical Densitometry (ISCD) recommends that country/regional reference values ideally should be used to improve precision in bone health assessment.
Objective: The aim of this study was to provide reference values for relevant bone health variables for healthy Mexican children and adolescents aged 5 to 18 years.
Methods: This was a cross-sectional, stratified and population-based study, that measured a representative sample of healthy Mexican children and adolescents with DXA. We constructed age- and sex-smoothed reference values for areal bone mineral density (aBMD) of total body less head (TBLH), total body (TB), lumbar spine (LS), and bone mineral apparent density (BMAD) for LS, by means of Generalized Additive Models for Location, Scale and Shape (GAMLSS).
Results: Reference data including the 3th, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 97th centiles, along with lambda (L), mu (M) and sigma (S) values, are given for each variable of interest for each sex at 0.25 years intervals. Reference values relative to height and Tanner-stage for both sexes are also provided. Finally, formulas to enable Z score estimation for clinical use are also presented
Conclusions: The sex, age, height, Tanner-stage and ethnic-specific reference data provided in this study should enable more precise assessment of bone health in the Mexican paediatric population. The data presented may also allow for future evaluation of potential similarities and differences across different ethnic groups.

1. Introduction

Bone health is determined by both non-modifiable factors (e.g. genetics, sex and ethnic ancestry) and modifiable factors (e.g. lifestyle, diet, and physical activity). Childhood and adolescence are critical periods of development where rapid skeletal linear growth requires adequate bone mineral accretion [1–3]. Several clinical conditions, such as chronic diseases that involve inflammation or malabsorption, cancer, immobility/bed rest associated with long-term illnesses (e.g. cerebral palsy), drug therapy (e.g. corticosteroids, anti-epileptics, chemotherapy, methotrexate), malnutrition, and other health conditions occurring during childhood and adolescence can compromise bone health and peak bone mass, thereby shaping increased susceptibility to osteopenia, osteoporosis and fractures later in life [2,4–8]. Healthcare professionals taking care of children and adolescents can and should assess bone health, especially when one or more of the previous conditions are

Abbreviations: DXA, Dual Energy X-ray Absorptiometry; TBLH, total body less head; BMC, bone mineral content; aBMD, areal bone mineral density; BMAD, bone mineral apparent density; LS, lumbar spine L1-L4; ISCD, International Society for Clinical Densitometry; GAMLSS, Generalized Additive Models for Location, Scale and Shape.

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present.

Although there are several methods to assess bone health, DXA is the most commonly used because it is rapid, easily tolerated, non-invasive, highly precise, involves a low radiation dose and is relatively more available and affordable [9,10].

According to the International Society for Clinical Densitometry ISCD, the assessment of bone health in children and adolescents with DXA should be done using scans of the total body less head (TBLH) and postero-anterior lumbar spine scans, and only in particular cases by forearm or proximal femur scans [11,12].

DXA measures bone mineral content (BMC) in a given anatomical region and estimates the areal bone mineral density (aBMD) [6]. Reference values for BMC and aBMD have been described for children and adolescents differentiated by age, sex, and ethnic ancestry in several studies from Europe [13] and the United States [6]. Further, to control for variability in bone- and/or body-size, adjustments for bone volume (bone mineral apparent density or BMAD in g/cm^3) and height-adjustment equations have been developed, to allow for more accurate assessment of bone status in children of short or tall stature [6,12,14,15].

Reference values should be generated from measurement of a sample of healthy children and adolescents, which adequately represent the population in which the reference data will be used. The sample must be large enough to appropriately characterize the expected variability associated with age and sex, and must include only individuals with adequate nutritional status and normal growth patterns, who do not suffer from chronic diseases, and who have not been exposed to drugs or physical limitations that are known to affect bone mineral accretion [16,17].

Regional sociocultural factors besides genetics can influence human growth and body composition, so country/regional level aBMD and BMAD reference values should ideally be available. Reference values for the Mexican population have been reported previously, based on a sample of healthy subjects aged 7–80 years [18]. However, this study's design, sample representativeness, and statistical methods do not meet the criteria described above, so there is a real clinical need for bone health reference values for Mexican children and adolescents.

The primary aim of this study was to construct age and sex smoothed reference values for aBMD of total body less head (TBLH), total body (TB), lumbar spine (LS), and BMAD for LS for healthy Mexican children and adolescents aged 5 to 18 years. Secondary aims were to provide reference values by sex and height, and sex and Tanner-stage.

2. Materials and methods

This research was part of the study "Reference values of body composition in Mexican children and adolescents", a population-based, cross-sectional study in healthy children and adolescents.

2.1. Study subjects & recruitment

From the complete list of preschool, elementary and secondary schools registered at the Secretaría de Educación Pública of Mexico City ($n = 7511$) [19] a stratified multistage random sampling was performed, considering school grade, public vs private school, and the school's county. This resulted in 15 schools being considered eligible and invited to participate, of which 13 agreed. Additionally, 15 high schools from Universidad Nacional Autónoma de México (UNAM), were invited to participate, with only three agreeing. Written invitations were delivered to parents, between March 2015 and November 2019. Family and friends of recruited subjects that met the inclusion criteria were also invited to participate. Circulating information about the study resulted in another four schools (2 elementary, 1 secondary, 1 high school) and one soccer club contacting us regarding possible participation, and these were included too.

Considering data dispersion in previously published aBMD reference values by Crabtree et al. [13], a sample size of 1500 subjects (i.e. 53 subjects per sex and year of age) was estimated to provide a fair representation of the distribution of the variables of interest.

Subjects interested in the study attended an appointment and were assessed for the following inclusion criteria: individuals from 4 to 20 years of age confirmed as healthy by clinical history and laboratory tests, Mexican ethnicity (i.e. the subject, parents and all four grandparents must have been born in Mexico, with Spanish as the maternal language), birth weight > 2.5 kg, no history of chronic diseases, no intake of drugs known to modify bone mass (e.g. hormonal therapy, corticosteroids, anti-epileptics, methotrexate, etc.), no clinical evidence of early puberty (defined as breast development in girls <8 years or pubic hair growth in boys <9 years), no history of ≥2 fractures; no history of pregnancy or current pregnancy. Because of the known effects of metabolic disturbances on bone health [20], we considered as exclusion criteria the presence of the following metabolic disturbances: impaired fasting glucose; low high-density cholesterol; high triglycerides; or insulin resistance according to the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents criteria [21].

All parents or guardians were asked to sign an informed consent form, and informed assent was obtained for subjects 7 years and older. The trial was designed and executed according to the Helsinki declaration and approved by our institution's research, ethics and biosafety committees, reference number HIM 2015-055. Funding was provided by CONACYT; grant number 2015-2 261682.

2.1.1. Clinical assessment & anthropometric measurements

Subjects were instructed to arrive at our institution after 8 hour fasting. First, a paediatrician assessed each subject (i.e. clinical history and physical examination) to confirm their health status and to register their sexual maturation according to Tanner's criteria [22,23]. If the subject was healthy, relevant clinical, demographic and family data was obtained. Anthropometry was performed with subjects wearing lightweight clothing, measuring weight and height (SECA® directprint 284 scale stadiometer), waist and hip circumferences according to World Health Organization (WHO) standards (SECA® 201 measuring tape). Body mass index (BMI) was calculated as weight (kg) over height squared (m^2) according to Quetelet's method [24], and z-scores of weight, height and BMI where computed according to growth charts from the WHO [25].

Blood samples were obtained to quantify serum glucose, insulin, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol.

Subjects with BMI Z scores of +3 or −3; values of glucose ≥100 mg/dL, total cholesterol ≥200 mg/dL; HDL cholesterol <40 mg/dL, or <45 mg/dL for post-pubertal girls; triglycerides ≥100 mg/dL for children under 10 years, or ≥130 mg/dL for children 10–19 years; blood pressure ≥90th percentile by age, height and sex according to the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents criteria [21]; and insulin resistance defined by HOMA-IR >3.5; were not included for the construction of the reference values. These metabolic biochemical abnormalities were considered as relevant exclusion factors given their known effects on bone-health, and to ensure the healthy status of the sample [20].

2.2. DXA measurements

Whole-body and postero-anterior lumbar spine (L1-L4) scans for each patient were performed, using Lunar-iDXA instrumentation (GE Healthcare, Madison, WI) according to the manufacturer's instructions for subject positioning and following ISCD recommendations [9]. We used ENCORE software version 15 to obtain aBMD and BMC values for TBLH, TB and lumbar spine. We calculated BMAD values by dividing BMC by three-dimensional bone volume, derived from its two-dimensional projected bone area in L1 to L4, BMC/bone area$^{1.5}$

according to Carter et al. and modified by Ward et al. as follows [14,15,26]:

$$\text{LS BMAD}\left(\text{g/cm}^3\right) = \frac{\text{L1 BMC} + \text{L2 BMC} + \text{L3 BMC} + \text{L4 BMC}}{\text{L1 } V + L2\ V + L3\ V + L4\ V}$$

All clinical assessments and DXA scans were done at a single research site. Calibration of the instrument was performed by an ISCD certified nurse on a weekly basis according to the manufacturer's instructions, to maintain quality control (Lunar iDXA by GE Healthcare). Technical precision error was estimated based on repeated scans of an independent sample of 30 voluntary children and adolescents resulting in 0.005 g/cm^2 root mean square standard deviation (RMS SD), with a Least Significant Change (LSC) of 0.014 g/cm^2 at 95% confidence level which was acceptable according to ISCD criteria [27].

2.3. Statistical analysis and construction of reference values

Descriptive statistics were calculated to characterize the sample. Subjects with incomplete or invalid measurements, as well as outliers for height, weight and BMI (>3 *z*-score) were eliminated. To construct the reference values as smoothed percentile growth curves, Generalized Additive Models for Location, Scale and Shape (GAMLSS) [28] were fitted by maximum likelihood in R language version 3.6.3 [29] within the R-Studio platform, version 1.2.5033. The reference values were defined by sex- and age-related centiles, sex- and height-specific centiles and sex- and sexual maturation-specific centiles, for the age range 5 to 18 years. In each case, centiles 3th, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 97th for each 0.25-year age group were estimated. The GAMLSS class of statistical models generalizes the LMS method [30] and yields age-related smooth trends. Data from subjects in the age groups of 4 and 19–20 years were considered in the curve-fitting procedure, because of their influence in the smoothing process, but specific reference values for these age-groups are not presented. Though GAMLSS models can incorporate two shape parameters, typically one for skewness and one for kurtosis, the models were fitted based on the Box-Cox-Cole-Green (BCCG) distribution which allows fitting smooth curves defining parameters for location (median (M), scale (coefficient of variation, S), and one shape parameter (skewness, L) as goodness-of-fit was not improved by fitting four-parameter distributions.

In common with the LMS method, the GAMLSS class specifies smoothing terms, typically cubic splines, to model continuous anthropometric variables and allows the derivation of age-related percentiles that can be used to estimate population standards. Penalised *p*-splines [31] specified the smooth terms with their degree of smoothing chosen using a generalized cross validation criterion.

To calculate a *z*-score for a new data point (*X*), in combination with the age- and sex-specific *L*, *M* and *S* reference values that we report below, the following formula is required:

$$z = \frac{\left(\frac{X}{M}\right)^L - 1}{L \times S}$$

Descriptive and other summary statistics and analyses were performed in IBM® SPSS® Statistics Version 20, and in the R language and environment for statistical computing, version 3.6.3 and LMS chartmaker Pro version 2.54.

3. Results

A total of 2104 children and adolescents aged 4.5–20 years were recruited and measured, whose weight, height and BMI were comparable to those reported in the Mexican National Health and Nutrition Survey (ENSANUT) 2018 [32] (see Supplementary Table 1).

A total of 1659 (79%), of these individuals were eligible to generate reference values. Reasons for exclusion were clinical conditions detected in the paediatric examination or biochemical samples [$n = 445$, (21%): 3 for precocious puberty, 24 for existing chronic conditions, and 418 subjects for metabolic alterations evident from the blood sampling].

Table 1
General characteristics of the sample.

Variable	Female (806, 49%)	Male (853, 51%)
Age (years)	12.6 ± 4.6	11.9 ± 4.3
Weight (kg)	42.3 ± 16.	42.2 ± 17.5
Weight z-score	−0.08 ± 1.03	−0.11 ± 1.12
Height (cm)	142.9 ± 18.6	145.5 ± 21.8
Height z-score	−0.51 ± 0.99	−0.3 ± 0.95
BMI (kg/m^2)	19.7 ± 4.0	19.3 ± 4.0
BMI Z-score	0.20 ± 1.01	0.02 ± 1.17
Puberal Tanner stage		
1	266, 33%	416, 49%
2	71, 9%	85, 10%
3	96, 12%	85, 12%
4	178, 22%	134, 16%
5	195, 24%	133, 16%
BMI category		
Underweight	33, 4%	62, 7%
Healthy weight	592, 73%	615, 72%
Overweight	132, 16%	111, 13%
Obesity	49, 7%	65, 8%

Comparisons between included and excluded subjects resulted in expected significant differences for the BMI category, where the included subjects' distribution consisted of 71% with healthy weight, 20% overweight, 7% obesity and 2% underweight, whereas among excluded subjects, 31% had healthy weight, 28% overweight, 41% obesity and 1% underweight (see Supplementary Table 2). No significant differences in socio-economic level were observed (see Supplementary Table 3).

We analysed data from 854 (51%) males and 805 (49%) females, where 675 (41%) of children were prepubertal (Tanner stage 1), 333 (20%) pubertal (Tanner stage 2 and 3), and 631 (38%) Tanner stage 4–5. Regarding nutritional status assessed by BMI category, 1183 (71%) subjects were in the healthy range, 331 (20%) had overweight, 108 (7%) had obesity and 37 (2%) were underweight. A summary of descriptive data of the sample is shown in Table 1.

Sex and age-smoothed centile values for aBMD of TBLH and LS are given in 0.25 years intervals in Tables 2–3. In Table 4 similar data for BMAD of lumbar spine is shown. Corresponding values for aBMD of TBLH by height are found in Table 5. Finally, in Table 6 the mean and SD of aBMD of TBLH and lumbar spine for each Tanner stage is shown. Values for aBMD of TB and BMC of TB, TBLH, and LS are shown in Supplementary Tables 4 to 7.

Sex and age-smoothed centile graphs for aBMD of TBLH, TB and lumbar spine and BMAD of lumbar spine by are presented in Figs. 1–2. Corresponding values for aBMD of TBLH and lumbar spine by sex and height are found in Fig. 3.

We observed differences in the graphical behaviour of values between sexes. Mean differences of aBMD TBLH and LS between sexes by each year of age are shown in Supplementary Table 8 and Supplementary Fig. 1, and by Tanner stage in Supplementary Table 9 and Fig. 2.

A comparison between these reference values and those previously published in other studies using the same device (GE-Lunar) is illustrated in Fig. 4, and Supplementary Fig. 3.

Finally, values of L, M and S for aBMD of TB, TBLH, LS and BMAD by age and sex or by height and sex are shown in Supplementary Tables 10 to 15.

4. Discussion

We have presented sex-specific and age-smoothed reference values for aBMD and BMC for TBLH, TB and lumbar spine, and BMAD for lumbar spine for a representative sample of healthy children and adolescents from Mexico City. These data provide a valuable reference against which all individuals from this population, with or without

Table 2
Smoothed percentiles for aBMD for total body less head for female and male 5 to 18 years.

Total body less head aBMD (g/cm^2)																		
Age	Female centile									Male centile								
	3th	5th	10th	25th	50th	75th	90th	95th	97th	3th	5th	10th	25th	50th	75th	90th	95th	97th
5	0.430	0.438	0.450	0.471	0.495	0.520	0.544	0.558	0.568	0.440	0.447	0.458	0.479	0.505	0.535	0.566	0.586	0.600
5.25	0.437	0.445	0.457	0.478	0.503	0.529	0.553	0.568	0.578	0.444	0.451	0.462	0.484	0.510	0.540	0.571	0.592	0.606
5.5	0.444	0.452	0.464	0.486	0.512	0.538	0.563	0.579	0.589	0.448	0.455	0.467	0.489	0.516	0.546	0.578	0.599	0.613
5.75	0.450	0.458	0.471	0.494	0.520	0.547	0.573	0.589	0.600	0.452	0.460	0.472	0.494	0.521	0.553	0.584	0.606	0.620
6	0.456	0.464	0.478	0.501	0.528	0.556	0.583	0.599	0.610	0.457	0.465	0.477	0.500	0.528	0.559	0.592	0.613	0.628
6.25	0.461	0.470	0.484	0.508	0.536	0.565	0.593	0.610	0.621	0.463	0.471	0.483	0.506	0.535	0.567	0.600	0.622	0.637
6.5	0.467	0.476	0.490	0.515	0.544	0.574	0.603	0.620	0.632	0.469	0.477	0.490	0.513	0.542	0.575	0.609	0.631	0.646
6.75	0.472	0.481	0.496	0.522	0.552	0.583	0.613	0.631	0.644	0.475	0.483	0.497	0.521	0.550	0.584	0.618	0.641	0.656
7	0.477	0.487	0.502	0.529	0.560	0.593	0.624	0.643	0.656	0.482	0.491	0.504	0.529	0.559	0.593	0.628	0.651	0.667
7.25	0.482	0.493	0.508	0.536	0.568	0.602	0.634	0.654	0.667	0.489	0.498	0.512	0.537	0.568	0.603	0.638	0.662	0.678
7.5	0.487	0.498	0.514	0.543	0.576	0.611	0.645	0.665	0.679	0.497	0.506	0.520	0.545	0.577	0.613	0.649	0.673	0.689
7.75	0.492	0.503	0.520	0.549	0.584	0.620	0.655	0.676	0.691	0.504	0.513	0.528	0.554	0.586	0.623	0.660	0.684	0.701
8	0.496	0.507	0.525	0.555	0.591	0.629	0.665	0.687	0.702	0.512	0.521	0.536	0.563	0.596	0.633	0.671	0.695	0.712
8.25	0.501	0.512	0.530	0.562	0.598	0.637	0.674	0.698	0.713	0.519	0.529	0.544	0.571	0.605	0.643	0.682	0.707	0.724
8.5	0.506	0.517	0.536	0.568	0.606	0.646	0.685	0.709	0.725	0.527	0.536	0.552	0.580	0.615	0.654	0.693	0.718	0.736
8.75	0.511	0.523	0.542	0.575	0.615	0.656	0.696	0.720	0.737	0.534	0.544	0.560	0.589	0.624	0.664	0.704	0.729	0.747
9	0.517	0.530	0.549	0.583	0.624	0.667	0.708	0.733	0.750	0.542	0.552	0.568	0.598	0.634	0.675	0.715	0.741	0.759
9.25	0.524	0.537	0.557	0.592	0.634	0.679	0.721	0.748	0.766	0.549	0.560	0.577	0.607	0.644	0.685	0.726	0.752	0.770
9.5	0.532	0.545	0.566	0.603	0.646	0.692	0.736	0.764	0.782	0.557	0.568	0.585	0.616	0.654	0.696	0.737	0.764	0.782
9.75	0.540	0.554	0.576	0.614	0.659	0.707	0.753	0.782	0.801	0.564	0.576	0.594	0.626	0.665	0.707	0.749	0.776	0.794
10	0.550	0.564	0.586	0.626	0.673	0.723	0.771	0.801	0.821	0.572	0.584	0.602	0.636	0.675	0.719	0.761	0.788	0.806
10.25	0.560	0.574	0.598	0.639	0.688	0.741	0.791	0.822	0.844	0.580	0.592	0.611	0.646	0.686	0.730	0.773	0.800	0.818
10.5	0.570	0.586	0.610	0.653	0.705	0.759	0.812	0.845	0.867	0.587	0.600	0.620	0.656	0.698	0.742	0.785	0.812	0.830
10.75	0.582	0.598	0.623	0.668	0.722	0.779	0.834	0.869	0.892	0.595	0.608	0.629	0.666	0.709	0.755	0.798	0.825	0.843
11	0.594	0.610	0.637	0.684	0.739	0.799	0.856	0.893	0.917	0.603	0.616	0.638	0.676	0.721	0.767	0.811	0.838	0.856
11.25	0.606	0.624	0.651	0.700	0.757	0.819	0.879	0.917	0.942	0.610	0.625	0.648	0.687	0.733	0.780	0.824	0.851	0.869
11.5	0.619	0.637	0.666	0.716	0.775	0.839	0.901	0.940	0.966	0.618	0.634	0.658	0.699	0.745	0.793	0.838	0.865	0.882
11.75	0.633	0.651	0.680	0.732	0.793	0.859	0.922	0.963	0.989	0.627	0.643	0.668	0.710	0.758	0.807	0.852	0.879	0.897
12	0.646	0.665	0.695	0.747	0.810	0.877	0.942	0.983	1.011	0.635	0.652	0.678	0.723	0.772	0.822	0.867	0.894	0.912
12.25	0.660	0.679	0.709	0.762	0.826	0.894	0.960	1.002	1.030	0.644	0.662	0.690	0.736	0.786	0.837	0.883	0.910	0.928
12.5	0.673	0.692	0.723	0.777	0.841	0.910	0.976	1.018	1.046	0.654	0.673	0.702	0.749	0.802	0.853	0.900	0.927	0.945
12.75	0.686	0.705	0.736	0.790	0.854	0.923	0.990	1.032	1.060	0.664	0.684	0.714	0.764	0.818	0.871	0.917	0.945	0.963
13	0.698	0.718	0.748	0.802	0.866	0.935	1.001	1.043	1.071	0.675	0.696	0.727	0.779	0.835	0.889	0.936	0.964	0.982
13.25	0.710	0.730	0.760	0.814	0.878	0.946	1.011	1.052	1.080	0.687	0.709	0.742	0.795	0.852	0.908	0.956	0.984	1.003
13.5	0.722	0.741	0.772	0.825	0.888	0.955	1.020	1.060	1.087	0.699	0.722	0.756	0.812	0.871	0.927	0.977	1.006	1.024
13.75	0.733	0.752	0.782	0.835	0.897	0.963	1.027	1.066	1.093	0.712	0.736	0.771	0.828	0.889	0.947	0.998	1.027	1.046
14	0.744	0.763	0.793	0.844	0.905	0.971	1.033	1.072	1.098	0.725	0.750	0.786	0.845	0.907	0.967	1.019	1.049	1.068
14.25	0.755	0.773	0.802	0.853	0.913	0.977	1.039	1.077	1.102	0.738	0.763	0.801	0.861	0.925	0.986	1.039	1.070	1.089
14.5	0.764	0.783	0.811	0.862	0.921	0.984	1.044	1.081	1.106	0.750	0.776	0.814	0.876	0.941	1.004	1.058	1.090	1.110
14.75	0.773	0.791	0.820	0.869	0.928	0.989	1.048	1.085	1.110	0.761	0.787	0.827	0.890	0.957	1.021	1.076	1.108	1.129
15	0.781	0.799	0.827	0.876	0.934	0.995	1.053	1.089	1.113	0.771	0.798	0.838	0.902	0.970	1.035	1.092	1.125	1.146
15.25	0.789	0.806	0.834	0.883	0.940	1.000	1.057	1.093	1.116	0.781	0.807	0.848	0.913	0.982	1.048	1.106	1.140	1.162
15.5	0.795	0.813	0.841	0.889	0.945	1.004	1.061	1.096	1.120	0.789	0.816	0.856	0.922	0.992	1.060	1.119	1.154	1.176
15.75	0.802	0.819	0.846	0.894	0.950	1.009	1.065	1.100	1.123	0.797	0.824	0.864	0.930	1.001	1.070	1.130	1.166	1.189
16	0.807	0.824	0.851	0.899	0.954	1.013	1.068	1.103	1.126	0.804	0.830	0.871	0.937	1.009	1.079	1.141	1.177	1.200
16.25	0.812	0.829	0.856	0.903	0.958	1.016	1.071	1.106	1.128	0.810	0.837	0.877	0.943	1.016	1.087	1.150	1.187	1.211
16.5	0.816	0.833	0.860	0.907	0.961	1.019	1.074	1.108	1.130	0.816	0.843	0.883	0.949	1.022	1.094	1.159	1.197	1.222
16.75	0.820	0.837	0.863	0.910	0.964	1.021	1.075	1.109	1.131	0.822	0.848	0.888	0.954	1.028	1.101	1.167	1.206	1.232
17	0.823	0.840	0.866	0.912	0.966	1.023	1.076	1.109	1.131	0.829	0.854	0.894	0.960	1.034	1.108	1.175	1.216	1.242
17.25	0.826	0.843	0.869	0.914	0.968	1.024	1.076	1.109	1.131	0.835	0.860	0.899	0.965	1.040	1.115	1.184	1.226	1.253
17.5	0.829	0.845	0.871	0.916	0.969	1.024	1.076	1.109	1.130	0.842	0.867	0.905	0.971	1.046	1.123	1.194	1.237	1.265
17.75	0.832	0.848	0.874	0.918	0.970	1.025	1.076	1.108	1.129	0.849	0.874	0.912	0.977	1.053	1.131	1.204	1.248	1.278
18	0.835	0.851	0.876	0.920	0.971	1.025	1.076	1.107	1.128	0.857	0.881	0.919	0.984	1.060	1.140	1.215	1.261	1.291

Table 3
Smoothed percentiles for aBMD of lumbar spine for female and male 5 to 18 years.

Lumbar spine aBMD (g/cm^2)																		
Age	Female centile									Male centile								
	3th	5th	10th	25th	50th	75th	90th	95th	97th	3th	5th	10th	25th	50th	75th	90th	95th	97th
5	0.466	0.486	0.515	0.565	0.621	0.677	0.727	0.756	0.776	0.499	0.511	0.531	0.566	0.609	0.657	0.705	0.735	0.756
5.25	0.472	0.491	0.521	0.572	0.627	0.684	0.734	0.764	0.784	0.502	0.514	0.534	0.570	0.614	0.662	0.710	0.741	0.762
5.5	0.478	0.497	0.527	0.578	0.634	0.690	0.741	0.772	0.792	0.505	0.518	0.538	0.574	0.618	0.667	0.715	0.747	0.768
5.75	0.483	0.503	0.533	0.584	0.641	0.697	0.749	0.780	0.800	0.508	0.521	0.542	0.578	0.623	0.672	0.721	0.752	0.773
6	0.489	0.509	0.539	0.590	0.647	0.704	0.756	0.788	0.808	0.512	0.525	0.546	0.583	0.628	0.678	0.727	0.758	0.779
6.25	0.495	0.515	0.545	0.596	0.654	0.712	0.764	0.796	0.816	0.515	0.528	0.549	0.587	0.633	0.683	0.732	0.764	0.786
6.5	0.501	0.521	0.551	0.603	0.660	0.719	0.772	0.804	0.824	0.519	0.532	0.554	0.592	0.638	0.689	0.738	0.770	0.792
6.75	0.507	0.527	0.558	0.609	0.667	0.726	0.780	0.812	0.833	0.522	0.536	0.558	0.596	0.643	0.694	0.745	0.777	0.798
7	0.513	0.533	0.564	0.616	0.674	0.734	0.788	0.820	0.841	0.526	0.540	0.562	0.601	0.649	0.700	0.751	0.783	0.805
7.25	0.520	0.540	0.571	0.623	0.682	0.741	0.796	0.829	0.850	0.530	0.544	0.566	0.606	0.654	0.707	0.758	0.790	0.812
7.5	0.527	0.546	0.577	0.630	0.689	0.750	0.805	0.838	0.860	0.534	0.548	0.571	0.612	0.660	0.713	0.764	0.797	0.819
7.75	0.533	0.554	0.585	0.638	0.697	0.758	0.814	0.848	0.870	0.538	0.553	0.576	0.617	0.666	0.719	0.771	0.804	0.826
8	0.541	0.561	0.592	0.645	0.706	0.767	0.824	0.858	0.880	0.542	0.557	0.581	0.622	0.672	0.726	0.778	0.812	0.834
8.25	0.549	0.569	0.600	0.654	0.715	0.777	0.834	0.868	0.891	0.547	0.562	0.586	0.628	0.678	0.733	0.786	0.819	0.842
8.5	0.557	0.577	0.609	0.663	0.724	0.787	0.845	0.880	0.903	0.551	0.566	0.591	0.634	0.685	0.740	0.793	0.827	0.850
8.75	0.565	0.586	0.618	0.672	0.734	0.798	0.856	0.892	0.915	0.556	0.571	0.596	0.640	0.692	0.747	0.801	0.835	0.858
9	0.575	0.595	0.627	0.682	0.745	0.809	0.869	0.905	0.928	0.561	0.576	0.602	0.646	0.699	0.755	0.809	0.844	0.867
9.25	0.584	0.605	0.638	0.693	0.757	0.822	0.882	0.919	0.943	0.566	0.582	0.607	0.652	0.706	0.763	0.818	0.852	0.876
9.5	0.595	0.616	0.649	0.705	0.769	0.835	0.896	0.933	0.958	0.571	0.588	0.614	0.659	0.714	0.772	0.827	0.862	0.885
9.75	0.606	0.627	0.660	0.717	0.782	0.849	0.911	0.949	0.974	0.577	0.594	0.620	0.667	0.722	0.780	0.836	0.872	0.895
10	0.617	0.639	0.672	0.730	0.796	0.864	0.927	0.965	0.991	0.583	0.600	0.627	0.674	0.730	0.790	0.846	0.882	0.906
10.25	0.629	0.651	0.685	0.743	0.810	0.879	0.943	0.983	1.009	0.589	0.607	0.634	0.683	0.739	0.800	0.857	0.893	0.917
10.5	0.642	0.664	0.698	0.757	0.825	0.896	0.961	1.001	1.027	0.596	0.614	0.642	0.691	0.749	0.810	0.868	0.905	0.929
10.75	0.655	0.677	0.712	0.772	0.841	0.912	0.979	1.019	1.046	0.603	0.622	0.650	0.700	0.759	0.821	0.880	0.917	0.941
11	0.669	0.691	0.726	0.787	0.857	0.929	0.997	1.039	1.066	0.611	0.630	0.659	0.710	0.770	0.833	0.893	0.930	0.955
11.25	0.682	0.705	0.741	0.802	0.873	0.947	1.016	1.058	1.086	0.619	0.638	0.668	0.721	0.782	0.846	0.907	0.944	0.969
11.5	0.696	0.719	0.755	0.818	0.890	0.965	1.035	1.078	1.107	0.628	0.647	0.678	0.732	0.794	0.859	0.921	0.959	0.984
11.75	0.710	0.734	0.770	0.833	0.906	0.983	1.054	1.098	1.127	0.637	0.657	0.689	0.743	0.807	0.873	0.936	0.974	1.000
12	0.724	0.748	0.785	0.849	0.923	1.001	1.073	1.118	1.147	0.647	0.667	0.699	0.755	0.820	0.888	0.951	0.990	1.016
12.25	0.738	0.762	0.799	0.864	0.939	1.018	1.092	1.138	1.168	0.656	0.678	0.711	0.768	0.834	0.903	0.968	1.007	1.034
12.5	0.752	0.776	0.814	0.879	0.956	1.035	1.110	1.157	1.187	0.667	0.688	0.722	0.781	0.849	0.919	0.985	1.025	1.052
12.75	0.765	0.789	0.828	0.894	0.971	1.052	1.129	1.176	1.207	0.678	0.700	0.735	0.795	0.864	0.935	1.002	1.043	1.070
13	0.778	0.803	0.841	0.908	0.987	1.069	1.146	1.194	1.226	0.689	0.711	0.747	0.808	0.879	0.952	1.020	1.062	1.089
13.25	0.791	0.816	0.855	0.922	1.001	1.085	1.163	1.211	1.244	0.700	0.723	0.760	0.823	0.895	0.969	1.039	1.081	1.109
13.5	0.803	0.828	0.867	0.936	1.016	1.100	1.179	1.228	1.261	0.711	0.735	0.773	0.837	0.911	0.987	1.057	1.100	1.129
13.75	0.815	0.840	0.880	0.949	1.029	1.114	1.195	1.245	1.278	0.722	0.747	0.786	0.852	0.927	1.005	1.076	1.120	1.149
14	0.827	0.852	0.892	0.961	1.042	1.128	1.210	1.260	1.294	0.734	0.759	0.799	0.866	0.944	1.023	1.095	1.140	1.169
14.25	0.837	0.863	0.903	0.973	1.055	1.142	1.224	1.275	1.309	0.745	0.771	0.812	0.881	0.960	1.040	1.114	1.159	1.189
14.5	0.848	0.873	0.914	0.984	1.067	1.154	1.237	1.289	1.324	0.756	0.783	0.825	0.896	0.976	1.058	1.133	1.179	1.209
14.75	0.858	0.884	0.924	0.995	1.078	1.166	1.250	1.302	1.337	0.767	0.795	0.837	0.910	0.992	1.075	1.152	1.198	1.228
15	0.868	0.893	0.934	1.005	1.089	1.178	1.262	1.315	1.350	0.778	0.806	0.850	0.924	1.008	1.093	1.170	1.217	1.248
15.25	0.877	0.903	0.943	1.015	1.099	1.189	1.274	1.327	1.363	0.788	0.817	0.862	0.938	1.023	1.109	1.188	1.236	1.267
15.5	0.886	0.911	0.952	1.024	1.109	1.199	1.285	1.339	1.374	0.798	0.828	0.874	0.951	1.038	1.126	1.206	1.254	1.285
15.75	0.894	0.920	0.961	1.033	1.118	1.209	1.295	1.349	1.385	0.808	0.838	0.885	0.964	1.053	1.142	1.223	1.272	1.303
16	0.902	0.928	0.969	1.041	1.127	1.218	1.305	1.360	1.396	0.818	0.849	0.897	0.977	1.067	1.158	1.240	1.289	1.321
16.25	0.910	0.936	0.977	1.049	1.135	1.227	1.314	1.369	1.406	0.827	0.859	0.908	0.990	1.081	1.173	1.257	1.306	1.339
16.5	0.917	0.943	0.985	1.057	1.143	1.235	1.323	1.378	1.416	0.836	0.868	0.918	1.002	1.095	1.189	1.273	1.323	1.356
16.75	0.924	0.950	0.992	1.064	1.151	1.243	1.332	1.387	1.425	0.844	0.878	0.929	1.014	1.109	1.204	1.289	1.340	1.373
17	0.931	0.957	0.999	1.071	1.158	1.250	1.340	1.396	1.433	0.853	0.887	0.939	1.026	1.123	1.219	1.305	1.356	1.389
17.25	0.938	0.964	1.005	1.078	1.165	1.258	1.347	1.404	1.441	0.861	0.896	0.949	1.038	1.136	1.233	1.320	1.372	1.406
17.5	0.944	0.970	1.012	1.085	1.171	1.265	1.355	1.411	1.449	0.869	0.905	0.960	1.050	1.149	1.248	1.336	1.388	1.422
17.75	0.951	0.977	1.018	1.091	1.178	1.272	1.362	1.419	1.457	0.877	0.914	0.969	1.062	1.163	1.263	1.352	1.404	1.439
18	0.957	0.983	1.024	1.097	1.185	1.278	1.369	1.426	1.465	0.885	0.922	0.979	1.073	1.176	1.277	1.367	1.420	1.455

Table 4
Smoothed percentiles for bone mineral apparent density (BMAD) for lumbar spine for female and male 5–18 years.

Lumbar spine BMAD (g/cm^3)																		
Age	Female centiles									Male centiles								
	3th	5th	10th	25th	50th	75th	90th	95th	97th	3th	5th	10th	25th	50th	75th	90th	95th	97th
5	0.217	0.224	0.235	0.253	0.274	0.296	0.316	0.328	0.335	0.220	0.224	0.231	0.245	0.263	0.284	0.307	0.323	0.335
5.25	0.217	0.224	0.235	0.254	0.275	0.296	0.316	0.328	0.335	0.219	0.223	0.231	0.244	0.262	0.283	0.306	0.322	0.333
5.5	0.217	0.224	0.235	0.254	0.275	0.296	0.316	0.327	0.335	0.218	0.223	0.230	0.244	0.261	0.282	0.305	0.321	0.332
5.75	0.218	0.225	0.236	0.254	0.275	0.296	0.316	0.327	0.335	0.218	0.222	0.230	0.243	0.261	0.282	0.304	0.319	0.331
6	0.218	0.225	0.236	0.254	0.275	0.296	0.315	0.327	0.335	0.217	0.222	0.229	0.243	0.260	0.281	0.303	0.318	0.329
6.25	0.218	0.225	0.236	0.254	0.275	0.296	0.315	0.327	0.335	0.217	0.221	0.229	0.243	0.260	0.281	0.302	0.317	0.328
6.5	0.218	0.225	0.236	0.254	0.275	0.296	0.315	0.327	0.335	0.216	0.221	0.229	0.242	0.260	0.280	0.302	0.317	0.327
6.75	0.218	0.225	0.236	0.254	0.275	0.296	0.315	0.327	0.334	0.216	0.221	0.228	0.242	0.260	0.280	0.301	0.316	0.326
7	0.219	0.225	0.236	0.254	0.275	0.295	0.315	0.326	0.334	0.216	0.221	0.228	0.242	0.260	0.280	0.301	0.315	0.325
7.25	0.219	0.226	0.236	0.254	0.274	0.295	0.314	0.326	0.334	0.216	0.220	0.228	0.242	0.260	0.280	0.301	0.315	0.325
7.5	0.219	0.226	0.236	0.254	0.274	0.295	0.314	0.326	0.333	0.216	0.220	0.228	0.242	0.260	0.280	0.300	0.314	0.324
7.75	0.219	0.226	0.236	0.254	0.274	0.295	0.314	0.325	0.333	0.216	0.220	0.228	0.242	0.260	0.280	0.300	0.314	0.323
8	0.219	0.226	0.236	0.254	0.274	0.295	0.314	0.325	0.333	0.215	0.220	0.228	0.242	0.260	0.280	0.300	0.314	0.323
8.25	0.219	0.226	0.237	0.254	0.274	0.295	0.314	0.325	0.333	0.215	0.220	0.228	0.242	0.260	0.280	0.300	0.313	0.322
8.5	0.220	0.227	0.237	0.255	0.275	0.295	0.314	0.325	0.333	0.215	0.220	0.228	0.242	0.260	0.280	0.300	0.313	0.322
8.75	0.220	0.227	0.238	0.255	0.275	0.296	0.314	0.326	0.333	0.215	0.220	0.228	0.242	0.260	0.280	0.299	0.312	0.321
9	0.221	0.228	0.238	0.256	0.276	0.296	0.315	0.326	0.334	0.215	0.220	0.228	0.242	0.260	0.279	0.299	0.312	0.321
9.25	0.222	0.229	0.239	0.257	0.277	0.297	0.316	0.327	0.335	0.215	0.220	0.228	0.242	0.260	0.279	0.299	0.312	0.320
9.5	0.223	0.230	0.240	0.258	0.278	0.299	0.317	0.329	0.336	0.215	0.220	0.228	0.242	0.260	0.279	0.299	0.311	0.320
9.75	0.225	0.231	0.242	0.260	0.280	0.300	0.319	0.330	0.338	0.215	0.220	0.228	0.242	0.260	0.280	0.299	0.311	0.320
10	0.226	0.233	0.244	0.261	0.281	0.302	0.321	0.332	0.340	0.215	0.220	0.228	0.243	0.260	0.280	0.299	0.311	0.319
10.25	0.228	0.235	0.246	0.263	0.284	0.304	0.323	0.335	0.342	0.215	0.220	0.228	0.243	0.260	0.280	0.299	0.311	0.319
10.5	0.230	0.237	0.248	0.266	0.286	0.307	0.326	0.337	0.345	0.215	0.220	0.228	0.243	0.261	0.280	0.299	0.311	0.319
10.75	0.233	0.240	0.250	0.268	0.289	0.309	0.329	0.340	0.348	0.215	0.220	0.229	0.243	0.261	0.280	0.299	0.311	0.319
11	0.235	0.242	0.253	0.271	0.292	0.312	0.332	0.343	0.351	0.215	0.221	0.229	0.244	0.262	0.281	0.300	0.311	0.319
11.25	0.238	0.245	0.256	0.274	0.295	0.316	0.335	0.347	0.354	0.216	0.221	0.230	0.245	0.263	0.282	0.300	0.312	0.320
11.5	0.241	0.248	0.258	0.277	0.298	0.319	0.338	0.350	0.358	0.216	0.222	0.230	0.245	0.263	0.283	0.301	0.313	0.320
11.75	0.243	0.250	0.261	0.280	0.301	0.322	0.342	0.354	0.361	0.217	0.222	0.231	0.246	0.264	0.284	0.302	0.313	0.321
12	0.246	0.253	0.264	0.283	0.304	0.326	0.345	0.357	0.365	0.218	0.223	0.232	0.248	0.266	0.285	0.303	0.315	0.322
12.25	0.249	0.256	0.267	0.286	0.307	0.329	0.349	0.361	0.369	0.219	0.224	0.233	0.249	0.267	0.286	0.305	0.316	0.323
12.5	0.252	0.259	0.270	0.289	0.310	0.332	0.352	0.364	0.372	0.220	0.226	0.235	0.251	0.269	0.288	0.306	0.318	0.325
12.75	0.254	0.261	0.273	0.292	0.313	0.335	0.355	0.367	0.375	0.221	0.227	0.236	0.252	0.271	0.290	0.308	0.320	0.327
13	0.257	0.264	0.275	0.294	0.316	0.338	0.358	0.370	0.378	0.223	0.229	0.238	0.254	0.273	0.292	0.310	0.322	0.329
13.25	0.259	0.266	0.277	0.297	0.318	0.341	0.361	0.373	0.381	0.224	0.230	0.240	0.256	0.275	0.295	0.313	0.324	0.331
13.5	0.261	0.268	0.280	0.299	0.321	0.343	0.363	0.376	0.384	0.226	0.232	0.242	0.258	0.277	0.297	0.315	0.326	0.334
13.75	0.263	0.270	0.282	0.301	0.323	0.345	0.366	0.378	0.386	0.228	0.234	0.244	0.261	0.280	0.300	0.318	0.329	0.336
14	0.265	0.272	0.284	0.303	0.325	0.347	0.368	0.380	0.388	0.230	0.236	0.246	0.263	0.282	0.302	0.321	0.332	0.339
14.25	0.267	0.274	0.286	0.305	0.327	0.349	0.370	0.382	0.391	0.231	0.238	0.248	0.265	0.285	0.305	0.323	0.334	0.342
14.5	0.268	0.276	0.287	0.307	0.329	0.351	0.372	0.384	0.392	0.233	0.240	0.250	0.268	0.288	0.308	0.326	0.337	0.344
14.75	0.270	0.277	0.289	0.308	0.330	0.353	0.373	0.386	0.394	0.235	0.242	0.252	0.270	0.290	0.310	0.328	0.339	0.347
15	0.271	0.279	0.290	0.310	0.332	0.354	0.375	0.388	0.396	0.237	0.244	0.254	0.272	0.292	0.313	0.331	0.342	0.349
15.25	0.273	0.280	0.292	0.311	0.333	0.356	0.376	0.389	0.397	0.238	0.245	0.256	0.274	0.295	0.315	0.333	0.344	0.351
15.5	0.274	0.281	0.293	0.313	0.335	0.357	0.378	0.390	0.399	0.240	0.247	0.258	0.276	0.297	0.317	0.335	0.346	0.354
15.75	0.275	0.283	0.294	0.314	0.336	0.359	0.379	0.392	0.400	0.241	0.248	0.260	0.278	0.299	0.319	0.338	0.348	0.356
16	0.276	0.284	0.295	0.315	0.337	0.360	0.380	0.393	0.401	0.242	0.250	0.261	0.280	0.301	0.321	0.340	0.350	0.358
16.25	0.278	0.285	0.297	0.316	0.338	0.361	0.381	0.394	0.402	0.244	0.251	0.263	0.282	0.303	0.323	0.342	0.352	0.359
16.5	0.279	0.286	0.298	0.317	0.339	0.362	0.383	0.395	0.403	0.245	0.253	0.264	0.283	0.304	0.325	0.343	0.354	0.361
16.75	0.280	0.287	0.299	0.318	0.340	0.363	0.383	0.396	0.404	0.246	0.254	0.266	0.285	0.306	0.327	0.345	0.356	0.363
17	0.281	0.288	0.299	0.319	0.341	0.364	0.384	0.397	0.405	0.247	0.255	0.267	0.287	0.308	0.329	0.347	0.358	0.365
17.25	0.281	0.289	0.300	0.320	0.342	0.364	0.385	0.397	0.405	0.248	0.256	0.269	0.289	0.310	0.331	0.349	0.360	0.367
17.5	0.282	0.290	0.301	0.321	0.343	0.365	0.385	0.398	0.406	0.250	0.258	0.270	0.290	0.312	0.333	0.351	0.362	0.369
17.75	0.283	0.290	0.302	0.321	0.343	0.366	0.386	0.398	0.407	0.251	0.259	0.272	0.292	0.314	0.335	0.353	0.364	0.370
18	0.284	0.291	0.302	0.322	0.344	0.366	0.387	0.399	0.407	0.252	0.261	0.273	0.294	0.316	0.337	0.355	0.366	0.372

Table 5
Smoothed percentiles for aBMD of TBLH for female and male by height.

TBLH aBMD (g/cm^2) by height (cm)

Height	Female centile							Height	Male centile						
	5th	15th	25th	50th	75th	85th	95th		5th	15th	25th	50th	75th	85th	95th
95	0.410	0.426	0.435	0.452	0.470	0.479	0.496	95	0.406	0.421	0.430	0.447	0.466	0.476	0.494
100	0.426	0.443	0.452	0.471	0.490	0.501	0.518	100	0.424	0.440	0.450	0.469	0.489	0.500	0.519
105	0.442	0.460	0.471	0.491	0.512	0.523	0.542	105	0.442	0.459	0.470	0.491	0.513	0.525	0.546
110	0.460	0.479	0.490	0.512	0.535	0.547	0.568	110	0.460	0.479	0.491	0.513	0.537	0.550	0.573
115	0.479	0.499	0.512	0.536	0.560	0.574	0.597	115	0.480	0.500	0.513	0.537	0.563	0.577	0.602
120	0.500	0.523	0.536	0.562	0.589	0.604	0.629	120	0.500	0.523	0.536	0.563	0.591	0.606	0.634
125	0.524	0.549	0.564	0.592	0.621	0.637	0.665	125	0.522	0.546	0.561	0.590	0.621	0.638	0.668
130	0.552	0.579	0.595	0.627	0.659	0.676	0.707	130	0.546	0.573	0.589	0.620	0.654	0.672	0.705
135	0.585	0.615	0.633	0.667	0.703	0.723	0.756	135	0.573	0.602	0.620	0.654	0.691	0.711	0.747
140	0.626	0.659	0.679	0.717	0.757	0.779	0.817	140	0.604	0.636	0.655	0.693	0.733	0.756	0.795
145	0.676	0.713	0.735	0.779	0.824	0.848	0.892	145	0.640	0.675	0.697	0.739	0.783	0.808	0.852
150	0.737	0.779	0.804	0.853	0.905	0.933	0.982	150	0.681	0.720	0.744	0.791	0.840	0.868	0.916
155	0.798	0.844	0.873	0.928	0.986	1.019	1.075	155	0.724	0.767	0.794	0.846	0.901	0.932	0.986
160	0.835	0.885	0.916	0.977	1.041	1.076	1.138	160	0.767	0.814	0.844	0.902	0.963	0.997	1.057
165	0.844	0.897	0.930	0.993	1.061	1.099	1.164	165	0.807	0.859	0.892	0.956	1.023	1.060	1.126
								170	0.843	0.901	0.936	1.006	1.079	1.120	1.192
								175	0.876	0.938	0.977	1.052	1.132	1.177	1.255
								180	0.906	0.973	1.015	1.097	1.183	1.232	1.317
								185	0.934	1.007	1.052	1.140	1.233	1.286	1.378

Table 6
Mean values for aBMD of TBLH, lumbar spine and BMAD by gender and Tanner sexual maturation stage.

Sexual maturation Tanner stage	Female						Male					
	TBLH aBMD		L1-L4 aBMD		BMAD		TBLH aBMD		L1-L4 aBMD		BMAD	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	0.570	0.069	0.682	0.090	0.274	0.031	0.609	0.086	0.683	0.087	0.263	0.029
2	0.693	0.077	0.781	0.095	0.278	0.026	0.745	0.079	0.779	0.091	0.262	0.025
3	0.851	0.108	0.984	0.138	0.310	0.035	0.893	0.123	0.962	0.156	0.282	0.035
4	0.945	0.086	1.124	0.124	0.336	0.032	0.998	0.099	1.083	0.120	0.302	0.028
5	0.963	0.080	1.164	0.121	0.341	0.033	1.064	0.113	1.147	0.138	0.310	0.033

disease, may now be compared to assess bone health.

The graphical representations of these reference values show a consistent behaviour with what has been previously reported in other populations, though with different values and hence reinforcing the need to have country/regional specific reference values.

The sigmoid-like aspect of these curves and sex-related differences are well known phenomena given the influence of sex-related hormones on bone metabolism, resulting in adult women reaching earlier and lower peak bone mass and smaller skeletal size than adult men. Ultimately these sex-differences have been associated with women bearing a higher risk of osteopenia, osteoporosis and related adverse bone health outcomes later in life [33–35].

Comparing our graphic data to other populations by visual inspection only, and considering studies using the same DXA equipment (GE Lunar), Mexican children seem to start with significantly lower values of aBMD for LS and TB when compared to their Dutch [36], Indian [37] and Korean [38] peers, but such differences decrease (vs Dutch and South Koreans) or even invert (vs Indians) as they reach 18 years of age. As expected, when adjustment for bone-volume is considered (i.e. BMAD) the Mexicans have significantly lower values of BMAD at age 18 than their Dutch and South Korean peers. Relevant to these findings is the fact that Dutch and South Koreans adults are significantly taller than their Mexican peers (i.e. average height is 182.0 cm and 168.7 cm among Dutch men and women respectively; Koreans 174.9 cm and 162.6 cm respectively; and Mexicans 169.0 cm and 156.8 cm, respectively) [39]. These findings highlight the relevance of regionalized DXA measurements reference values to increase the precision of bone health assessment in populations with different patterns of skeletal growth, as illustrated in Fig. 4b.

Two previous studies have reported reference values for bone health parameters in subjects with Mexican ancestry. First, Kelly et al. published reference values of aBMD for TB and TBLH from the subgroup of Mexican Americans included in the US NHANES study [40]. Our observations replicate their data in terms of the sigmoid-like curve parameters (i.e. observed sex-differences and ages where inflection points are evident), but although the values seem similar, it is important to note that their measurements were done with different DXA instrumentation (Hologic) and they should not be considered equivalent. In another study conducted in Mexico, Tamayo et al. published reference values for T and Z scores of aBMD for the non-dominant proximal femur, lumbar spine, TBLH, head, arm, trunk, hip, ribs, and pelvis for children, adolescents and adults, also measured with Lunar DXA [18]. Several aspects of this study indicate the need for more robust reference values for Mexican children and adolescents. Specifically, their sampling and recruitment were not done at population-level, healthy-status was not clearly defined for the children and adolescents included, and the statistical methods were not appropriate to describe correctly the distribution of the data. Notably, they present *Z*-scores with fixed standard deviation values across all the studied subjects from 7 to 80 years; their reported values for Z = 0 (i.e. the median) TBLH aBMD from 7 to 15 years are the highest ever reported in the literature, and the graphic representation of their data contrasts with previously discussed reference values by not showing a sigmoid shape, undermining the known effects of puberty and growth (Fig. 4).

Of further relevance, the assessment of bone health of children and adolescents is a rare event in paediatric care in Mexico, despite prevalent clinical needs (e.g. cancer, chronic renal disease, metabolic, nutritional, immunoinflammatory diseases, etc.). The major reasons for this are that DXA devices are scarce in Mexico, and there is a lack of awareness of the benefits of this assessment. Moreover, even if a clinician wanted to

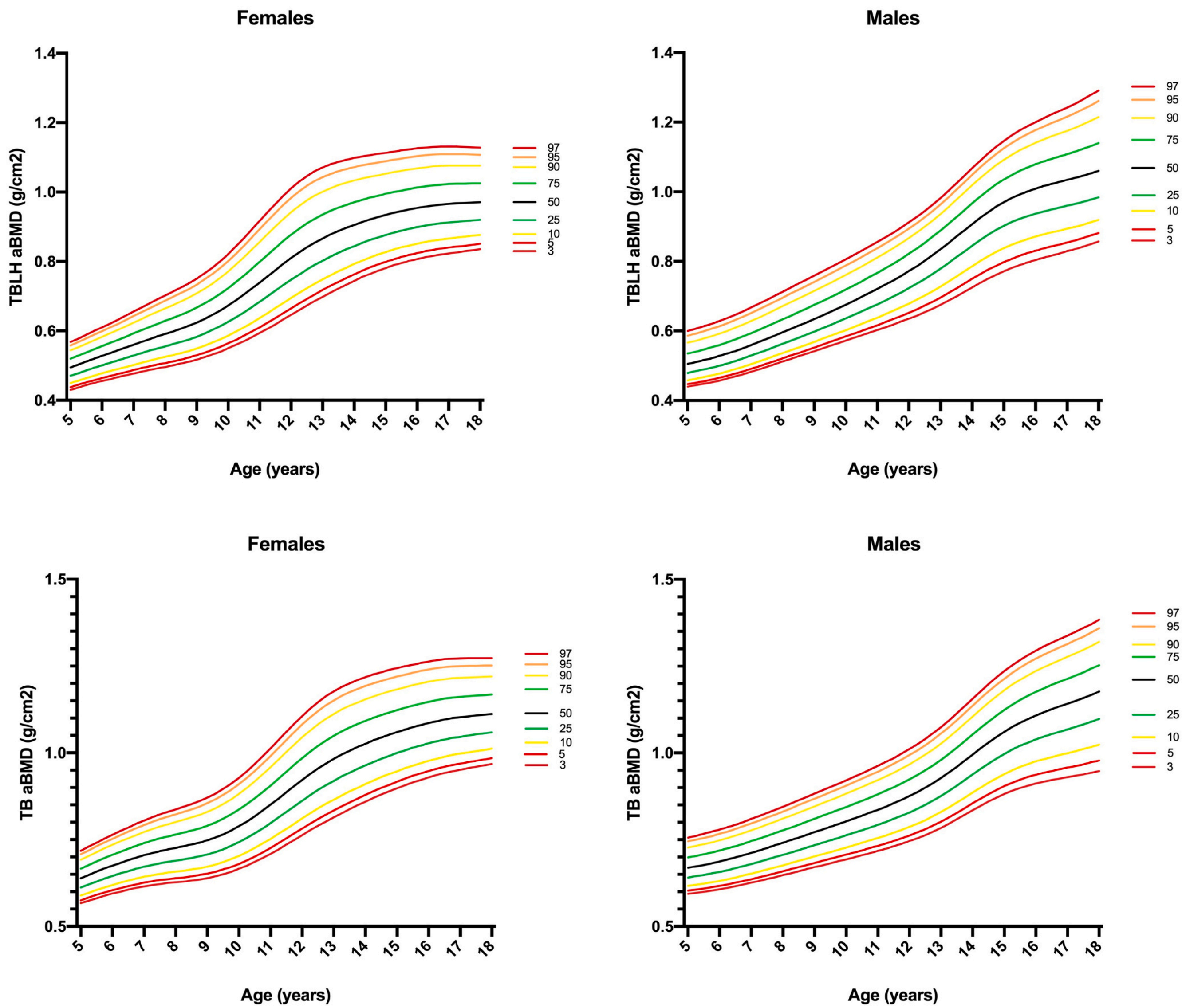

Fig. 1. Reference percentiles curves for aBMD of TBLH and TB for female and male 5 to 18 years.

evaluate bone health in a paediatric patient, there was also the limitation of that no device has integrated reference values for the Mexican population in their interpretation software, thus results are expressed in terms of comparisons typically done with reference to NHANES-White values [41], which may not be appropriate.

The strengths of this study are its large sample size, the generation of reference values addressing values for age, sex, pubertal status, height and skeletal size; and the fact that they were derived only from healthy subjects (including clinical and metabolic assessment).

However, there are also several limitations of the study. First, according to data from the ENSANUT survey conducted in 2018 the Mexican population is geographically divided into four areas: North, Centre, Mexico City and the Metropolitan Area, and South, with differences discernible only when North and South are compared [32]. Here we only present data from subjects living in Mexico City and its Metropolitan Area, and those from rural areas and indigenous populations as well as from other territories of Mexico may not share the same characteristics of our sample. Therefore, caution should be made when comparing subjects from such areas. Nevertheless, the magnitude of the ancestry effect in the bone health status, as documented by Wetzsteon et al., Zengin et al., and Leslie et al. among others [42–44] and the fact that Mexico City and the Metropolitan Area includes approximately 20% of the country's population, supports the use of these reference values in all Mexican children and adolescents across the country, while further studies in these subpopulations may enrich or validate these reference values.

Another limitation is the fact that our reference values can only be used to compare measurements performed with similar instrumentation (i.e. Lunar DXA), given the well-recognized variability between manufacturers' devices and models and their associated software [45]. As previously pointed by Crabtree et al., it is desirable and possible to perform in-vivo cross-calibration and validation between different DXA devices in the same population to facilitate bone health assessment independently from the available device [13]. Also, Zemel's group has recently published that even when using similar technologies significant intermachine differences in DXA measurements may play a role in modifying the likelihood of being diagnosed with low bone density according to the specific device or centre where DXA is performed. Such differences appear to be of the greatest magnitude in the TBLH measurements, and least for total hip aBMD [46]. Because our study was monocentric, we were not able to capture the magnitude of such differences, and caution should be considered when applying our reference values in the clinical setting.

We believe that for future studies, a multicentric approach

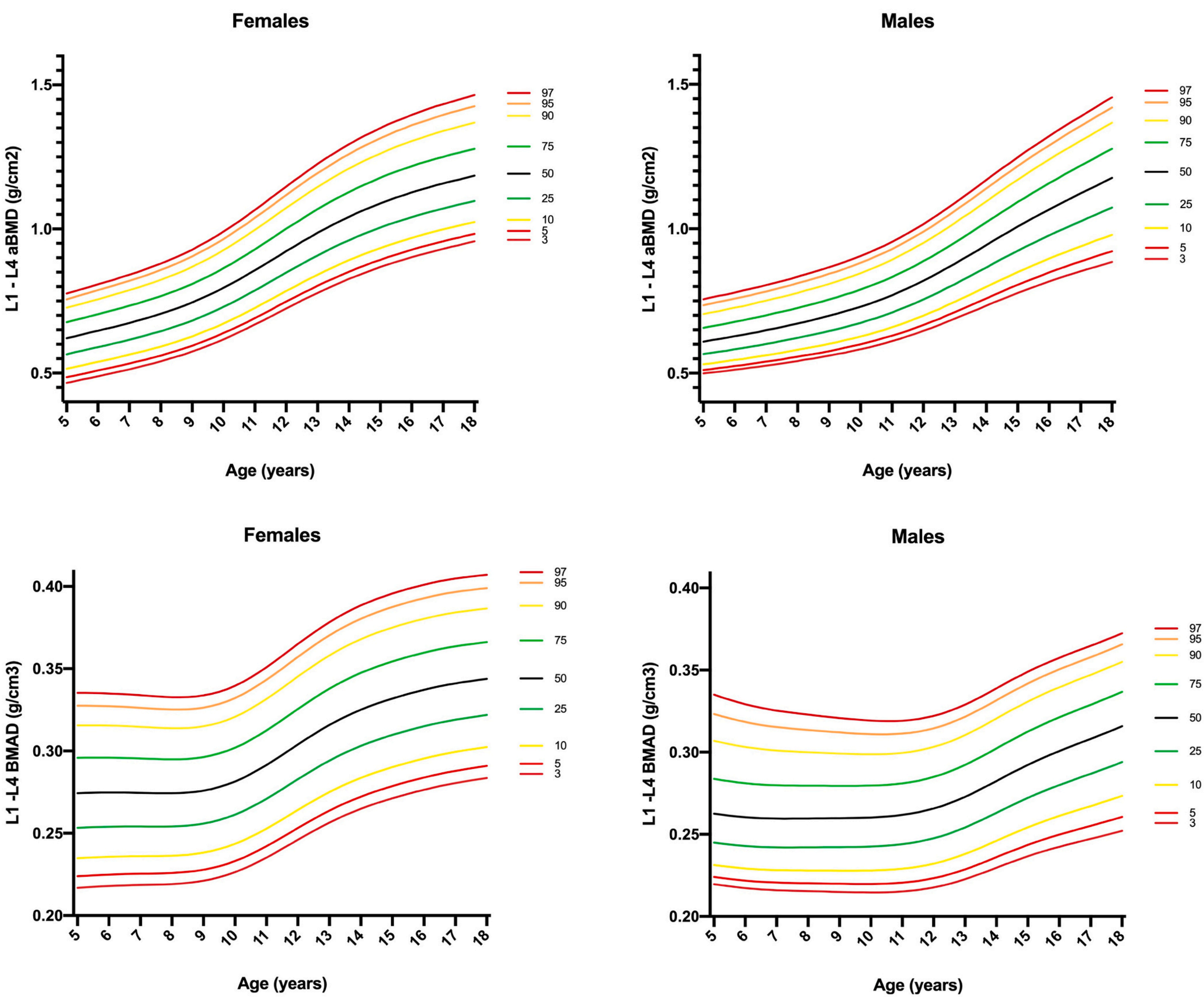

Fig. 2. Reference percentiles curves for aBMD of lumbar spine (upper) and BMAD (lower) for Male and Female 5 to 18 years.

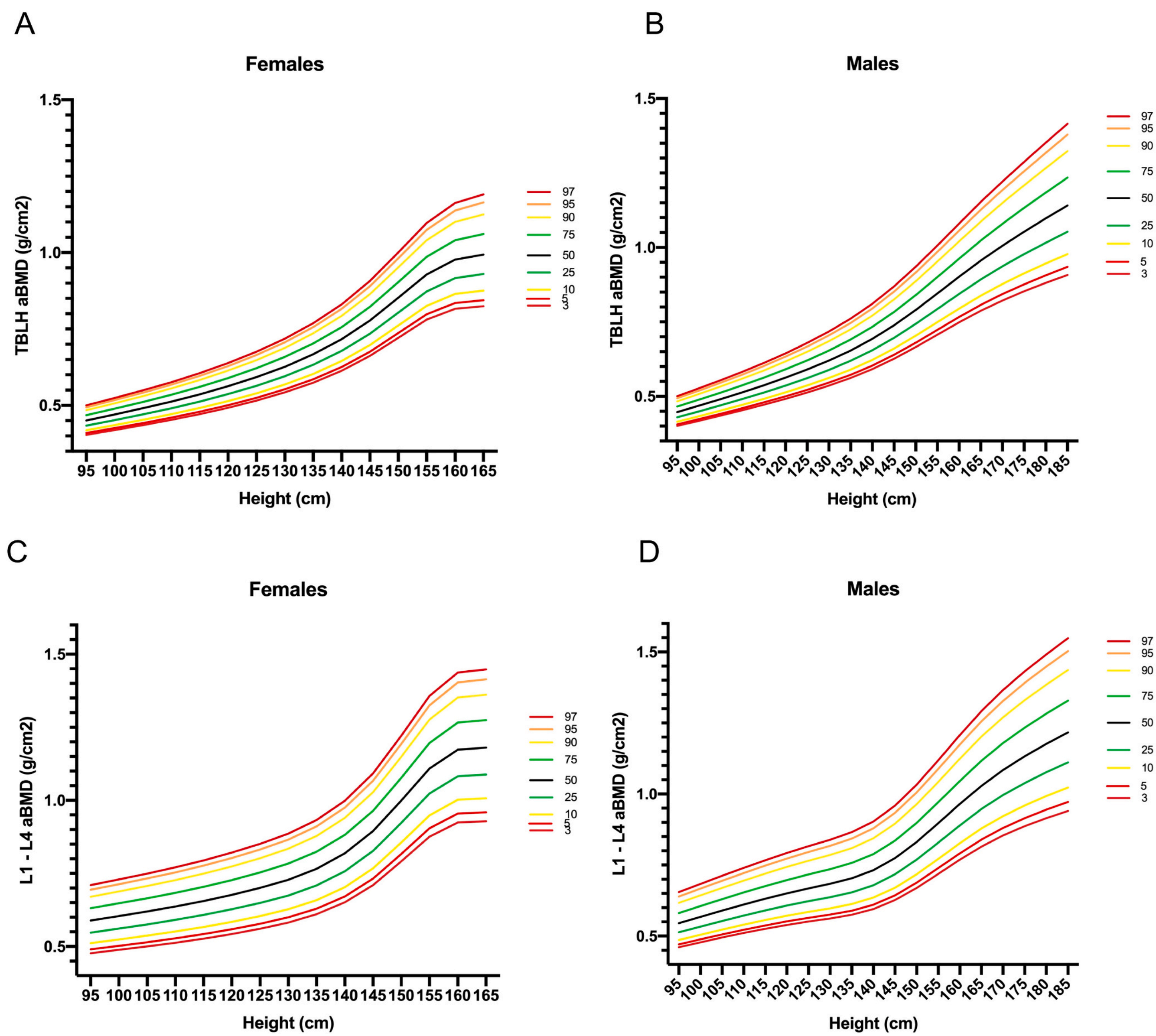

Fig. 3. Reference percentiles curves for aBMD of total body less head (A female, B male) and lumbar spine (C female, D male) for height and sex.

a

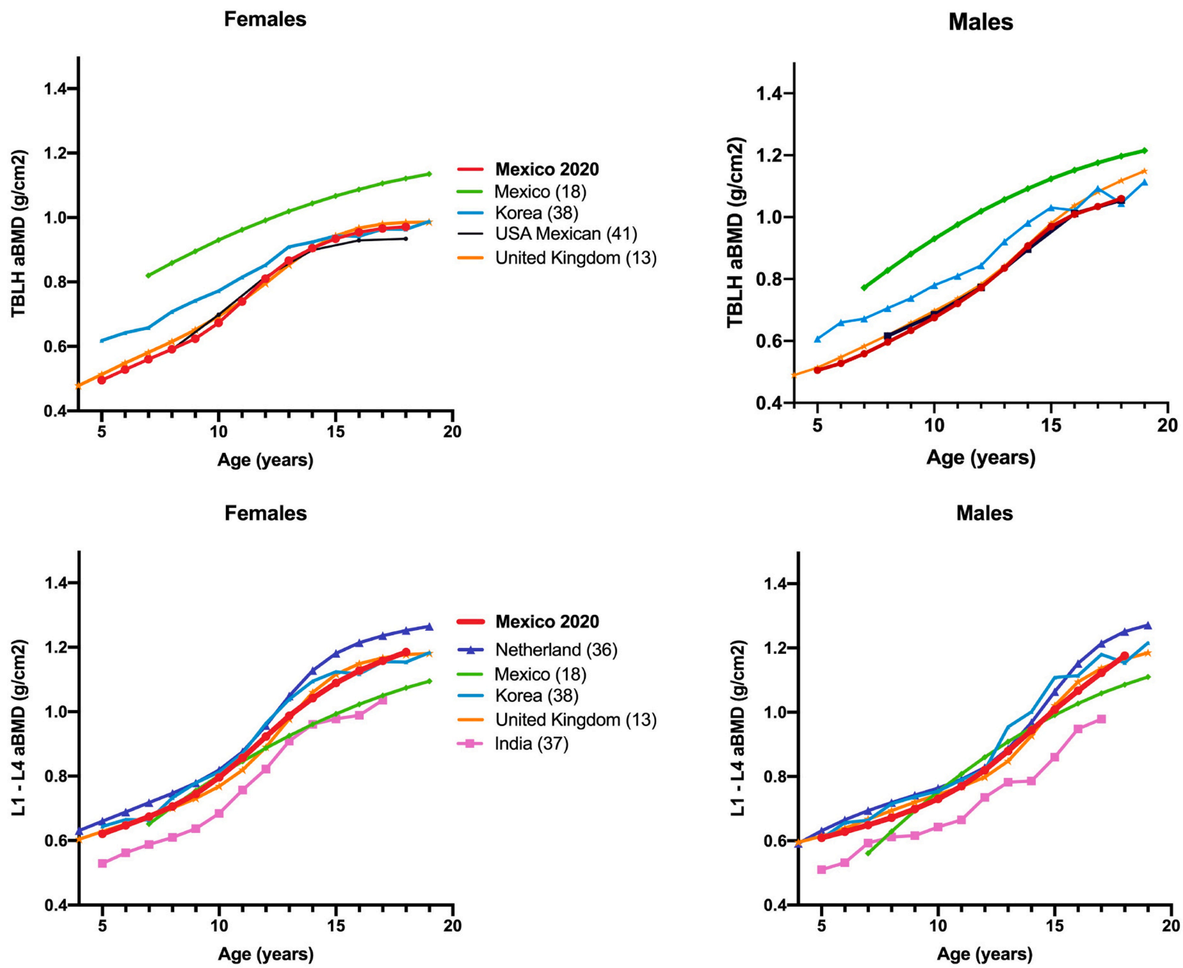

Fig. 4. a. Comparison between the behaviour of reference values published in other studies. Upper: Total body less head, Lower: lumbar spine.
Data in the plot: Mexico 2020: p50 values; Mexico (18): Z score 0 values; Korea (38) Mean values; USA Mexican (41): M 50th values; United Kingdom (13): M values; Netherland (36): Mean values; India (37): Means values.
b. Comparison between the behaviour of reference values published in other studies. Upper: Total body, Lower: BMAD lumbar spine.
Data in the plot: Mexico 2020: p50 values; Korea (38) Mean values; USA Mexican (41): M 50th values; United Kingdom (13): white, M values; Netherland (36): Mean values; India (37): Means values.

incorporating different technologies, and ideally with in-vivo and in-vitro cross-validations may offer a much more robust way to incorporate such variations within the construction of reference values of DXA.

Also, although our approach is conventional for deriving reference data, the cross-sectional character of this study does not allow us to establish bone growth patterns, hence further studies are needed to describe bone growth trajectories and outcomes such as osteoporosis and fractures.

Finally, according to relevant previous observations published by Zemel et al. [47], we consider that caution is required when using the reference values for height and sex. A common clinical practice when assessing subjects of short or tall stature is to use the corresponding *Z*-scores of BMD for height; this approach should not be applied as the standard or only method, because in the most common clinical context (i.e. assessing bone health in a short-stature subjects) it results in the comparison of older-age short-stature subjects with those of younger subjects with similar stature who most frequently differ in terms of sexual maturation, hence the comparison may be biased and misleading. For the moment, we suggest that short or tall subjects may be better assessed if all Z-scores (i.e. for age, for height and for Tanner-stage) are incorporated in the clinical exercise on a case-by-case basis.

5. Conclusions

The existence of population-specific reference values allows for comparisons between different populations. Populations from different geographical and ethnic background vary in both their bone phenotype, and the associated health implications. Current clinical practice should take into consideration such differences and adapt accordingly. We have contributed to this aim, by generating new reference values for aBMD of TBLH, TB and LS and BMAD for healthy children and adolescents from Mexico City and Metropolitan Area.

CRediT authorship contribution statement

All authors have read and agree to the published version of the manuscript. Conceptualization, D.L.-G.; methodology, D.L.-G., A.P.-G., J.C.W. and P.C.; software, M.C.-B., D.L.-G.; validation, M.C.-B., J.C.-W. and D.L.-G.; formal analysis, M.C.-B., J.C.W., D.L.-G,; investigation, D.L.-G., A.P.-G., J.C.W.; resources, D.L.-G. and P.C.; data curation, D.L.-G.; writing—original draft preparation, D.L.-G., A.P.-G., J.C.W.; writing—review and editing, D.L.-G., A.P.-G., J.C.W, M.F., and P.C.; supervision, D.L.-G., J.C.W., M.F., and P.C.; project administration, D.L.-

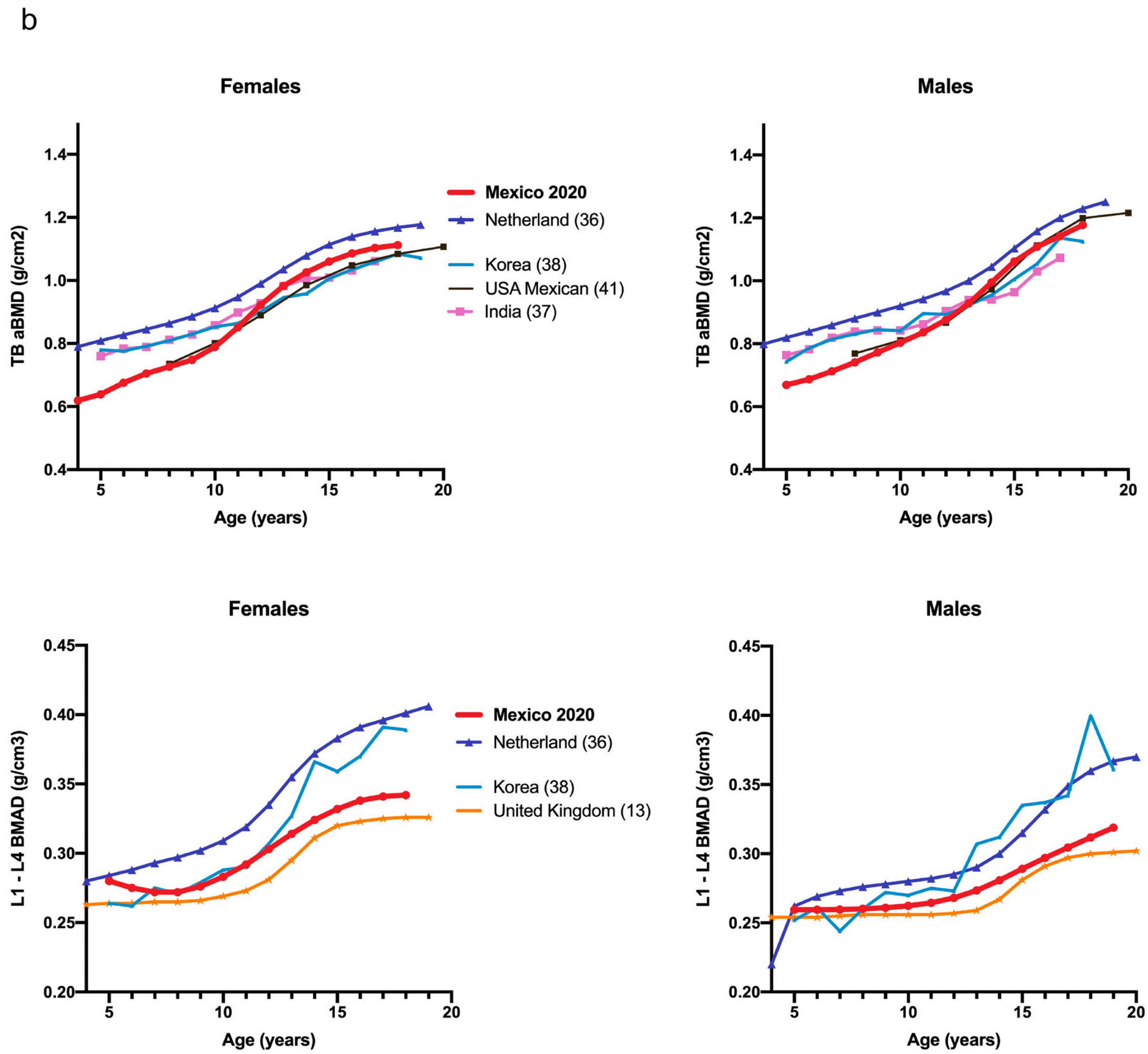

Fig. 4. (*continued*).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2020.115734.

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