Normative Bone Mineral Density Z-Scores for Canadians Aged 16 to 24 Years: The Canadian Multicenter Osteoporosis Study

Wei Zhou¹, Lisa Langsetmo¹, Claudie Berger¹, Jonathan D. Adachi², Alexandra Papaioannou², George Ioannidis², Colin Webber², Stephanie A. Atkinson², Wojciech P. Olszynski³, Jacques P. Brown⁴, David A. Hanley⁵, Robert Josse⁶, Nancy Kreiger^{7,11}, Jerilynn Prior⁸, Stephanie Kaiser⁹, Susan Kirkland⁹, David Goltzman^{7,10}, Kenneth Shawn Davison^{*,4}, and CaMos Research Group^a

¹CaMos Methods Centre, McGill University, Montreal, Quebec, Canada

²Departments of Clinical Epidemiology and Biostatistics and Medicine, McMaster University, Hamilton, Ontario, Canada

³Department of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

⁴Department of Rheumatology and Immunology, Laval University, Quebec City, Quebec, Canada

⁵Departments of Medicine and Community Health Sciences, University of Calgary, Calgary, Alberta, Canada

⁶Departments of Medicine, University of Toronto, Toronto, Ontario, Canada

⁷CaMos National Coordinating Centre, McGill University, Montreal, Quebec, Canada

⁸Department of Medicine and Endocrinology, University of British Columbia, Vancouver, British Columbia, Canada

⁹Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada

¹⁰Department of Medicine, McGill University, Montreal, Quebec, Canada

¹¹Department of Public Health Sciences, University of Toronto, Toronto, Ontario, Canada

Abstract

The objectives of the study were to develop bone mineral density (BMD) reference norms and BMD Z-scores at various skeletal sites, to determine whether prior fracture and/or asthma were related to BMD, and to assess possible geographic variation of BMD among Canadian youth aged 16–24 yr. Z-Scores were defined as the number of standard deviations from the mean BMD of a healthy population of the same age, race, and sex. Z-Scores were calculated using the reference sample defined as Canadian Caucasian participants without asthma or prior fracture. Reference standards were created for lumbar spine (L1–L4), femoral neck, total hip, and greater trochanter, by each year of age (16–24 yr), and by sex. The Z-score norms were developed for groups noted earlier. Mean Z-scores between the asthma or fracture subgroups compared with the mean Z-scores in the reference sample were not different. There were minor differences in mean BMD

*Address correspondence to: Kenneth Shawn Davison, PhD, 2086 Byron St Victoria, BC V8R 1L9, Canada. ebmedicine@gmail.com.

^aSee Acknowledgments section for complete list of the members.

across different Canadian geographic regions. This study provides age, sex, and skeletal site-specific Caucasian reference norms and formulae for the calculation of BMD Z-scores for Canadian youth aged 16–24 yr. This information will be valuable to help to identify individuals with clinically meaningful low BMD.

Keywords

Age; bone mineral density; normative; sex; skeletal site

Introduction

It has been suggested that osteoporosis is a disease of pediatric origin, in that, a failure to obtain sufficient bone mass during growth (1), particularly in the years surrounding puberty, will result in a suboptimal peak bone mass (PBM). A relatively low PBM coupled with the normal loss of bone mass through adulthood results in low bone mineral density (BMD), which is a major risk factor for fracture (2,3). However, for individual BMD measures to have diagnostic value, they require to be compared with normative values for those of similar sex and age derived from a healthy population. Comparison of individuals with population norms allows the identification of those who may require lifestyle modifications or clinical intervention in an attempt to increase their BMD and minimize their fracture risk. Population norms also enable researchers to assess whether a given health condition may impair the normal acquisition or maintenance of bone.

In adults, BMD is typically expressed as a “T-score,” which provides a relative comparison of the BMD measured with that of PBM in a sex-matched healthy population. The World Health Organization reference standard for osteoporosis diagnosis is a T-score of -2.5 or less (4), which may be used in postmenopausal women, and men aged 50 yr and older (5). In contrast to adults, the use of T-scores is not recommended for children and young adults, as they have not completed linear growth and/or bone mineral acquisition, with their PBM likely not yet achieved (6). In particular, adolescence is a period in which there are rapid changes in bone size and bone mineral accrual, with the timing of pubertal gains highly variable between, and within, groups of girls and boys (7,8). The International Society of Clinical Densitometry (ISCD) recommends the use of Z-scores when interpreting dual-energy X-ray absorptiometry (DXA) results in children, premenopausal women, and men younger than 50 yr (5). There are several different definitions of Z-score (9); when non-sex- or non-ethnic-specific reference data are used to calculate Z-scores, there is a tendency to misclassify subjects (10). In this study, the Z-score is calculated according to the ISCD definition of Z-score (10) as the number of standard deviations (SDs) from the mean BMD of a healthy population of the same age, race, and sex.

The ongoing Canadian Multicenter Osteoporosis Study (CaMos), which includes a youth cohort (ages 16–24 yr), provides an opportunity to study BMD in the Canadian youth population.

In view of the ISCD guidelines for assessing a healthy population, we *a priori* decided to exclude those with diseases or conditions with potential to influence BMD norms.

Therefore, we excluded individuals who were oral or parenteral steroid users and those with a diagnosis of inflammatory bowel disease (IBD) or asthma because of their frequent use of corticosteroids, and we also excluded individuals with any previous fractures. Because geographic variation in BMD has been noted in the CaMos adult cohort (11), we examined geographic variation of BMD and Z-scores in the CaMos youth cohort.

The objectives of this study were to develop BMD reference norms and BMD Z-scores at various skeletal sites, to determine whether prior fracture and/or asthma were related to BMD, and to assess possible geographic variation of BMD among Canadian youth aged 16–24 yr.

Materials and Methods

The CaMos study consists of both an adult cohort and a youth cohort. This investigation focused exclusively on the youth cohort (12). The youth cohort was recruited in 2004–2006 to aid in the identification of the period of PBM and to study the determinants of bone accrual. It consisted of 1001 participants aged 16–24 yr living within 50 km of 1 of 9 CaMos study centers: Vancouver, Calgary, Saskatoon, Hamilton, Toronto, Kingston, Quebec City, Halifax, and St. John's. The sampling frame and recruitment strategy were similar to those used to recruit the original adult cohort. Households were randomly selected from a list of residential telephone listings, and 1 eligible participant was randomly selected from each household, using a sex- and age-stratified design. If a person selected was away from home temporarily (such as attending university), he or she was still considered eligible and was contacted at his or her temporary residence. Selected household members who refused participation were asked to provide answers to a 1-page questionnaire on major risk factors for osteoporosis, including age, sex, race, fracture history, family history of osteoporosis, and smoking status. Baseline data collection used an extensive interviewer-administered questionnaire including sociodemographic information, medical and fracture history, family history, physical activity, tobacco smoking, food intake, and the Rand Short Form-36 Questionnaire (13). Clinical assessments included height, weight, and BMD by DXA. Ethical approval for the study was obtained from the ethics review board at each institution involved in the study, and all participants, as well as at least 1 parent for those younger than 18 yr, gave written informed consent in accordance with the Helsinki declaration.

Population reference norms for North American adults have shown a strong correlation between racial background and BMD (14). Racial background was determined by the response to the following open-ended question: "How would you best describe your race or color?" Those who responded "White" or "Caucasian" to this question were considered as a single group, henceforth Caucasian. Because of the low sample size for other racial backgrounds, it was not possible to determine race-specific Z-scores for non-Caucasian Canadian youth. This study included all Caucasian youth cohort participants who had at least 1 BMD measurement at any skeletal site (spine or hip) and did not report the use of oral or parenteral corticosteroids and did not have IBD. Exclusion of 20 participants who did not have BMD measurements at any skeletal site (spine or hip), 110 non-Caucasian participants, and 34 participants who were corticosteroid users or had IBD, left 837 participants in the study sample for the analysis: 398 males and 439 females.

The participants were further classified into 3 subgroups: a reference sample of those without asthma or a prior fracture (from any type of trauma), those with asthma, and those having sustained a fracture in their past. Among those with asthma, 30 of the 67 females had taken inhaled corticosteroids (ICS), and 47 of the 93 males had taken ICS. The mean (SD) durations of ICS use were 55.5 (72.2) mo for females and 70.7 (65.3) mo for males. Only 1 of the ICS users was on calcium supplementation.

Bone Mineral Density

The BMD of the lumbar spine (L1–L4), femoral neck, total hip, and greater trochanter were measured by DXA using Hologic QDR 4500, Discovery or Delphi (Hologic, Inc., Bedford, MA), or Lunar DPX or Prodigy densitometers (GE Lunar, Madison, WI). Machine calibration was completed daily according to DXA manufacturers' instructions. Daily and weekly quality assurance tests were performed as recommended by the manufacturers. Longitudinal stability was monitored using a machine-specific spine phantom, local to each site, as per standard procedure, which was either a Lunar aluminum spine phantom (GE Lunar, Madison, WI) or a Hologic anthropomorphic spine phantom (Hologic, Inc., Bedford, MA). Of the 9 CaMos centers, 5 used GE Lunar machines, and 4 used Hologic machines. Lunar data were converted into equivalent Hologic values by standard methods (15–19). All densitometers were calibrated at the start of the study and once each year thereafter using the Bio-Imaging Bona Fide Spine Phantom (Bio-Imaging technologies, Newtown, PA) that was circulated among centers to ensure site-to-site comparability. All Hologic and Lunar measurements were reanalyzed by 2 technicians at a central site.

Statistical Analyses

Z-Score values were calculated using the reference sample defined as Caucasian participants without asthma or a prior fracture and stratified by sex and age. Z-Scores were defined by the standard equation using healthy age- and sex-matched reference BMD and SD:

$$Z\text{-score} = \frac{(\text{Measured BMD} - \text{Matched mean BMD})}{\text{Matched SD}}.$$

Reference standards were developed for each of the 4 skeletal sites: lumbar spine (L1–L4), femoral neck, total hip, and greater trochanter, by each age year (16–24 yr) and by sex.

The normality of the BMD measurements was assessed for all Caucasian participants in the study sample and for each combination of sex, age, and skeletal site, using the Shapiro-Wilk test (20). Outliers were identified by examining histograms, boxplots (21), and normal probability plots. The estimation of a mean from a distribution, including outliers, may be unduly influenced by exceptional values and may not accurately represent the mean of the underlying distribution. There were 8 participants with 1 or more BMD values that deviated by 3 or more SDs from the mean BMD in its sex-, age- and skeletal site-specific stratum. Two individuals whose BMD values were all more than 3 SDs from the mean stratum-specific BMD were excluded from the study sample; for the others, only the outlier BMD measurement was excluded from the data. BMD values were normally distributed in 68 out of the 72 possible sex-age-skeletal site combinations. The 4 remaining non-normally

distributed BMD values were for the femoral neck, total hip, and greater trochanter of 18-yr-old women, and the greater trochanter of 19-yr-old women. In these subgroups, the Box-Cox transformation (22) was applied to normalize these BMD measurements.

The mean and SD of the reference sample were computed from the reanalyzed BMD data. These parameters were used as the reference standard to calculate BMD Z-scores for all Caucasian participants. The mean BMD and mean Z-scores with 95% confidence intervals (CIs) were also calculated within the subgroups with asthma and previous fracture. Mean BMD and mean Z-scores were compared among the preplanned subgroups and the reference sample by observing the respective graphical outputs and comparing the CIs (23). We assessed for age group heterogeneity. In the absence of heterogeneity, analyses were combined across age groups. Among those with asthma, mean Z-scores of corticosteroid users vs nonusers were compared by age groups of 16–19 and 20–24 yr to ensure sufficient sample size. Among those with prior fracture, mean Z-scores of those with low-trauma fracture vs those with severe trauma fracture were compared. Nine center-specific mean Z-scores with 95% CI were calculated for all skeletal sites and were compared among centers. We also evaluated the regional differences by using Bayesian hierarchical models. A separate model was created for each sex and each skeletal site. We used samples sizes of 5000 for each parameter. The criterion of Raftery and Lewis (24) was used to ensure convergence and to estimate the number of iterations required. Multivariate linear regression modeling was used to assess the association between centers and body mass index (BMI) on Z-scores.

Lastly, CaMos mean BMD and SD for the CaMos youth cohort were compared with those of a published study in the United States by Bachrach et al (25) and the third National Health and Nutrition Examination Survey (NHANES III). In the Bachrach study, mean BMD values were reported in 2-yr age groups from 9–10 yr to 21–22 yr and an age group of 23–25 yr. For comparison purposes, we considered the combined age groups noted. The age range in the youth cohort was 16–24 yr; hence, both the youngest and oldest youth were missing for this comparison. The NHANES III data were collected from men and women 20 yr of age and older. CaMos mean BMD and SD in 20- to 24-yr-old were compared with those of NHANES III aged 20–29 yr in the non-Hispanic white category.

SAS version 9.1 for Windows (SAS Institute Inc., Cary, NC) and BUGS software (MRC Biostatistics Unit, Cambridge, UK and Imperial College, London, UK) were used for all analyses.

Results

Of the 4446 eligible household members contacted, 1001 agreed to participate in the study, and 1026 refused full participation but completed the brief refusal questionnaire. The baseline characteristics of CaMos youth cohort are shown in Table 1. The study sample, 837 Caucasian participants with BMD measurements, differed somewhat from those excluded (who were lacking BMD measurements, were non-Caucasian, had IBD, or were corticosteroid users) and from those who completed the refusal questionnaire. In the study sample, the average measured height was higher than that in those excluded but similar to

the average self-reported height of the refusal sample. The average weight and BMI in the study sample were higher than the values in those excluded and in the refusal sample. Furthermore, the participants in the study sample were more engaged in regular activity than those who chose not to participate. The rate of prevalent fractures and family history of osteoporosis were higher in the study sample compared with the excluded and refusal samples.

The sample size for each age in the study sample varied from 31 (7.1%) to 69 (15.7%) in women and from 24 (6.0%) to 69 (17.3%) in men. Within the 3 separate strata (reference group, those with asthma, and prevalent fractures) of the study sample, the average BMI and weight in the female reference sample were slightly lower than those in the females with asthma or who had previously fractured. In males, there were no differences in the prevalence of asthma or previous fracture. There were also no differences in average height among subgroups in females and males and no differences in age of menarche among subgroups in females.

The mean BMD of the study sample, stratified by age, sex, and skeletal site, is shown in Fig. 1. The mean BMD and SD of the reference sample, stratified by age, sex, and skeletal site, are also provided (Table 2). The mean Z-scores of the asthmatic and previously fractured subgroups are all approx 0 for all ages and at all sites, and all 95% CIs overlapped (Fig. 2). There were no significant differences between the mean BMD Z-scores at the lumbar spine and total hip in subgroups with asthma or fracture compared with the mean Z-scores in the reference sample, and results for the femoral neck and trochanter sites were also similar.

There was no significant trend or heterogeneity by age. There were also no significant differences between mean BMD Z-scores of the reference sample and subgroups either with previous fracture or asthma after combining results over all ages. Among the subgroup with asthma, there were also no significant differences between mean Z-scores in ICS users compared with nonusers. Within the subgroup with prior fractures, there were no differences between mean Z-scores of those with low-trauma fractures vs high-trauma fractures.

The mean Z-scores with 95% CIs by geographical center and skeletal site are shown in Fig. 3. The mean lumbar spine Z-scores were -0.42 (95% CI: $-0.70, -0.14$) for females and -0.58 (95% CI: $-0.91, -0.26$) for males in Calgary, which were significantly lower than most of the other centers; the 95% CIs of the mean Z-score differences between Calgary and other centers did not include 0. The mean Z-score differences ranged from 0.5 to 0.7 for females and from 0.4 to 0.7 for males. The mean total-hip Z-scores in St-John's— 0.25 (95% CI: $-0.56, 0.06$) for females and -0.37 (95% CI: $-0.63, -0.11$) for males—were significantly lower than those in Saskatoon and Quebec City for females and those in Saskatoon, Kingston, and Quebec City for males. The comparison of the mean Z-scores by center in femoral neck and trochanter led to similar results as with the comparisons in lumbar spine and total hip; there were also between-center differences noted. Even when adjusted for sex, age, and BMI, the geographical center was still associated with Z-scores.

The mean BMD of the total hip and femoral neck in the CaMos youth cohort were compared with the data of the study in the United States by Bachrach et al (25) for youth of same age.

The standardized mean differences (SMD) (26,27) were computed using the SD of Bachrach et al (25), and virtually all the SMDs were small and nonsignificant (Fig. 4), with the exception of SMD for total hip BMD in 21- to 22-yr-old men and femoral neck BMD in 15- to 16-yr-old women, which were still small (0.4) but statistically significant (the CIs did not include 0).

We also compared the mean BMD of the total hip, femoral neck, and trochanter of CaMos 20- to 24-yr-olds with those of NHANES III 20- to 29-yr-old non-Hispanic whites (14). The SMD, which were computed using SD of NHANES III, were all small (range from 0.1 to 0.4) but significant statistically for total-hip BMD in women and total-hip, femoral neck, and trochanter BMD in men.

Discussion

This is the first study of BMD in healthy Canadian youth (ages 16–24 yr) from a large multicentered population-based cohort. Canadian reference standards for BMD of the total hip, femoral neck, trochanter, and lumbar spine in males and females aged 16–24 yr are provided to allow for the calculation of age- and sex-specific BMD Z-scores in Caucasian youth.

DXA-assessed BMD is confounded by skeletal size, in that those with unusually large bones will have higher BMD measures and those with unusually small bones will have lower BMD measures than those with average bone size but similar volumetric BMD (28–30). Stratification by age partially corrects for this size-based confounding associated with DXA measurements, but care needs to be taken to identify those smaller or larger than their counterparts of similar age and to view them in the light of their maturational status as well.

There are existing reference BMD data for the United States: a longitudinal study in a convenience sample of 423 healthy youth (9–25 yr of age) by Bachrach et al (25) and NHANES III data (20 yr and older) (14). The CaMos sample was 16–24 yr randomly selected population-based sample. Comparisons are somewhat imprecise as the age groups and methodologies differ. The reported reference means and SDs for BMD in our study were similar to the reference values for the total hip and femoral neck of Bachrach study (15–25 yr) in the United States (25). The similarities existed despite the inclusion of non-Caucasian youth in the American study compared with our Caucasian-only reference sample. There were no 15-yr-old participants in the CaMos sample; this might be a cause for the femoral neck BMD in 15- to 16-yr-old Canadian females to be slightly lower than that of the US cohort. The fact that our Canadian sample (20–24 yr) was younger than the reference sample of NHANES III (20–29 yr) might explain why we found slightly higher values than NHANES III for total-hip BMD in males and females and for femoral neck and trochanter BMD in males.

There were no significant differences between the mean lumbar spine or total-hip BMD in the youth with asthma or who had suffered a previous fracture compared with the reference sample; therefore, the inclusion of those with asthma and/or fracture would not have appreciably changed the reference values. Prior fractures are important risk factors for low

BMD and fracture in adults (31,32), and the long-term use of corticosteroid inhalers in the treatment of asthma is associated with bone loss in a dose-related fashion (33–37). However, the effect of long-term therapy of ICS on bone mass in children and youth is controversial. It has been reported that ICS had significant negative effect on bone metabolism in children (38), resulting in lower BMD (39); but in other studies, the use of ICS in children and youth with asthma was not appreciably associated with BMD (40,41). Our current data in this adolescent/youth population support the contention that no significant effect is observed. However, the lack of difference between the referent and the corticosteroid group should not necessarily be interpreted to mean that the 2 groups possess the same fracture risk—corticosteroids have been demonstrated to decrease bone strength relatively independently of BMD, so that, despite similar mean BMD measurements, the group that had used corticosteroids likely possessed a greater risk of fracture (42). Furthermore, the inclusion of all previous fractures instead of just including low-trauma fractures, because of the low number of low-trauma fractures, may have contributed to the null association we found between the history of fracture and BMD.

There were only minor differences between mean lumbar spine and total-hip BMD and Z-scores in the different Canadian geographical centers in CaMos. The differences that occurred, however, remained significant when adjusted for BMI. There were also between-center differences noted in the CaMos adult cohort. Again, in the adult cohort, there was no clear and consistent association between these differences and fracture incidence (11). Furthermore, because the differences among centers were minor and the sample size within each center was small, it seemed reasonable to merge all the centers for the purpose of creating population reference norms and Z-score values for Canadian youth.

The study sample frame encompasses roughly 40% of the Canadian population; it did not include the Territories, Manitoba, New Brunswick, Prince Edward Island, or extremely rural areas. Limitations of our study included a relatively low response rate for the youth cohort (22.5% participants and 23.1% partial responders who refused but completed a refusal questionnaire), which may affect the representative nature of the sample. Although there is no obvious source or direction of bias in measured variables, as in all longitudinal observational cohort studies, limitations include possible selection bias. On average, the study sample tended to be slightly heavier and more physically active than those who responded only partially. On the other hand, the rate of previous fracture and family history of fracture were higher in the study sample than in the refusal sample. This may, in part, be explained by the fact that the participants were informed of the nature of the study and were asked to complete an information sheet regarding family medical history before the interview. Because our study sample differed from the refusal sample in factors associated with both higher and lower BMD, it is unknown whether the reference values over- or underestimate true population means. Moreover, the spine and total body, excluding the head, are the preferred skeletal sites for measurement for children younger than 19 yr (5); but BMD scans were only performed for the lumbar spine and hip sites in CaMos because of the standard procedure initially set up for the adult cohort.

One strength of this investigation was the randomly selected age- and sex-stratified population-based cohort of 1001 males and females from within a 50-km radius of 9 centers

across Canada and the inclusion of both urban and rural youth. Therefore, the reference sample is representative of Canadian youth who are healthy and Caucasian. A refusal questionnaire was used to better assess selection bias. This study provides reference data for the evaluation of BMD at multiple skeletal sites for each gender and for each year of age from 16 through 24 yr. Finally, there was consistency and validation of our BMD findings with those of a previously published study from the United States of similar-aged youth and the NHANES III data.

In summary, this study provides age- and skeletal site-specific reference norms and formulae for the calculation of BMD Z-scores for Canadian youth aged 16–24 yr. We have demonstrated that there are only minor differences in mean BMD across different geographic regions of Canada and have shown that, in 2 groups with a potential risk for lower BMD values, 1 with asthma and 1 with previous fracture, the mean BMD is similar to that of the Canadian youth reference sample.

Acknowledgments

The Canadian Multicenter Osteoporosis Study was funded by the Canadian Institutes of Health Research; Merck Frosst Canada Ltd.; Eli Lilly Canada Inc.; Novartis Pharmaceuticals Inc.; and The Alliance for Better Bone Health —sanofiaventis and Procter & Gamble Pharmaceuticals Canada Inc.; Servier Canada Inc.; Amgen Canada Inc.; The Dairy Farmers of Canada; and The Arthritis Society. The authors thank all the participants in the Canadian Multicenter Osteoporosis Study. The authors would also like to thank Mrs. Louise Mailloux and Diane Bastien from the CaMos DXA Analysis Centre for reanalyzing the DXA.

CaMos Research Group: David Goltzman (co-principal investigator, McGill University, Montreal); Nancy Kreiger (co-principal investigator, University of Toronto, Toronto); Alan Tenenhouse (principal investigator emeritus, Toronto). CaMos Coordinating Centre, McGill University, Montreal, Quebec: Suzette Poliquin (national coordinator), Suzanne Godmaire (research assistant), Claudie Berger (study statistician). Memorial University, St. John's Newfoundland: Carol Joyce (director), Christopher Kovacs (co-director), Emma Sheppard (coordinator). Dalhousie University, Halifax, Nova Scotia: Stephanie Kaiser (co-directors), Susan Kirkland (co-directors), Barbara Stanfield (coordinator). Laval University, Quebec City, Quebec: Jacques P. Brown (director), Louis Bessette (co-director), Marc Gendreau (coordinator). Queen's University, Kingston, Ontario: Tassos Anastasiades (director), Tanveer Towheed (co-director), Barbara Matthews (coordinator). University of Toronto, Toronto, Ontario: Bob Josse (director), Sophie Jamal (co-director), Tim Murray (past director), Barbara Gardner-Bray (coordinator). McMaster University, Hamilton, Ontario: Jonathan D. Adachi (director), Alexandra Papaioannou (co-director), Laura Pickard (coordinator). University of Saskatchewan, Saskatoon, Saskatchewan: Wojciech P. Olszynski (director), K. Shawn Davison (co-director), Jola Thingvold (coordinator). University of Calgary, Calgary, Alberta: David A. Hanley (director), Jane Allan (coordinator). University of British Columbia, Vancouver, British Columbia: Jerilynn C. Prior (director), Millan Patel (co-director), Brian Lentle (radiologist), Yvette Vigna (coordinator).

References

1. Dent, CE, Frame, B, Parfitt, AM., Duncan, H., editors. Clinical aspects of metabolic bone disease. Excerpta Medica; Amsterdam, The Netherlands: p. 376–387.
2. Bachrach LK. Consensus and controversy regarding osteoporosis in the pediatric population. *Endocr Pract.* 2007; 13:513–520. [PubMed: 17872354]
3. Faulkner RA, Bailey DA. Osteoporosis: a pediatric concern? *Med Sport Sci.* 2007; 51:1–12. [PubMed: 17505116]
4. Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. *Osteoporos Int.* 1994; 4:368–381. [PubMed: 7696835]
5. Lewiecki EM, Gordon CM, Baim S, et al. International Society for Clinical Densitometry 2007 Adult and Pediatric Official Positions. *Bone.* 2008; 43:1115–1121. [PubMed: 18793764]
6. Gafni RI, Baron J. Overdiagnosis of osteoporosis in children due to misinterpretation of dual-energy x-ray absorptiometry (DEXA). *J Pediatr.* 2004; 144:253–257. [PubMed: 14760271]

7. Bailey DA, Martin AD, McKay HA, et al. Calcium accretion in girls and boys during puberty: a longitudinal analysis. *J Bone Miner Res.* 2000; 15:2245–2250. [PubMed: 11092406]
8. Sabatier JP, Guaydier-Souquieres G, Laroche D, et al. Bone mineral acquisition during adolescence and early adulthood: a study in 574 healthy females 10–24 years of age. *Osteoporos Int.* 1996; 6:141–148. [PubMed: 8704353]
9. Carey JJ, Delaney MF, Love TE, et al. DXA-generated Z-scores and T-scores may differ substantially and significantly in young adults. *J Clin Densitom.* 2007; 10:351–358. [PubMed: 17662630]
10. The Writing Group for the ISCD Position Development Conference. Diagnosis of osteoporosis in men, premenopausal women, and children [Position Statement]. *J Clin Densitom.* 2004; 7:17–26. [PubMed: 14742884]
11. Langsetmo L, Hanley DA, Kreiger N, et al. Geographic variation of bone mineral density and selected risk factors for prediction of incident fracture among Canadians 50 and older. *Bone.* 2008; 43:672–678. [PubMed: 18640295]
12. Kreiger N, Tenenhouse A, Joseph L, et al. Research note: the Canadian Multicentre Osteoporosis Study (CaMos) —background, rationale, methods. *Can J Aging.* 1999; 18:376–387.
13. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992; 30:473–483. [PubMed: 1593914]
14. Looker AC, Wahner HW, Dunn WL, et al. Updated data on proximal femur bone mineral levels of US adults. *Osteoporos Int.* 1998; 8:468–489. [PubMed: 9850356]
15. Genant HK, Grampp S, Gluer CC, et al. Universal standardization for dual x-ray absorptiometry: patient and phantom cross-calibration results. *J Bone Miner Res.* 1994; 9:1503–1514. [PubMed: 7817795]
16. Hui SL, Gao S, Zhou XH, et al. Universal standardization of bone density measurements: a method with optimal properties for calibration among several instruments. *J Bone Miner Res.* 1997; 12:1463–1470. [PubMed: 9286763]
17. Lu Y, Fuerst T, Hui S, Genant HK. Standardization of bone mineral density at femoral neck, trochanter and Ward's triangle. *Osteoporos Int.* 2001; 12:438–444. [PubMed: 11446558]
18. Ozdemir AK, Ozdemir HD, Polat NT, et al. The effect of personality type on denture satisfaction. *Int J Prosthodont.* 2006; 19:364–370. [PubMed: 16900819]
19. Fan B, Lu Y, Genant H, et al. Does standardized BMD still remove differences between Hologic and GE-Lunar state-of-the-art DXA systems? *Osteoporos Int.* 2009 [Epub ahead of print].
20. Shapiro SS, Wilk MB. An analysis of variance test for normality (complete sample). *Biometrika.* 1965; 52:591–611.
21. Tukey, JW. *Exploratory data analysis.* Addison-Wesley; Reading, MA: 1977.
22. Box GEP, Cox DR. An analysis of transformation. *J R Stat Soc Ser B.* 1964; 26:211–252.
23. Joseph L, Reinhold C. Statistical inference for continuous variables. *AJR Am J Roentgenol.* 2005; 184:1047–1056. [PubMed: 15788572]
24. Raftery AE, Lewis SM. One long run with diagnostics: implementation strategies for Markov chain Monte Carlo. *Stat Sci.* 1992; 7:493–497.
25. Bachrach LK, Hastie T, Wang MC, et al. Bone mineral acquisition in healthy Asian, Hispanic, black, and Caucasian youth: a longitudinal study. *J Clin Endocrinol Metab.* 1999; 84:4702–4712. [PubMed: 10599739]
26. Higgins, JPT., Green, S., editors. *Cochrane handbook for systematic reviews of interventions version 5.0.2.* The Cochrane Collaboration; [updated September 2009]. Available online at www.cochrane-handbook.org
27. Glass GV. Primary, secondary and meta-analysis of research. *Educ Res.* 1976; 5:3–8.
28. Kroger H, Kotaniemi A, Vainio P, Alhava E. Bone densitometry of the spine and femur in children by dual-energy x-ray absorptiometry. *Bone Miner.* 1992; 17:75–85. [PubMed: 1581707]
29. Webber CE, Sala A, Barr RD. Accounting for body size deviations when reporting bone mineral density variables in children. *Osteoporos Int.* 2009; 20:113–121. [PubMed: 18543053]
30. Carter DR, Bouxsein ML, Marcus R. New approaches for interpreting projected bone densitometry data. *J Bone Miner Res.* 1992; 7:137–145. [PubMed: 1570758]

31. Nelson HD, Morris CD, Kraemer DF, et al. Osteoporosis in postmenopausal women: diagnosis and monitoring. *Evid Rep Technol Assess (Summ)*. 2001 Feb;28:1–2.
32. Papaioannou A, Kennedy CC, Cranney A, et al. Risk factors for low BMD in healthy men age 50 years or older: a systematic review. *Osteoporos Int*. 2009; 20:507–518. [PubMed: 18758880]
33. Israel E, Banerjee TR, Fitzmaurice GM, et al. Effects of inhaled glucocorticoids on bone density in premenopausal women. *N Engl J Med*. 2001; 345:941–947. [PubMed: 11575285]
34. Kemp JP, Osur S, Shrewsbury SB, et al. Potential effects of fluticasone propionate on bone mineral density in patients with asthma: a 2-year randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc*. 2004; 79:458–466. [PubMed: 15065610]
35. Hanania NA, Chapman KR, Sturtridge WC, et al. Dose-related decrease in bone density among asthmatic patients treated with inhaled corticosteroids. *J Allergy Clin Immunol*. 1995; 96:571–579. [PubMed: 7499672]
36. Sivri A, Coplu L. Effect of the long-term use of inhaled corticosteroids on bone mineral density in asthmatic women. *Respirology*. 2001; 6:131–134. [PubMed: 11422892]
37. Fujita K, Kasayama S, Hashimoto J, et al. Inhaled corticosteroids reduce bone mineral density in early postmenopausal but not premenopausal asthmatic women. *J Bone Miner Res*. 2001; 16:782–787. [PubMed: 11316007]
38. Allen HD, Thong IG, Clifton-Bligh P, et al. Effects of high-dose inhaled corticosteroids on bone metabolism in prepubertal children with asthma. *Pediatr Pulmonol*. 2000; 29:188–193. [PubMed: 10686039]
39. Boot AM, de Jongste JC, Verberne AA, et al. Bone mineral density and bone metabolism of prepubertal children with asthma after long-term treatment with inhaled corticosteroids. *Pediatr Pulmonol*. 1997; 24:379–384. [PubMed: 9448228]
40. Egan JJ, Maden C, Kalra S, et al. A randomized, double-blind study comparing the effects of beclomethasone and fluticasone on bone density over two years. *Eur Respir J*. 1999; 13:1267–1275. [PubMed: 10445600]
41. Griffiths AL, Sim D, Strauss B, et al. Effect of high-dose fluticasone propionate on bone density and metabolism in children with asthma. *Pediatr Pulmonol*. 2004; 37:116–121. [PubMed: 14730656]
42. Luengo M, Picado C, Del Rio L, et al. Vertebral fractures in steroid dependent asthma and involutional osteoporosis: a comparative study. *Thorax*. 1991; 46:803–806. [PubMed: 1771602]

Fig. 1. Mean bone mineral density (BMD) by sex, age, and skeletal site in study sample. (A) Youth female—mean BMD by age and skeletal site; (B) youth male—mean BMD by age and skeletal site.

Fig. 2.

Comparison of the mean Z-scores by sex and skeletal site in subgroups with asthma and fracture. The dashed line represents the values of the reference sample. (A) Female lumbar spine bone mineral density (BMD); (B) male lumbar spine BMD; (C) female total-hip BMD; (D) male total-hip BMD.

Fig. 3.

Mean Z-scores (95% confidence intervals) by center and skeletal site. (A) Female lumbar spine bone mineral density (BMD); (B) male lumbar spine BMD; (C) female total-hip BMD; (D) male total-hip BMD. VR, Vancouver; CA, Calgary; SK, Saskatoon; HA, Hamilton; TO, Toronto; KN, Kingston; QC, Quebec City; HX, Halifax; ST, St. John's. The dashed line represents the values of the reference sample.

Fig. 4.

Comparison of mean BMD by sex and skeletal site between CaMos youth cohort and that of the United States. **(A)** Comparison of TH BMD by age and sex: CaMos and data of Bachrach et al; **(B)** comparison of FN BMD by age and sex: CaMos and data of Bachrach et al; **(C)** comparison of TH, FN, and TR BMD: CaMos 20–24 yr and NHANES III 20–29 yr. BMD, bone mineral density; TH, total hip; FN, femoral neck; TR, trochanter; NHANES III, National Health and Nutrition Examination Survey.

Table 1

Baseline Characteristics of the Canadian Multicenter Osteoporosis Study Youth Cohort (Aged 16–24 yr)—Data Include Mean $\pm$ Standard Deviation (95% Confidence Interval) or frequency (percentage)

Characteristic	Study sample					
	Reference sample	Asthma	Previous fracture	Total	Excluded	Refusal
Females	N = 251	N = 67	N = 145	N = 439	N = 99	N = 432
Height (cm)	164.9 ± 6.5 (164.1, 165.7)	163.8 ± 6.2 (162.4, 165.2)	166.1 ± 6.4 (165.0, 167.1)	165.1 ± 6.5 (164.5, 165.7)	161.1 ± 6.6 (159.5, 162.8)	164.5 ± 6.8 (163.9, 165.2)
Weight (kg)	61.3 ± 11.0 (60.0, 62.7)	65.5 ± 15.1 (62.1, 69.0)	64.8 ± 11.5 (63.0, 66.7)	63.0 ± 12.0 (61.9, 64.1)	59.5 ± 14.4 (55.9, 63.0)	59.7 ± 11.6 (68.3, 69.0)
BMI (kg/m ²)	22.5 ± 3.8 (22.1, 23.0)	24.4 ± 5.4 (23.2, 25.6)	23.5 ± 4.1 (22.9, 24.2)	23.1 ± 4.2 (22.7, 23.5)	22.8 ± 4.7 (21.6, 23.9)	22.0 ± 3.6 (21.6, 22.3)
Age of menarche (yr)	12.5 ± 1.3 (12.4, 12.7)	12.5 ± 1.4 (12.2, 12.8)	12.6 ± 1.3 (12.4, 12.8)	12.5 ± 1.3 (12.4, 12.7)	12.1 ± 1.0 (11.8, 12.3)	12.4 ± 1.4 (12.3, 12.5)
Previous fracture ^a	—	29 (38.2)	151 (100)	151 (32.8)	13 (19.4)	94 (21.8)
Family history of osteoporosis ^a	70 (26.8)	27 (35.5)	50 (33.1)	135 (29.4)	16 (23.9)	66 (15.3)
Regular physical activity ^a	171 (65.5)	52 (68.4)	104 (68.9)	307 (66.7)	35 (52.2)	250 (57.9)
Males	N = 164	N = 93	N = 186	N = 398	N = 77	N = 594
Height (cm)	178.7 ± 7.8 (177.6, 179.9)	178.4 ± 7.1 (177.0, 179.9)	179.3 ± 7.0 (178.3, 180.3)	178.9 ± 7.3 (178.2, 179.6)	174.9 ± 7.0 (173.1, 176.7)	179.0 ± 7.6 (178.4, 179.6)
Weight (kg)	77.6 ± 15.4 (75.2, 79.9)	77.4 ± 15.0 (74.4, 80.4)	78.0 ± 13.4 (76.0, 79.9)	77.6 ± 14.5 (76.2, 79.0)	77.9 ± 23.6 (71.8, 84.0)	75.9 ± 14.5 (74.7, 77.1)
BMI (kg/m ²)	24.2 ± 4.4 (23.6, 24.9)	24.3 ± 4.5 (23.4, 25.2)	24.2 ± 4.1 (23.7, 24.8)	24.2 ± 4.3 (23.8, 24.7)	25.3 ± 6.8 (23.6, 27.1)	23.6 ± 4.0 (23.3, 24.0)
Previous fracture ^a	—	49 (50.0)	193 (100)	193 (47.0)	18 (28.6)	222 (37.7)
Family history of osteoporosis ^a	46 (27.2)	33 (33.7)	49 (25.4)	114 (27.7)	8 (12.7)	97 (16.3)
Regular physical activity ^a	115 (68.0)	73 (74.5)	142 (73.6)	293 (71.3)	34 (54.0)	401 (67.5)

Abbr: BMI, body mass index.

^aFor previous fracture, family history of osteoporosis, and regular physical activity, data represent frequency (percentage).

Bone Mineral Density Mean (g/cm²) and SD of Canadian Multicenter Osteoporosis Study Caucasian Reference Sample (Aged 16–24 yr) by Sex, Age, and Skeletal Site

Table 2

Age (yr)	N	Lumbar spine (g/cm ²)		Total hip (g/cm ²)		Femoral neck (g/cm ²)		Greater trochanter (g/cm ²)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Females									
16	38	1.007	0.115	0.963	0.111	0.858	0.103	0.711	0.092
17	35	1.023	0.126	0.977	0.106	0.879	0.091	0.721	0.095
18	35	1.013	0.096	0.981	0.101	0.885	0.087	0.720	0.092
19	27	0.991	0.102	0.944	0.118	0.847	0.113	0.692	0.106
20	21	1.026	0.078	1.010	0.101	0.900	0.097	0.731	0.096
21	26	1.068	0.117	1.004	0.122	0.885	0.106	0.739	0.104
22	27	1.017	0.127	0.932	0.121	0.831	0.110	0.663	0.106
23	30	1.015	0.099	0.976	0.112	0.864	0.108	0.705	0.110
24	21	1.035	0.126	0.979	0.115	0.848	0.105	0.703	0.101
Males									
16	22	0.972	0.126	1.061	0.161	0.939	0.148	0.809	0.140
17	33	1.037	0.146	1.075	0.135	0.956	0.122	0.830	0.112
18	19	1.030	0.111	1.091	0.134	0.962	0.109	0.821	0.137
19	16	1.065	0.097	1.080	0.129	0.971	0.136	0.804	0.131
20	18	1.093	0.143	1.106	0.176	1.017	0.186	0.845	0.154
21	24	1.083	0.091	1.110	0.110	0.971	0.106	0.842	0.091
22	9	1.035	0.118	1.088	0.129	0.964	0.119	0.802	0.092
23	15	1.058	0.153	1.055	0.161	0.949	0.145	0.802	0.170
24	11	1.071	0.084	1.062	0.088	0.911	0.129	0.787	0.075

There was no significant trend or heterogeneity by age.

Abbr: SD, standard deviation.