Adjusting Bone Mass for Differences in Projected Bone Area and Other Confounding Variables: An Allometric Perspective

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ABSTRACT

The traditional method of assessing bone mineral density (BMD; given by bone mineral content [BMC] divided by projected bone area [A_p], BMD = BMC/A_p) has come under strong criticism by various authors. Their criticism being that the projected bone "area" (A_p) will systematically underestimate the skeletal bone "volume" of taller subjects. To reduce the confounding effects of bone size, an alternative ratio has been proposed called bone mineral apparent density [BMAD = BMC/$(A_p)^{3/2}$]. However, bone size is not the only confounding variable associated with BMC. Others include age, sex, body size, and maturation. To assess the dimensional relationship between BMC and projected bone area, independent of other confounding variables, we proposed and fitted a proportional allometric model to the BMC data of the L2–L4 vertebrae from a previously published study. The projected bone area exponents were greater than unity for both boys (1.43) and girls (1.02), but only the boy's fitted exponent was not different from that predicted by geometric similarity (1.5). Based on these exponents, it is not clear whether bone mass acquisition increases in proportion to the projected bone area (A_p) or an estimate of projected bone volume $(A_p)^{3/2}$. However, by adopting the proposed methods, the analysis will automatically adjust BMC for differences in projected bone size and other confounding variables for the particular population being studied. Hence, the necessity to speculate as to the theoretical value of the exponent of A_p, although interesting, becomes redundant. (J Bone Miner Res 2002;17: 703–708)

Key words: projected bone area, confounding variables, allometric model, multiplicative error, exercise

INTRODUCTION

THERE IS still considerable debate regarding the most appropriate method of normalizing or adjusting the effects of bone size when assessing bone mineral content (BMC) of the spine and other skeletal regions. The traditional method is to calculate a bone mineral density (BMD), obtained by calculating the ratio of the total BMC (g) divided by the projected area of the specified region A_p (cm^2), given by BMD = BMC/A_p (g/cm^2). However, this areal BMD ratio has come under strong criticism[1,2] because, theoretically, the projected bone area A_p will not

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accurately reflect the skeletal bone volume being assessed. In reality, the projected area will systematically underestimate the skeletal bone volume of taller subjects. Assuming that bone mass acquisition increases in proportion to the skeletal bone volume, the traditional BMD ratio will overestimate the BMD of taller subjects while underestimating the BMD of shorter subjects.

Clearly, to compare the BMD of mutually exclusive groups (e.g., active subjects vs. inactive subjects) that also are known to differ in bone size (e.g., height), the confounding effect of bone size or projected bone area must be removed before valid inference about the benefits of physical activity on bone density can be made. To reduce the confounding effects of bone size, Carter and coworkers[1,2] recommend reporting an alternative ratio referred to as the bone mineral apparent density (BMAD), estimated by the ratio BMAD = $BMC/(A_p)^{3/2}$ (g/cm^3). Carter et al.[1] provided empirical support for the assumption that BMC increases proportionally to skeletal bone volume using allometric scaling,[3] that is, assuming the power law relationship, BMC = $a(A_p)^b$, where a and b are fitted constants. When they fitted an allometric model to the BMC results of 75 healthy women, the fitted exponent b was found to be 1.4, not different from the theoretical value of 1.5 predicted by geometric similarity.

Unfortunately, their conclusion may have been a little premature. Bone size is not the only confounding variable associated with BMC. Age is another well-known determinant that is likely to confound valid inference when comparing lifestyle and environmental differences in bone density. For example, bone density peaks during mid-adolescence or early adulthood and declines thereafter.[4–6] If the taller subjects of the 75 healthy women used in the study by Carter et al.[1] also were younger, the projected bone area A_p exponent 1.4 would have been inflated by this known association with age. As explained previously, to compare the BMD of two mutually exclusive groups (e.g., strength trained athletes vs. endurance trained athletes) that were also known to differ in age, once again the confounding effect of age also must be removed before valid inference can be made about the effects of either type of activity on bone density. Other determinants likely to confound valid inference when comparing differences in BMC include body mass, lean body mass, and maturation.[6–8]

Most authors recognize the need to control or adjust for differences in the confounding variables of age, body size, and pubertal status. However, the means by which these "adjustments" can be made varies considerably. Some authors simply divide measurements of bone density, either BMD or BMC, by weight or body mass[9–11] in an attempt to remove the effect of body size. Others use either multiple regression or the analysis of covariance (ANCOVA) to adjust simultaneously for the confounding effects of variables such as age, weight, height, etc.[1,7,8,10,12–18]. Even within these studies, there is considerable variation in the way these confounding variables are incorporated into the adopted multiple regression or ANCOVA models.

Those studies adopting a multiple regression approach usually assume a linear association between BMC and the covariates. However, bone density peaks during mid-adolescence or early adulthood. Clearly, in such studies, a "linear" adjustment for age will fail to explain the nonlinear developmental changes in bone density. Other studies incorporate some of the confounding variables as either log-transformed or as polynomial terms.[1,13] Although the rationale for using log-transformed univariate or polynomial terms in their correlation and regression analyses was not the prime focus of their studies, Katzman[2] and later Carter[1] recognize the need to use a "dimensional" or geometric approach when normalizing site-specific and whole body BMC for difference in bone thickness and body size. Further justification for using log-transformed predictor variables can be provided by observing the distribution of BMC and BMD when plotted against the confounding variables such as age, body mass, or height. For example, Figs. 2 and 3 of Katzman et al.[2] and Fig. 7 of Bonjour et al.[4] provide evidence of a "shot-gun" effect, that is, a systematic increase in error variation in bone density with age and height, respectively. This characteristic in data, known as heteroscedasticity, will contradict the constant error-variance assumption required for multiple regression and ANCOVA. Fortunately, the use of a log transformation will naturally help to overcome this tendency to diverge, supporting the use of a proportional model with a multiplicative error term[19] to describe the developmental changes in bone density.

As described previously, Carter et al.[1] provided empirical support for the allometric model BMC = $a(A_p)^b$ when the fitted exponent b was found to be 1.4, not significantly different from the theoretical exponent of 1.5. Based on this result, the authors inferred that BMC increases in proportion to a volumetric estimate of bone size $(A_p)^{3/2}$, an inference that of course may have been reasonable assuming the 75 female subjects were relatively homogeneous in other factors (confounding variables) known to effect BMC. Unfortunately, because of the wide range in body mass (43.6–95.0 kg) and age (17–40 years) of the 75 female subjects, the likely confounding effects of body mass (or lean body mass) and age had been overlooked, possibly leading to the fitted exponent of 1.4 being incorrectly estimated. For example, the taller female subjects also might be younger and have a greater proportion of lean body mass. As such, fitting of the simple allometric model BMC = $a(A_p)^b$ will almost certainly lead to an inflated estimate of the projected bone area A_p exponent, casting serious doubt on the validity of the inference drawn. The dangers of ignoring other known confounding variables will be highlighted later.

To identify population or lifestyle differences (e.g., physical activity and diet) in BMC and separate the relative contribution of these known confounding variables, there is a need to incorporate all such variables simultaneously into an appropriate model for BMC. Hence, the purpose of this article is to develop and extend the allometric model for BMC, originally proposed by Carter et al.,[1] to not only explain the proportional association with projected bone area but, at the same time, adjust for the other confounding variables. The proposed model will provide greater insight into the dimensional relationship between BMC, bone size, age, sex, body size (body mass and lean body mass, etc.), and maturation and, at the same time, provide a more valid

basis of assessing population or lifestyle differences associated with BMC. The value of the model and proposed methods will be illustrated using an example from a previously published longitudinal study by Cheng et al.[20]

MATERIALS AND METHODS

Subjects

Details of the study design can be found in Cheng et al.[20] Briefly, measurements of BMC of the L2–L4 vertebrae and complete records of relevant information were available for 179 healthy Chinese adolescents (92 boys and 87 girls). Subjects were 11–16 years old at the start of the study. All measurements were taken once a year during 3 consecutive years (1991–1993) $\sim$12 months apart (12.6 $\pm$ 0.7 months).

Statistical methods

Carter et al.[1] recognized the value of using the following allometric model to describe the proportional relationship between BMC and the projected area A_p:

$$BMC = a(A_p)^b, \quad (1)$$

where a and b are fitted constants.

Extending this model to include other confounding variables, similar to the models used by Nevill et al.,[21] the following multiplicative allometric model for the BMC of the L2–L4 vertebrae was proposed:

$$BMC = A_p^{k_1} \cdot mass^{k_2} \cdot height^{k_3}$$
$$\cdot \exp(a_i + b_i \cdot age + c_i \cdot age^2) \cdot \epsilon_{ij}, \quad (2)$$

where A_p is the projected area of the L2–L4 vertebrae. All parameters are fixed with the exception of the constant and age parameters a_i, b_i, and c_i, which are allowed to vary randomly from subject to subject, and the proportional error ratio ϵ_{ij}, which is used to describe the error variance between visit occasions. The subscripts i and j are used to indicate random variation from subject to subject and within subjects (between visit occasions), respectively. In the case of a cross-sectional study, in which there is just one observation per subject, the subscript i would be omitted.

The model [Eq. (2)] can be linearized with a log transformation, and a multilevel regression analysis on $\log_e(BMC)$ then can be used to estimate the unknown parameters. The transformed log-linear multilevel regression model becomes

$$\log_e(BMC) = k_1 \cdot \log_e(A_p) + k_2 \cdot \log_e(mass)$$
$$+ k_3 \cdot \log_e(height) + a_i + b_i \cdot age + c_i \cdot age^2 + \log_e(\epsilon_{ij}).$$
$$(3)$$

Note that categorical factors can be incorporated into subsequent analyses by introducing them as fixed dummy indicator variables, for example, stage of pubic hair development.

Multilevel modeling[22,23] is an appropriate method of analyzing such longitudinal (repeated measures) data. Note that for a cross-sectional study, ordinary multiple regression/ANCOVA could be applied using the model in Eq. (3) without the subscript i. Multilevel modeling is an extension of ordinary multiple regression/ANCOVA where the data have a hierarchical or clustered structure. A hierarchy consists of units or measurements grouped at different levels. One example is repeated measure data where individuals are measured on more than one occasion. In the present example, the subjects or individuals, assumed to be a random sample, represent the level 2 units, with the subjects' repeated measurements recorded at each visit being the level 1 units. The two levels of hierarchical or nested observational units are the visit occasions at level 1 (within individuals) and the sample of children (between individuals) at level 2.

Separate multilevel regression analyses were performed on the BMC of the L2–L4 vertebrae for boys and girls. The maximum log-likelihood criterion, originally recommended by Cox[24] to compare models with different structural forms, will be used to compare the quality of fit of the log-transformed allometric model in Eq. (3) with the equivalent additive multiple regression model (not log-transformed).[21]

RESULTS

The BMC of the L2–L4 vertebrae versus projected bone area A_p are plotted for both boys and girls in Figs. 1A and 1B, respectively. The nonlinear association between BMC of the L2–L4 vertebrae and projected bone area A_p (for boys) and the tendency for the BMC data (for boys and girls) to diverge with increasing bone size (heteroscedastic error variance) confirms the need for a proportional allometric model with a multiplicative error term [Eq. (2)].

The parsimonious solutions of the multilevel regression analyses of BMC of the L2–L4 vertebrae for boys and girls is given in Tables 1 and 2, respectively, having adjusted for the developmental changes in projected bone area A_p, body mass, the sum of four skinfold thicknesses, age, and maturation.

The boys and girls exponents of the projected bone area A_p were 1.431 (SEE = $\pm$0.0817) and 1.015 (SEE = $\pm$0.0609), respectively. Only the fitted exponent of the boys (1.431) was not significantly different from that predicted by geometric similarity (1.5). The girls' fitted exponent 1.015 was significantly below this theoretical parameter of 1.5, but not different from unity. The parsimonious solutions also identified a significant increase in BMC associated with body mass together with a decline in BMC associated with the log-transformed sum of skinfold thickness. Taken together, these two body size components strongly support the notion that BMC of the L2–L4 vertebrae develops proportionally to "lean" body mass. Both analyses identified an additional contribution of the "age" term (0.0493 for boys and 0.0447 for girls), indicating that BMC of the L2–L4 vertebrae is still increasing at over 4%/year (obtained by taking the antilogs of the age parameters 0.0493
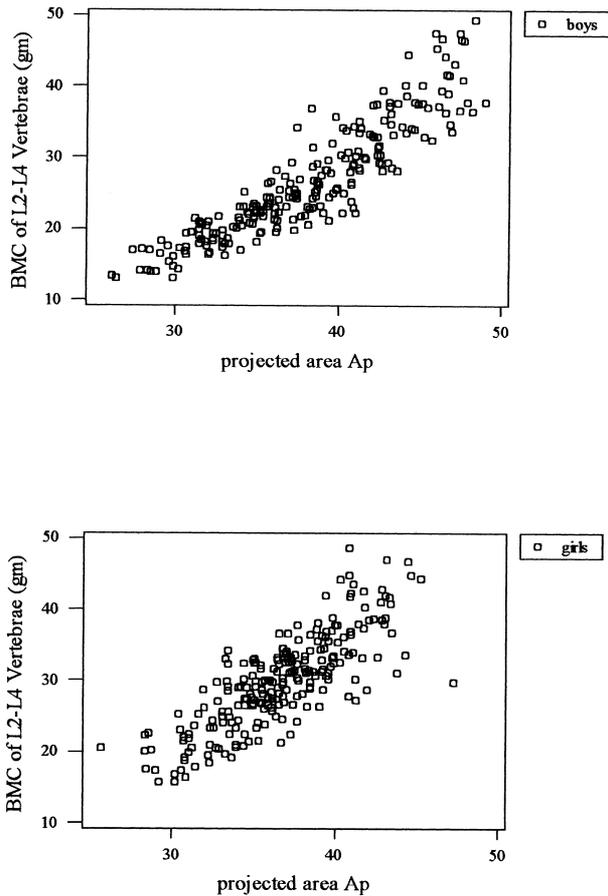
FIG. 1. The BMC (g) of the L2–L4 lumber vertebrae versus projected bone area A_p for (A) boys and (B) girls.

TABLE 1. THE MULTILEVEL REGRESSION ANALYSIS OF LOG-TRANSFORMED BMC OF THE L2–L4 VERTEBRAE FOR BOYS ADJUSTED FOR THE PROJECTED SKELETAL AREA (A_p), BODY MASS, HEIGHT, SUM OF SKINFOLDS, AGE, AND MATURATION

Fixed explanatory variables	Estimate	±SEE
Constant	−0.1547	±1.225
$\mathrm{Log}_e(A_p)$	1.431	±0.0817
$\mathrm{Log}_e(\text{mass})$	0.5691	±0.0912
$\mathrm{Log}_e(\text{height})$	−0.6899	±0.2959
$\mathrm{Log}_e(\text{sum of skinfolds})$	−0.1317	±0.0240
Age	0.0493	±0.0083
Stage 2 (boys; Δ)	−0.0313	±0.0127
The variance of the random variable (constant) at levels 1 and 2		
Level 1 (within individuals)		
Constant		0.0035 ± 0.0004
Level 2 (between individuals)		
Constant		0.0045 ± 0.0009

Values are means ± SEE. Age was adjusted about the origin using the mean age = 13.3 years. Maturation was assessed using the five stages of pubic hair development. The boys' group (pubic hair stage 1) was used as the baseline measure and other groups were compared with it, indicated by (Δ).

and 0.0447) in addition to the observed proportional increase in bone size and body size, that is, having already controlled for bone size, body mass, and sum of skinfold thicknesses. A significant (3.1%) reduction in BMC of the L2–L4 vertebrae was observed for boys at stage 2 of pubic hair development. Similarly, a significant (4.6% and 2.4%) reduction in BMC of the L2–L4 vertebrae was observed for girls at stages 2 and 3, respectively, of their pubic hair development. The age[2] term parameter (for boys and girls) failed to make a significant contribution to the prediction of the BMC of the L2–L4 vertebrae.

To highlight the dangers of fitting the simple allometric model alone to describe the relationship between BMC and the projected bone area A_p originally proposed by Carter et al.[1] but ignoring the impact of the other confounding variables, we fitted the model in Eq. (1) separately to the boys and girls data of Cheng et al.[20] The fitted exponents were inflated greatly as $b = 2.055$ (SEE = ±0.053) for boys and $b = 1.694$ (SEE = ±0.084) for girls. Clearly, both of these estimated exponents are significantly greater than those reported in Tables 1 and 2 and also "erroneously" significantly greater than the theoretical value of 1.5, predicted by geometric similarity assuming spines of equal volumetric density.

The superiority of the allometric model was confirmed using the maximum log-likelihood quality-of-fit criterion. The maximum log-likelihood criterion for the boys' multilevel regression analysis described in Table 1 was −491.7, much greater than the maximum log-likelihood criterion based on the equivalent additive model given by −547.8. The maximum log-likelihood criterion for the girls' multilevel regression analysis described in Table 2 was −482.4. Again, this was greater than the maximum log-likelihood criterion based on the equivalent additive model for girls, found to be −513.8. Note that in these comparisons, the same number of predictor variables was used in both the log-transformed and -nontransformed models.

DISCUSSION

The BMC of the L2–L4 vertebrae clearly increases in proportion to the projected bone area A_p (Figs. 1A and 1B). This, together with a tendency for the BMC data to diverge ("shot-gun" effect) with increasing bone size (heteroscedastic error variance), confirms the need to describe the developmental changes in BMC using a proportional model with allometric body size components and a multiplicative error term.[25] The superiority of the allometric model was confirmed when the maximum likelihood criteria were found to be greater for the analyses using the allometric models (log-transformed) compared with the analyses based on the equivalent additive multiple regression models (not log-transformed). Because the maximum likelihood criteria were greater using the allometric model, the error variances

TABLE 2. THE MULTILEVEL REGRESSION ANALYSIS OF LOG-TRANSFORMED BMC OF THE L2–L4 VERTEBRAE FOR GIRLS ADJUSTED FOR THE PROJECTED SKELETAL AREA (A_p), BODY MASS, SUM OF SKINFOLDS, AGE, AND MATURATION

Fixed explanatory variables	Estimate	±SEE
Constant	−2.477	±0.2471
$Log_e(A_p)$	1.015	±0.0609
$Log_e(mass)$	0.7162	±0.0626
$Log_e(sum\ of\ skinfolds)$	−0.1361	±0.0216
Age	0.0447	±0.0054
Stage 2 (girls) (Δ)	−0.0466	±0.0130
Stage 3 (girls) (Δ)	−0.0241	±0.0092
The variance of the random variable (constant) at levels 1 and 2		
Level 1 (within individuals)		
Constant	0.0016 ± 0.0002	
Level 2 (between individuals)		
Constant	0.0084 ± 0.0014	

Values are means ± SEE. Age was adjusted about the origin using the mean age = 13.3 years. Maturation was assessed using the five stages of pubic hair development. The girls' group (pubic hair stage 1) was used as the baseline measure and other groups were compared with it, indicated by (Δ).

associated with the boys' and girls' analyses automatically will be less. Consequently, this will lead to more powerful and valid tests of significance when subsequently comparing population and/or lifestyle differences.

As anticipated by Carter et al.,[1] the exponents of the projected bone area A_p were greater than unity for both boys (1.431; SEE = ±0.0817) and girls (1.015; SEE = ±0.0609). However, only the boys' fitted exponent of 1.431 was not significantly different from that predicted by geometric similarity (1.5) for spines of equal volumetric density. In the case of the girls' results, the fitted exponent of 1.015 was significantly below 1.5 but not significantly different from unity. Based on these projected bone size exponents, it is not clear whether bone mass acquisition increases in proportion to the projected bone area or an estimate of projected bone volume. However, the possibility that bone mass acquisition increases in proportion to a surface area law, inherently assumed by the ratio BMD, should not be dismissed. Strength increases in proportion to the cross-sectional area of the muscle being assessed, and aerobic power increases in proportion to body mass raised to the power ($m^{2/3}$), also obeying a surface area law.[3,25] Thus, such well-known physiological examples should not preclude the possibility that bone mass acquisition also may increase in proportion to the projected skeletal bone area.

The difference in the boys' and girls' exponents was not anticipated, although we recognize that these parameters are population specific (Chinese adolescent boys and girls). Whether similar differences exist in other (e.g., adult) populations provides considerable scope for further research. However, this is an opportune moment to emphasize that

although the parameter estimates are population specific, the modeling methods proposed generally are applicable to most populations.[19] Clearly, when comparing lifestyle and/or environmental differences in bone density of adolescent boys, researchers adopting the traditional BMD ratio, as used in the original study by Cheng et al.,[20] could draw inappropriate or invalid inferences from such data. In contrast, based on the girls fitted exponent, the traditional ratio BMD appears appropriate to adjust BMC for differences in projected bone size. However, by including the term $log_e(A_p)$ as a predictor/covariate in a log-linear regression or ANCOVA, the analysis will automatically adjust or scale BMC for differences in projected bone size, leaving the necessity to estimate the theoretical value of the exponent of A_p, of less importance.

Having controlled for differences in projected bone size, the analysis identified a further significant increase in BMC associated with body mass, together with a decline in BMC associated with the sum of four skinfold thicknesses, log-transformed. These two body size components, taken together, strongly support the notion that BMC of the L2–L4 vertebrae develops proportionally to lean body mass. (The log-transformed sum of four skinfolds is known to be related directly to body density, that is, in turn, inversely related to percentage of body fat[26]). This result supports the findings of another longitudinal study that found a positive relationship between gains in lean body mass and bone mineral acquisition,[8] as well as indirectly supporting the association between muscle strength and bone strength.[27,28]

The multilevel regression analyses also identified an additional contribution of the age (over 4%/year) for both boys and girls, indicating that BMC of the L2–L4 vertebrae was still growing throughout the assessment period (11–16 years), having already controlled for differences in bone size, body mass, and skinfold measurements. The analyses failed to identify a significant contribution from the age^2 terms, suggesting that BMC of the L2–L4 vertebrae was not approaching its peak for either boys or girls during the assessment period.

A significant reduction in BMC of the L2–L4 vertebrae was observed at the early stages of maturation, having controlled for the differences in the confounding variables, projected bone size, body size, etc. This delay in BMC development was identified for boys at stage 2 of pubic hair development and at stages 2 and 3 for girls. It would appear that at the onset of the growth spurt, linear growth (e.g., an increase in stature) proceeds the development of bone density, a phenomenon that appears more pronounced in girls. This delay or lag in the development of bone density during the growth spurt, confirmed by Frost,[28] has been thought responsible for the observed increase in fractures during adolescence.[29]

In conclusion, this study confirms the concerns of Carter et al.[1] and Katzman et al.[2] that traditional BMD will not always adequately remove the confounding effects of projected bone size. However, based on the fitted A_p exponents, the alternative BMAD ratio would appear appropriate only for the Chinese adolescent boys. The traditional BMD ratio would appear more appropriate for the Chinese adolescent

girls. Indeed, by dividing BMC by $(A_p)^{1.5}$, the BMAD ratio will "overadjust" the girls' BMC for differences in projected bone size and thus underestimate the BMAD of the taller girls. However, by including the projected bone area A_p as well as other confounding variables as covariates in a log-linear regression or ANCOVA, the recommended analysis will automatically adjust or scale BMC for differences in projected bone size and other confounding variables for the particular population being studied. Hence, the necessity to speculate as to the theoretical value of the exponent of A_p, although interesting, becomes redundant and any inference made about population or lifestyle differences on bone density will not be invalidated by any systematic changes in either bone size, body size, age, and/or maturation.

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