# Nutritional Supplementation During Early Childhood and Bone Mineralization During Adolescence[1,2]

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**ABSTRACT** To assess the long-term impact of nutritional supplementation on bone mineralization during adolescence, we studied 356 Guatemalan adolescents who participated from birth to 7 y of age in a controlled supplementation trial. Bone mineralization of the distal radius was assessed using single photon absorptiometry. Children who consumed more cumulative energy from the supplement during childhood had greater bone mineral content, bone width and bone mineral density during adolescence than those who consumed less energy. The associations remained after controlling for each subject's age and gender, and for the type of supplement consumed, but became statistically nonsignificant after adjusting for weight and stature. Because intake of supplement also was associated positively with weight and stature during adolescence, it is concluded that supplementing malnourished children can have a demonstrable long-term impact on bone mineralization, but that the effects are probably not beyond those due to improvements in overall somatic growth associated with supplementation. J. Nutr. 125: 1104S–1110S, 1995.

INDEXING KEY WORDS:

• *bone mineralization* • *nutritional supplementation* • *adolescence* • *malnutrition*

Adult levels of bone mineralization are largely achieved during the first two decades of life (Garn and Wagner 1969, Newton-John and Morgan 1971). Consequently, there is considerable interest in identifying determinants of this process in childhood and adolescence. Malnutrition is associated with low levels of bone density, diminished cortical bone and delays in skeletal maturation (Himes 1978, Himes et al. 1975, Martorell et al. 1979). Dietary interventions can enhance bone mineralization and skeletal maturation in infants and children who are undernourished in the short-term (Guzmán et al. 1965, Himes et al. 1990, Martorell et al. 1979), but the long-term permanency of such improvements is unknown.

From 1969 to 1977, the Institute of Nutrition of Central America and Panama (INCAP) conducted a longitudinal study of child growth and development in four rural communities in Guatemala (Martorell et al. 1995a). As part of this study, free food supplements were provided on demand to all inhabitants in the four communities. Findings from this study showed that early nutritional intervention can improve significantly the physical growth and development, bone growth and skeletal maturation of mild to moderately malnourished infants and children (Himes et al. 1990, Martorell et al. 1979, Schroeder et al. 1995).

In 1988–89, the former participants of the INCAP longitudinal study, by then adolescents and young adults, were the subjects of a follow-up study. This has provided a unique opportunity to assess the long-term impact of an intervention designed to improve the growth and development of malnourished children.

Specifically, the objective of the analyses presented here was to determine whether there is an effect of early nutritional supplementation on bone mineralization during adolescence. Further, because some evidence indicates that enhancement in bone mineralization may be independent of other more general so-

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matic and maturational responses to supplementation (Himes 1978, Himes et al. 1990), a secondary objective was to determine if there is evidence of a long-term, bone-specific response to supplementation, beyond what may be expected from concurrent somatic responses in body size.

## MATERIALS AND METHODS

The design and methods of the original INCAP longitudinal study have been described in detail elsewhere (Martorell et al. 1995a); thus, only details of the study pertinent to the analyses presented here are described. Two supplements were provided on demand in four rural communities in Guatemala; two of the villages received Atole, a high-caloric, high-protein drink, whereas the other two villages received Fresco, a low-caloric, no-protein drink. Also, Atole contained calcium and phosphorus whereas Fresco did not contain these minerals. Both supplements contained identical concentrations of iron, fluoride and some vitamins. Villagers were allowed to consume as much or as little supplement as they desired, and consumption was measured to the nearest 10 mL on a daily basis for all pregnant and/or lactating mothers and children 0–7 y of age. The growth and development of children during the first 7 y of age were studied in all subjects who were ≤7 y of age in 1969, when the study began, and in all children born into the study from 1969 to 1977, when the study ended.

The follow-up study, which began in 1988, was a cross-sectional follow-up of participants from the four study villages (Martorell et al. 1995a). Bone mineralization was measured on a subsample of 372 healthy adolescents and young adults stratified by age, gender and village, who had been exposed to nutritional supplementation during early childhood and who agreed to participate in the assessments of physical performance (for details, see Haas et al. 1995). At the time of examination, the subjects were 11—27 y of age. Measurements of bone mineral concentration (BMC), radial bone width (BW) and bone density (BD = BMC/BW) were made at the one-third distal site using a Norland Model 2780 Digital Bone Densitometer (Fort Atkinson, WI). The bone measures were obtained using single-photon absorptiometry from a $^{125}$I source (Sorenson and Camerson 1967). Such measures are highly correlated with body calcium and with skeletal weight and are an appropriate method for assessing bone mineralization in the appendicular skeleton (Mazess 1983). Anthropometric dimensions, including stature and weight, were taken by trained observers using recommended methods (Lohman et al. 1988). The exact age of each subject was known from the birth records of the longitudinal study.

Of those 372 subjects examined, the files of 11 subjects were found to have missing data for either height, weight or bone mineralization measures and the files of 5 subjects could not be linked with those from the original INCAP longitudinal study and, therefore, no information was available on supplement intakes during early childhood. The analyses presented here relate to those 356 subjects for whom complete data on all variables of interest were available.

The effects of early nutritional supplementation on adolescent bone mineralization, weight and stature were analyzed relative to the total cumulative amount of energy consumed from the supplements by the subjects during the first 7 y of their lives. Cumulative intakes were determined in part by age; for example, those born in 1962 could only have been supplemented in their seventh year of life whereas those born in 1969 could have received supplement from birth to 7 y. Cumulative intakes were also determined by individual patterns of attendance and consumption (Schroeder et al. 1992). Because of the upwardly skewed nature of the distribution of values of cumulative energy intake of supplement, a square root transformation was used for all analyses. Preliminary analyses demonstrated that such transformation reduced skewness and kurtosis to acceptable levels. The five outcome measures were transformed to gender specific z-scores (standard deviation scores) to allow for comparisons of the magnitude of the response to energy supplementation among outcomes. The results are presented in standard deviation units for each outcome measure per 100 square root of kcal, ($\text{SD}/100\sqrt{\text{kcal}}$) which can be thought of as the effects on status during adolescence of consuming ~10,000 kcal/41,840 kJ of supplemental energy during childhood.

The effects of early supplemental energy intake on adolescent bone mineralization, weight and stature were examined using the multiple linear regression techniques of Statistical Analysis Systems (SAS Institute 1992a) to control for covariates and potentially confounding variables. Random effects models (SAS Institute 1992b) were developed to estimate the unadjusted effects of energy supplementation on each of the three bone measures, weight and stature and the effects after adjusting for age, gender (males = 1, females = 0) and supplement type (Atole = 1, Fresco = 0). Use of these models allowed us to treat supplement type as a random variable. Finally, weight and/or stature were included in the bone mineralization models to address the secondary objective of testing for the presence of a bone-specific response to supplementation. Effects were considered statistically significant at $P < 0.05$.

Various functional forms of all variables were considered. For example, we compared the fit of gender-specific simple linear and curvilinear models relating each subject's age and the five outcome measures. Although in general the curvilinear relationships provided better fits to the data, the addition of either weight or height to the bone mineralization models removed the effects of the higher-order age terms and interactions, suggesting that the higher-ordered terms for age were colinear with height and weight and thus, their inclusion would "over-control" for the effects of age on bone mineralization status in the models. Therefore, gender-specific linear terms for age (ie., age + gender + gender*age) were fit in the models for bone mineralization, and the higher order terms, $age^2$ and $age^2$*gender were added to the models to describe age-related variations in weight and stature. Interactions between amount and type of supplement consumed also were evaluated for inclusion in the models. Because we were interested in evaluating the potential importance of these interactions, they were considered statistically significant at $P < 0.10$.

## RESULTS

Presented in **Table 1** are descriptive characteristics of the study sample stratified by supplement type. In general, there are few significant differences in the variables associated with supplement type. The means for most outcome measures appear greater among adolescents who consumed Atole during childhood, but the differences reach statistical significance ($P < 0.05$) for stature and radial bone width only among girls.

There are few adolescent samples available that provide mean radial density measures that may be used as comparisons. In **Figure 1**, the means for bone mineral content (a,b) and bone density (c,d) are plotted against age for boys (a,c) and for girls (b,d) with data for German adolescents (Runge et al. 1980). Guatemalan boys and girls have less bone mineral content and bone density compared with German adolescents but the overall pattern of age-associated changes appears similar. The Guatemalan adolescents approximate the fifth percentile of the NCHS reference data for stature and weight (Martorell et al. 1995b).

Effects of energy supplementation on bone mineralization, weight and stature are presented in **Table 2** with the genders pooled. Presented in the first column, are estimates of the unadjusted effect of supplementation on each outcome measure. Again, the effects on each variable are measured in standard deviation units per 100 square root of kcal, ($SD/100\sqrt{kcal}$) which translated back, means the consumption of ~10,000 kcal/41,840 kJ of supplement during childhood. As shown, early energy supplementation significantly increased each of the outcome measures to similar degrees.

In the next column of Table 2, are estimates of the effects of supplement consumed on each outcome variable after adjusting for each subject's gender and age. As stated earlier, the specification of the age variables in the models depended on the outcome of interest (see Materials and Methods for specification). The effects of supplementation are diminished by this adjustment, but significant effects of supplementation on bone mineralization can still be demonstrated. The effects of supplementation on weight and stature are reduced to a greater extent by this adjustment, and remain statistically significant at the 0.05 level only for stature. The *P* level for the coefficient in the weight model is 0.08, however, and is still suggestive of a supplementation effect.

Finally, in the third column of Table 2, are estimates of the effect of supplement consumed on bone mineralization, weight and stature after adjusting for the type of supplement consumed during early childhood. Differences in bone mineralization associated with village of residence (as opposed to supplement type, per se) were observed; however, after adjustment, statistically significant effects of the amount of calories from supplement consumed during childhood on bone mineralization during adolescence are still observed, irrespective of supplement type. The magnitude of these effects is similar

**TABLE 1**

***Descriptive characteristics of the sample by gender and type of supplement*[1]**

| | Boys | | Girls | |
|---|---|---|---|---|
| Characteristics | Atole | Fresco | Atole | Fresco |
| *n* | 100 | 88 | 79 | 89 |
| Age *y* | 16.7 ± 0.4 | 16.7 ± 0.4 | 16.8 ± 0.4 | 16.6 ± 0.4 |
| Weight *kg* | 44.9 ± 1.1 | 43.3 ± 1.2 | 41.8 ± 0.9 | 42.0 ± 1.0 |
| Stature *cm* | 153.6 ± 1.2 | 151.4 ± 1.3 | 148.6 ± 0.8* | 145.7 ± 0.8 |
| BMC *g/cm* | 0.78 ± 0.02 | 0.77 ± 0.02 | 0.66 ± 0.01 | 0.64 ± 0.01 |
| BW *cm* | 1.22 ± 0.02 | 1.18 ± 0.02 | 1.06 ± 0.01* | 1.03 ± 0.01 |
| BD *g/cm²* | 0.63 ± 0.01 | 0.64 ± 0.01 | 0.61 ± 0.01 | 0.62 ± 0.01 |
| Supplement *kcal* | 161,531 ± 17,063* | 42,346 ± 4,514 | 161,493 ± 20,911* | 50,979 ± 5,670 |

[1] Values are means ± SE. * $P < 0.05$ (Atole versus Fresco). Abbreviations used: BMC, bone mineral content; BW, bone width; BD, bone density.

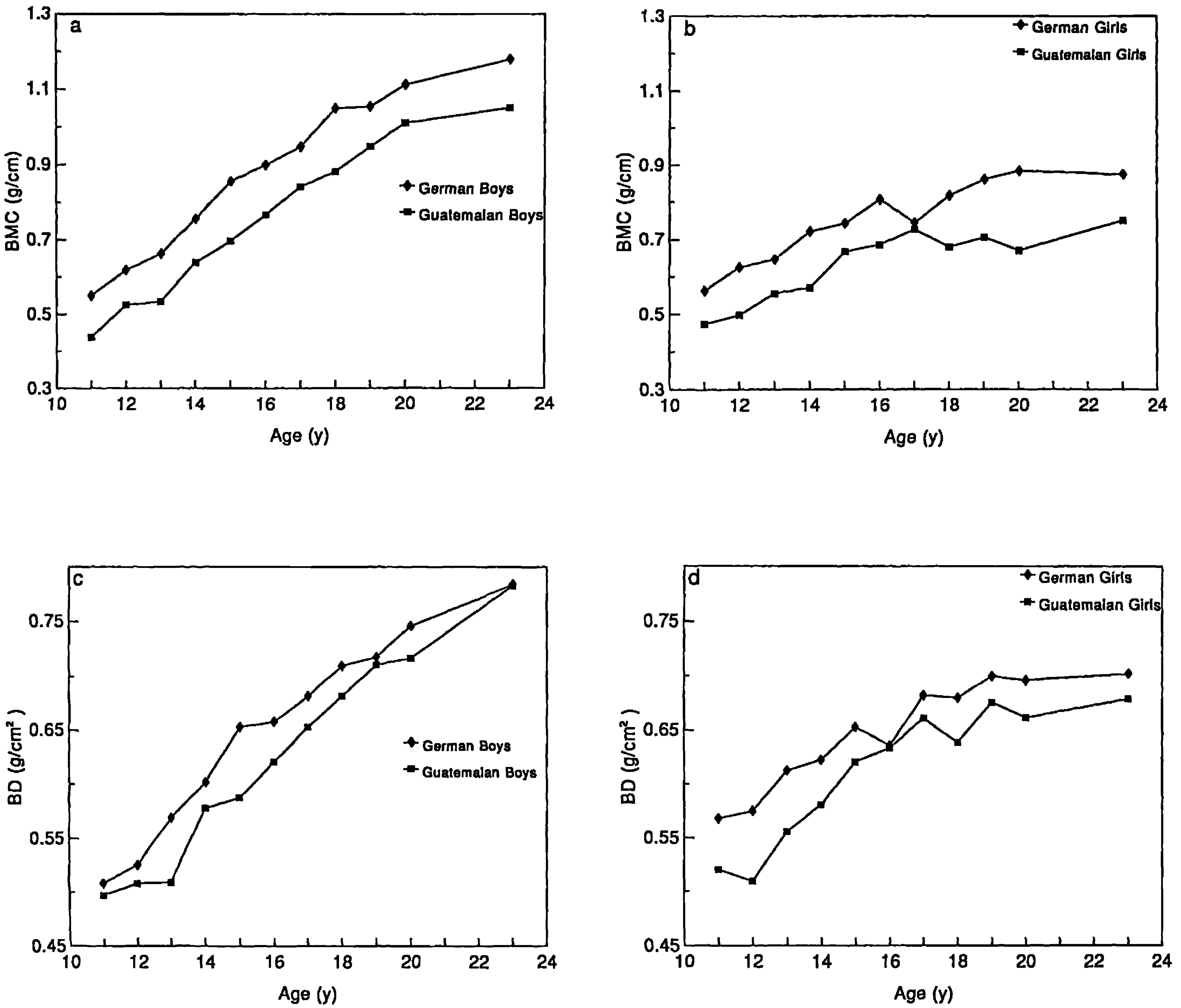


***FIGURE 1*** Bone mineral content (BMC) and bone density (BD) in Guatemalan and German boys and girls (Runge et al. 1980). Values are the means of BMC (a,b) and BD (c,d) over 1-y age intervals plotted at each interval midpoint for boys (a,c) and girls (b,d) separately.

across the three bone measures (~0.06–0.09 SD/100 $\sqrt{\text{kcal}}$). As shown, the effects of supplementation on weight and stature become statistically nonsignificant for both weight and stature after adjusting for type of supplement consumed.

To test for bone-specific effects of the supplementation, weight and stature, were added, separately and in combination, to the regression models (**Table 3**). As shown here, the effects of supplement on bone mineralization are no longer statistically significant.

Interaction terms between supplement type and cumulative supplemental energy intake were not statistically significant in any models, again supporting the conclusion of energy effects per se, excluding effects due to protein, calcium or phosphorus.

## DISCUSSION

Our results suggest that the amount of energy consumed from supplement during early childhood had a significant and positive effect on the bone mineralization of these Guatemalan adolescents and young adults. Although studies have related short-term improvements in diet and nutritional status to enhanced bone growth, mineralization, and skeletal maturation

**TABLE 2**

***Effects of supplementation during early childhood on bone mineralization, weight and stature during adolescence***[1]

| Outcome measures (SD units) | Supplementation effects (100√kcal) | | |
|---|---|---|---|
| | Unadjusted[2] | Adjusted[3] | Adjusted[4] |
| BMC | 0.198 ± 0.026* | 0.072 ± 0.019* | 0.076 ± 0.020* |
| BW | 0.182 ± 0.026* | 0.097 ± 0.024* | 0.094 ± 0.024* |
| BD | 0.152 ± 0.022* | 0.040 ± 0.015* | 0.058 ± 0.016* |
| Weight | 0.212 ± 0.025* | 0.035 ± 0.020 | 0.033 ± 0.021 |
| Stature | 0.220 ± 0.025* | 0.054 ± 0.023* | 0.028 ± 0.025 |

[1] Values are the beta coefficients ± SE for the supplementation terms estimated using linear regression. All are expressed in SD/100√kcal units. * $P < 0.05$. Abbreviations used: BMC, bone mineral content; BW, bone width; BD, bone density; SD, standard deviation.

[2] Unadjusted effect of supplementation.

[3] Effect adjusted for each subject's gender, age (see text).

[4] Effect adjusted for gender, age and for type of supplement consumed.

of malnourished children (Guzmán et al. 1965, Himes et al. 1990, Martorell et al. 1979), we are unaware of other studies reporting positive effects of nutritional supplementation during early childhood on bone mineralization during adolescence and young adulthood.

The magnitude of the supplementation effects diminished, but remained significant after controlling for the three most important confounding factors: age, gender and supplement type. This is an important point, because these three factors together account for 33–65% of the variation in bone mineralization in these data. Further, because the correlations between age and body size are high (0.6–0.8) in this age group, the presence of age in the model also controls partially for variation in bone mineralization associated with body size. The persistence of the effects of energy supplementation after controlling for supplement type is important in light of the fact that only Atole contained protein, calcium and phosphorus—nutrients often cited for their important roles in bone development. Available evidence indicates no major deficiencies in calcium or phosphorus in this population (Flores 1971, INCAP 1969, Lechtig et al. 1972).

The effects of amount of supplemental energy consumed on bone mineralization became statistically nonsignificant after controlling for weight and stature at adolescence. The amount of supplemental energy consumed was associated positively with weight and with stature in these adolescents and young adults, after controlling for age and gender, but not supplement type. These results suggest that the effects of supplemental energy on bone mineralization were operating through the increases in weight and stature associated with supplementation.

The interpretation of these results also did not change in further analyses ($n = 352$) considering maturational age (deviation in RUS age from chronological age) as well as chronological age in the models. Further, analyses by Pickett et al. (1995) and Khan et al. (1995) suggest no overall effects of supplementation on skeletal maturation or menarcheal status respectively. Thus, although maturation and menarcheal status influence bone mineralization during adolescence apart from chronological age (Himes and Huang 1993), these results suggest that the observed effects of supplementation on bone mineralization are not likely to be operating through changes in maturation related to supplementation. From this, we conclude that the observed effects of energy supplementation on bone mineralization were probably no greater than those associated with the overall somatic growth response in body size associated with supplementation and were probably mediated by this general somatic response to supplementation.

Two methodological limitations of the study, however, should be mentioned. These relate to the lack of randomization at the level of the individual in the design of the longitudinal study and the selection of subjects for the bone mineralization substudy.

In the longitudinal study, the subjects were not randomly assigned to differing levels of supplementation; that is, the children chose how much supplement they would consume (Schroeder et al. 1992). Thus, the positive relationships between amount of supplement consumed during early childhood and bone mineralization during adolescence could result from selection bias if better-off children (i.e., larger children with bigger, more dense bones) chose to consume more supplement. Results from analyses of the longitudinal study have provided arguments against this possibility by demonstrating that rates of growth in weight and length were associated positively with level of sup-

**TABLE 3**

***Effects of supplementation during early childhood on bone mineralization during adolescence: effects adjusted for current weight and stature***[1]

| Bone status measures (SD units) | Supplementation effects (100√kcal) | | |
|---|---|---|---|
| | Adjusted[2] | Adjusted[3] | Adjusted[4] |
| BMC | 0.013 ± 0.016 | 0.015 ± 0.017 | 0.024 ± 0.018 |
| BW | 0.020 ± 0.023 | 0.017 ± 0.022 | 0.005 ± 0.022 |
| BD | 0.019 ± 0.014 | 0.024 ± 0.015 | 0.015 ± 0.014 |

[1] Values are the beta coefficients (±SE) for the supplementation terms estimated using linear regression. All are expressed in SD/100√kcal units. * $P < 0.05$. Abbreviations used: BMC, bone mineral content; BW, bone width; BD, bone density; SD, standard deviation.

[2] Adjusted for each subject's gender, age, the type of supplement consumed and weight.

[3] Adjusted for each subject's gender, age, the type of supplement consumed and stature.

[4] Adjusted for each subject's gender, age, the type of supplement consumed and weight and stature.

plementation after controlling for important confounding factors such as initial body size, socioeconomic status, home diet and diarrheal diseases (Schroeder et al. 1995). The limitations of this type of analysis are discussed in greater detail by Habicht et al. (1995).

Although the preceding arguments lend credence to the interpretation of the results as effects of energy supplementation on bone mineralization, it is important to note, that this selection bias issue could have been addressed directly if we had controlled for variation in bone mineralization during early childhood. This was not possible because such bone measures were not collected during the longitudinal study. Measures of the dimensions of the second metacarpal, however, were available for the majority of the subjects ($n$ = 314; median age of measure = 3 mo), and from these measures, estimates of the bone cortical area can be made (Garn 1970). This area estimate has been shown to be closely related to bone mineral content (Horsman and Kirby 1972). When the regression models were fit again, controlling for this indicator of early childhood bone mineral content, the basic conclusions drawn from the analyses remained the same, although, in these analyses, there was some evidence of bone-specific effects of supplementation on both BMC and BD ($P$ levels of 0.05–0.10).

During the follow-up study, bone mineralization measures were taken on only a subsample of the subjects. The subjects were selected based on their age, gender, village and willingness to participate in another substudy on physical work capacity (Haas et al. 1995). Given that this sample of adolescents and young adults may be different from the rest of the follow-up sample, sample-selection bias could exist. Therefore, analyses were performed comparing the weight, stature, and intake of supplement of subjects in the follow-up study who did, or did not, have bone measurements taken. Subjects who participated in the bone mineralization substudy were younger, lighter and shorter, but had consumed the same amount of supplemental energy during early childhood as compared with the rest of the subjects in the follow-up study. Further analyses demonstrated that the groups were not different in weight, but were shorter after controlling for age, gender and supplement type. The positive relationship between the amount of supplemental energy consumed during childhood and weight and stature during adolescence was not different between the groups for weight, but was for stature, with the bone group having a significantly more positive effect of supplementation. In summary, as suggested previously by Rivera et al. (1992), these analyses indicate that the subjects chosen for the subsample were not representative of all subjects participating in the follow-up study, and were, perhaps, those who responded more to supplementation. Thus, the magnitude of the supplementation effects on bone mineralization presented here may be somewhat overstated.

Despite these limitations, the results provide important evidence that participation in nutritional supplementation programs can have demonstrable long-term nutritional benefits on bone mineralization for mild to moderately malnourished children. Supplementation trials of mild to moderately malnourished children using different designs and methodologies have been conducted in other populations in developing countries (Gopalan et al. 1973, Mora et al. 1981). Following up these participants could provide further evidence of the long-term impact of food supplementation programs and provide further support for the results presented here.

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