# Gender-Dependent Skeletal Effects of Vitamin D Deficiency in a Younger Generation

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**Context:** The major health threats caused by vitamin D deficiency in the young generation have not been fully elucidated.

**Objective:** The aim of this study was to investigate skeletal and nonskeletal effects of vitamin D deficiency and to study the optimal level of serum 25-hydroxyvitamin D [25(OH)D] in young people.

**Design and Setting:** The Fourth Korea National Health and Nutrition Examination Surveys (KNHANES IV) was conducted in 2008–2009.

**Participants:** A total of 4276 people (1926 men and 2350 women) aged 10–40 yr were selected from 16 administrative districts of South Korea.

**Main Outcome Measures:** We measured age-specific changes in bone mineral density (BMD) according to serum 25(OH)D.

**Results:** Serum 25(OH)D was less than 25 nmol/liter in 18.8% of participants, 25 to less than 50 nmol/liter in 50.0%, 50 to less than 75 nmol/liter in 27.0%, and 75 nmol/liter or greater in 4.2%. Vitamin D deficiency was more frequent in women than in men. There were gender differences in the skeletal effects of vitamin D deficiency. In men between 10 and 22 yr old, BMD was significantly higher in the vitamin D-sufficient group, and in men between 23 and 40 yr old, a positive correlation between serum 25(OH)D and BMD was observed. However, in women, we could not find significant differences in BMD according to vitamin D status. Vitamin D deficiency in younger generations had no remarkable effects on most nonskeletal parameters or on the prevalence of concomitant diseases except for rheumatoid arthritis.

**Conclusions:** Vitamin D plays an essential role in skeletal health of young people. Moreover, the presence of gender-dependent skeletal effects was an important observation of this study. Reassurance of serum 25(OH)D up to 20–30 ng/ml or higher is necessary, especially during the modeling phase in men. **(*J Clin Endocrinol Metab* 97: 1995–2004, 2012)**

Recent epidemiological studies have suggested that vitamin D deficiency is prevalent in all age groups and has become a major health concern (1). However, the supply of vitamin D from dietary sources is limited, and biochemical synthesis of vitamin D from sunlight exposure is no longer adequate due to changing lifestyles and concerns for skin cancer (2, 3). Therefore, fortification of daily food products or vitamin D supplements should be considered around the world.

Maximizing peak bone mass (PBM) in childhood should offer protection against bone loss later in life, which may lead to osteoporosis. This bone loss is characterized by compromised bone strength and increases in the likelihood of fractures, which are serious health problems

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Abbreviations: BMD, Bone mineral density; CSA, cross-sectional area; CSMI, cross-sectional moment of inertia; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; 25(OH)D, 25-hydroxyvitamin D; PBM, peak bone mass; VDR, vitamin D receptor.

in the elderly. It has been estimated that a 10% increase in peak bone mineral density (BMD) could delay the onset of osteoporosis by 13 yr (4). The major determinants of PBM include genetic factors, gender, endocrine status (such as sex hormones, GH, and IGF-I), calcium intake, exercise, and so on (5). After reaching PBM, bone mass gradually decreases in men, whereas it is maintained until perimenopausal age in women. Recently, we reported that vitamin D deficiency is a greater threat to the younger generation in Korea; in 65.0% of men and 79.9% of women aged 20–29 yr, serum 25-hydroxyvitamin D [25(OH)D] was less than 20 ng/ml (6). However, few studies have evaluated the major health threats caused by vitamin D deficiency in the youth or the differences in skeletal and nonskeletal health across different age groups.

The optimal level of serum 25(OH)D is still heavily debated. The Institute of Medicine (IOM) reports stressed that a serum 25(OH)D level of 20 ng/ml is sufficient to ensure bone health, but the results for nonskeletal benefits are inconclusive (7). The impact of recent reports on the Dietary Reference Intakes for calcium and vitamin D from the IOM led physicians to decrease their vitamin D recommendations to patients. Contrary to IOM recommendations, The Endocrine Society released new guidelines in 2011 to treat vitamin D deficiency. The key points from The Endocrine Society's clinical guidelines are that a minimum serum 25(OH)D level of 30 ng/ml (rather than 20 ng/ml) is recommended and to guarantee sufficiency between 40 and 60 ng/ml for both children and adults (2). Some experts insist that the Recommended Daily Allowance, by definition, should meet the needs of 97.5% of the population, and a skeletal need at higher levels should be fulfilled.

Therefore, we hypothesized that vitamin D plays an essential role in skeletal and nonskeletal health in young people. To better understand the optimal level of serum 25(OH)D, we analyzed BMD, geometric indices, biochemical parameters, metabolic profiles including homeostatic model assessment of insulin resistance (HOMA-IR), and associated diseases. We found a gender difference in the skeletal effects of vitamin D deficiency. Moreover, although the correlation coefficient was low, there was a positive relationship between serum 25(OH)D and BMD. Also, small additional benefits of BMD greater than 30 ng/ml were found only in males aged 10–22 yr old.

## Subjects and Methods

### Study participants

This study was based on data acquired from the second (2008) and third years (2009) of the Fourth Korea National Health and Nutrition Examination Surveys (KNHANES IV), which was conducted from July 2007 to December 2009. The KNHANES was a cross-sectional and national survey conducted by the Division of Chronic Disease Surveillance, Korea Centers for Disease Control and Prevention, starting in 1998. This survey was composed of a health interview survey, a nutrition survey, and a health examination survey. Data were collected by means of household interviews and direct standardized physical examinations conducted in mobile examination centers. The 16 administrative districts where this survey was performed include both urban and rural areas. Seoul (the capital city of South Korea) and the surrounding metropolitan area (Gyeonggi), and six other metropolitan cities (Busan, Incheon, Gwangju, Daejeon, Daegu, and Ulsan) of South Korea comprised the urban areas. The rest of the regions (Gangwon, Chungbuk, Chungnam, Gyeongbuk, Gyeongnam, Jeonbuk, Jeonnam, and Jeju) were rural areas. Almost all regions of South Korea are located between 33°N and 38°N of latitude; thus, the latitude of area was not considered in this study. Seasons were classified as spring (March to May), summer (June to August), fall (September to November), and winter (December to February). The samples were collected throughout the four seasons as follows: 16.6% in spring, 31.4% in summer, 30.3% in fall, and 21.8% in winter. Also, there was no gender difference among the seasons in which the samples were collected.

Among the 16 administrative districts, the 500 survey regions were drawn from the population and housing census. Based on the 2005 population and housing census in South Korea, the sampling frame was made. A stratified, multistage probability sampling design was used to select household units. For the KNHANES IV, nationwide stratified sampling was conducted; there were more than 260,000 primary sampling units each year, and 200 sampling frames from primary sampling units were randomly sampled. Participants were classified according to age (child, adult, and elderly), gender, type of housing (apartment, nonapartment), and residential area (urban, rural), and in each stratum, survey clusters were selected. Twenty-three households within a cluster were sampled using a systemic sampling method. In the second (2008) and third years (2009) of the KNHANES IV, 25,250 individuals were sampled, and 19,841 subjects participated in this survey; the response rate was about 82%. Among those who participated in the survey between January 2008 and December 2009, BMD values were available for 10,730 participants: 4796 men and 5934 women. Among them, we selected 4276 participants (mean age 28.96 ± 8.15 yr)—1926 men and 2350 women aged 10–40 yr. The mean age of menarche was 13.26 ± 1.45 yr, and 70.9% of the women had their first period at ages between 12 and 14. Participants with a history of osteoporosis treatment were excluded. Serum 25(OH)D levels were obtained from all 16 administrative districts of South Korea and were available for all participants. These participants signed an informed consent form.

### Biochemical analysis

During the survey, blood samples were collected from all participants for biochemical analysis. Fasting plasma glucose, total cholesterol, triglyceride, and high-density lipoprotein (HDL)-cholesterol levels were determined by enzymatic methods using commercially available kits: Pureauto S GLU, Pureauto SCHO-N, Pureauto S TG-N, and Cholestest N HDL (Daiichi Pure Chemicals, Tokyo, Japan) and a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). Insulin levels were measured using a gamma counter

(1470 Wizard; Perkin-Elmer, Turku, Finland) with an immunoradiometric assay (Biosource, Nivelles, Belgium). The intra- and interassay coefficients of variation were 1.6–2.2 and 6.1–6.5%, respectively. Serum 25(OH)D levels were measured using a gamma counter (1470 Wizard, Perkin-Elmer) with an RIA (DiaSorin, Stillwater, MN). The intra and interassay coefficients of variation were 2.9–5.5 and 6.3–12.9%, respectively. We converted 25(OH)D levels to nanomoles per liter, multiplying them by 2.5.

## Bone densitometry and geometric analysis

BMD was measured at the left hip in the posteroanterior projection using dual x-ray absorptiometry equipment (QDR4500A; Hologic Inc., Waltham, MA) located in mobile examination centers. As described previously, we further analyzed bone structural properties using the Hip Structure Analysis program included in the APEX software of Hologic Inc. The measurements by the Hip Structure Analysis program included cross-sectional area (CSA), cross-sectional moment of inertia (CSMI), buckling ratio, and mean cortical thickness in each of the narrow neck regions (8).

## Statistical analysis

Statistical analyses were conducted using PASW version 18.0 for Windows (SPSS Inc., Chicago, IL) and SAS version 9.2 (SAS Institute Inc., Cary, NC). Student's *t* test and one-way ANOVA were used to compare differences in mean values of baseline parameters among the groups. To investigate differences in skeletal and nonskeletal outcomes according to the degree of vitamin D deficiency, serum 25(OH)D levels were categorized into four groups: less than 25 nmol/liter, 25 to less than 50 nmol/liter, 50 to less than 75 nmol/liter, and 75 nmol/liter or greater. We used the group with serum 25(OH)D levels 50 to less than 75 nmol/

**TABLE 1.** Baseline characteristics

| Characteristic | Total | Men | Women |
|---|---|---|---|
| n | 4276 | 1926 | 2350 |
| Age (yr) | 28.96 ± 8.15 | 28.61 ± 8.34 | 29.24 ± 7.98 |
| Height (cm) | 165.49 ± 9.03 | 172.26 ± 7.51 | 159.95 ± 5.82 |
| Body weight (kg) | 62.48 ± 13.33 | 70.16 ± 12.87 | 56.18 ± 9.98 |
| Waist circumference (cm) | 76.75 ± 10.62 | 80.97 ± 10.28 | 73.29 ± 9.59 |
| Body mass index (kg/m$^2$) | 22.66 ± 3.67 | 23.55 ± 3.62 | 21.92 ± 3.56 |
| Systolic blood pressure (mm Hg) | 106.13 ± 12.97 | 112.14 ± 13.34 | 101.61 ± 10.66 |
| Diastolic blood pressure (mm Hg) | 70.56 ± 11.19 | 75.24 ± 11.47 | 67.03 ± 9.56 |
| Calcium intake per day (mg) | 487.34 ± 313.34 | 555.86 ± 344.90 | 438.72 ± 278.92 |
| Current smoker (%) | 25.2 | 46.1 | 8.1 |
| Regular walking (%)[a] | 46.3 | 49.5 | 43.7 |
| Regular exercise (%)[b] | 26.0 | 29.9 | 22.9 |
| Serum 25(OH)D (nmol/liter) | 44.15 ± 15.65 | 47.05 ± 16.65 | 41.80 ± 14.35 |
| <25 nmol/liter (%) | 18.8 | 14.2 | 22.6 |
| 25 to <50 nmol/liter (%) | 50.0 | 48.0 | 51.6 |
| 50 to <75 nmol/liter (%) | 27.0 | 31.5 | 23.3 |
| ≥75 nmol/liter (%) | 4.2 | 6.3 | 2.5 |
| Fasting glucose (mg/dl) | 90.69 ± 13.93 | 91.82 ± 14.00 | 89.76 ± 13.81 |
| Insulin (μIU/ml) | 10.30 ± 5.56 | 10.71 ± 6.43 | 9.96 ± 4.70 |
| HOMA-IR[c] | 2.34 ± 1.50 | 2.47 ± 1.76 | 2.23 ± 1.22 |
| Total cholesterol (mg/dl) | 173.68 ± 31.85 | 177.57 ± 34.39 | 170.48 ± 29.23 |
| HDL-cholesterol (mg/dl) | 53.82 ± 12.20 | 50.01 ± 10.94 | 56.95 ± 12.29 |
| Triglyceride (mg/dl) | 110.93 ± 96.13 | 139.32 ± 117.59 | 87.67 ± 65.45 |
| LDL-cholesterol (mg/dl) | 105.09 ± 28.33 | 109.36 ± 26.92 | 100.64 ± 29.10 |
| Total alkaline phosphatase (U/liter) | 272.18 ± 211.95 | 321.56 ± 247.69 | 230.28 ± 164.88 |
| Serum creatinine (mg/dl) | 0.89 ± 0.29 | 1.04 ± 0·27 | 0·77 ± 0.25 |
| Lumbar spine (g/cm$^2$) | 0.97 ± 0.13 | 0.97 ± 0.14 | 0.97 ± 0.13 |
| Femur trochanter (g/cm$^2$) | 0.67 ± 0.09 | 0.70 ± 0.09 | 0.65 ± 0.08 |
| Femoral neck (g/cm$^2$) | 0.81 ± 0.13 | 0.87 ± 0.13 | 0.77 ± 0.11 |
| Femur total (g/cm$^2$) | 0.94 ± 0.13 | 1.00 ± 0.13 | 0.90 ± 0.11 |
| FN cortical thickness (mm) | 1.90 ± 0.31 | 2.00 ± 0.33 | 1.80 ± 0.26 |
| FN CSA (cm$^2$) | 3.13 ± 0.62 | 3.54 ± 0.60 | 2.80 ± 0.41 |
| FN CSMI (cm$^4$) | 3.00 ± 1.09 | 3.83 ± 0.99 | 2.32 ± 0.56 |
| FN buckling ratio | 9.68 ± 2.00 | 9.83 ± 2.06 | 9.55 ± 1.93 |

Data are expressed as mean ± SD, unless indicated otherwise. All analyses presented here include data of a random subgroup of participants. Blood pressure data were available for 1248 participants, calcium intake per day for 3631 participants, total alkaline phosphatase for 3028 participants, serum creatinine for 1248 participants, and LDL-cholesterol for 827 participants. BMD was available for 4258, and geometric index was available for 2876 participants. LDL, Low-density lipoprotein; FN, femur neck.

[a] Regular walking was defined as more than a 30-min walk for more than five times per week, regardless of indoor or outdoor walking.

[b] Regular exercise was defined as moderate or severe exercise on a regular basis, regardless of indoor or outdoor exercise (more than 30 min at a time and more than five times per week in case of moderate exercise such as swimming slowly, tennis doubles, volleyball, badminton, table tennis, and carrying light objects; more than 20 min at a time and more than three times a week in case of severe exercise such as running, climbing, cycling fast, swimming fast, football, basketball, jump rope, squash, tennis singles, and carrying heavy objects).

[c] HOMA-IR was calculated with insulin and fasting glucose level as: fasting glucose (milligrams per deciliter) × insulin (μIU per milliliter)/405.

liter as the reference group. Spline plots with 95% confidence intervals and analysis of covariance, adjusted for possible confounding factors, such as age, body mass index, season, regular walking, and regular exercise, were performed to examine the relationship between serum 25(OH)D level and BMD. The criteria for season, regular walking, and regular exercise were the same as described by Choi *et al.* (6). The association between serum 25(OH)D itself and each BMD was determined by Pearson's correlation coefficient. Multivariate logistic regression analyses were used to examine odds ratio of concomitant disease between groups with 25(OH)D less than 50 and at least 50 nmol/liter, adjusted for age, sex, body mass index, and seasons. The $\chi^2$ test was used to inquire into the prevalence of concomitant diseases according to serum 25(OH)D levels. $P$ values $<0.05$ were considered statistically significant.

### Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

The baseline characteristics of all the participants are presented in Table 1. The average age was 28.61 ± 8.34 yr in men and 29.24 ± 7.98 yr in women. As previously reported, in the younger generation, vitamin D deficiency was more frequent in women than in men. The mean value of serum 25(OH)D was 47.05 ± 16.65 nmol/liter in men and 41.80 ± 14.35 nmol/liter in women. Moreover, serum 25(OH)D was less than 25 nmol/liter in 18.8% of subjects, 25 to less than 50 nmol/liter in 50.0%, 50 to less than 75 nmol/liter in 27.0%, and 75 nmol/liter or greater in 4.2%. Both total body fat mass and percentage were significantly

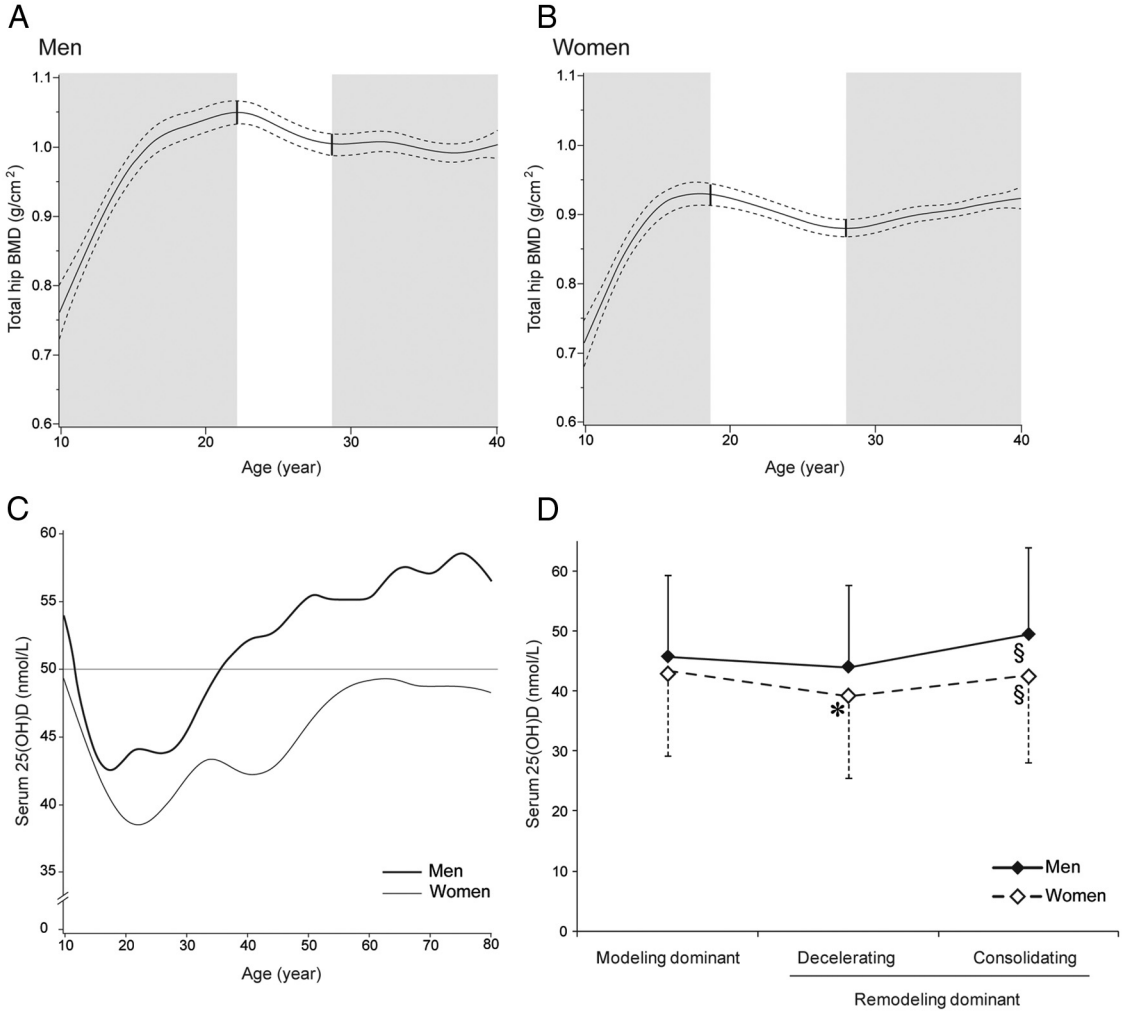


**FIG. 1.** BMD (A and B) and serum 25(OH)D (C and D) in young generation. In both sexes, BMD showed a "spooning pattern" with age (A and B). Based on the age-specific changes in BMD, the participants were divided into three age groups per gender: 10–22, 23–29, and 30–40 yr in men; and 10–19, 20–28, and 29–40 yr in women. Vitamin D deficiency was most frequent in young people (C). The phases were named the modeling phase, decelerating phase, and consolidating phase, respectively (D). The change in mean 25(OH)D level according to phase was similar to that of BMD. *, $P < 0.001$, compared with the modeling phase; §, $P < 0.001$, compared with the decelerating phase.

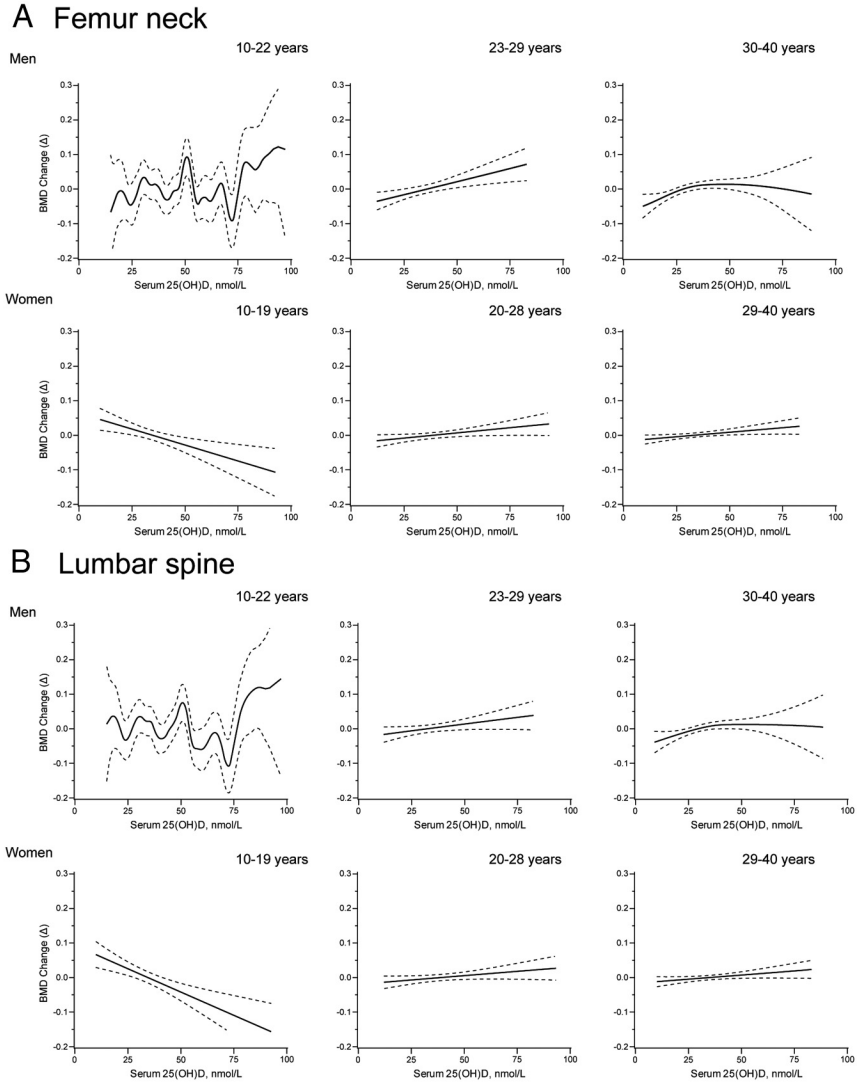


**FIG. 2.** Correlation between BMD and serum 25(OH)D according to three phases. For each phase, the BMD change (Δ) of the femur neck (A) and lumbar spine (B) varied according to the level of 25(OH)D. BMD (g/m$^2$) change (Δ) on the y-axis was compared with the mean BMD value (0.0) of each phase. *Dotted lines* represent 95% confidence intervals.

higher in women, whereas BMD and geometric indices were significantly higher in men, except for lumbar spine BMD.

## Age-related changes in BMD and serum 25(OH)D

Figure 1 demonstrates changes in BMD and mean serum 25(OH)D according to age. Interestingly, in both sexes, a "spooning pattern" of total hip BMD with age was shown in Fig. 1, A and B. In young men, BMD increased from age 10, reaching its highest level at age 22, then decreased, reaching its lowest level at age 29, after which it remained relatively constant until age 40. For young women, BMD changes showed similar trends, but a peak occurred at age 19 and the minimum at age 28. Based on these age-specific findings, we divided the participants into three age groups: 10–22, 23–29, and 30–40 yr in men, and 10–19, 20–28, 29–40 yr in women. The phases were named the modeling phase, decelerating phase, and consolidating phase, respectively. As shown in Fig. 1C, vitamin D deficiency was most frequent in the younger generation. Moreover, serum 25(OH)D, which had the lowest mean level in the decelerating phase, presented similar patterns in both sexes according to phase (Fig. 1D).

## Skeletal effects of vitamin D

As shown in Fig. 2A, in young men, there was no linear relationship between BMD change and serum 25(OH)D level in the modeling phase, after which femur neck BMD had a positive correlation with serum 25(OH)D (R = 0.14, $P$ = 0.002 in the decelerating phase; R = 0.10, $P$ = 0.003 in the consolidating phase). In women 20 yr or older, there was a weak positive correlation between femur neck BMD and serum 25(OH)D level (R = 0.08, $P$ = 0.04 in the decelerating phase; R = 0.06, $P$ = 0.03 in the consolidating phase); however, there seemed to be a negative association in the modeling phase (R = −0.17; $P$ = 0.002). In both sexes, these tendencies in femur neck BMD were similar to that in the lumbar spine BMD (Fig. 2B).

We further analyzed the mean BMD values in each group according to serum 25(OH)D level to evaluate the significance of the results obtained from the spline plots. Intriguingly, there were gender differences in the skeletal effects of vitamin D (Table 2). In males aged 10–22 yr, BMD was significantly higher in the group with 25(OH)D levels of at least 75 nmol/liter than in the reference 50–75 nmol/liter group; on the other hand, BMD in men aged 23 yr or older was significantly lower in the vitamin D-deficient group. In young women, there were no significant differences in BMD according to 25(OH)D. Also, no meaningful results were observed for any geometric indices except femur neck CSA in men (Table 2 and Supplemental Tables 1 and 2, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

## Nonskeletal effects of vitamin D

Anthropometric characteristics, biochemical parameters, and metabolic profiles including HOMA-IR according to serum 25(OH)D level are presented in Table 3.

**TABLE 2.** BMD and geometric index according to serum 25(OH)D level

| | Serum 25(OH)D (nmol/liter) | | | | | |
|---|---|---|---|---|---|---|
| | <25 | 25 to <50 | 50 to <75 | ≥75 | F | *P* value |
| BMD (g/cm$^2$)[a] | | | | | | |
| Men | | | | | | |
| 10–22 yr old[b] | n = 71 | n = 234 | n = 135 | n = 17 | | |
| Lumbar spine | 0.88 ± 0.15 | 0.88 ± 0.14 | 0.86 ± 0.19 | 0.97 ± 0.19** | 4.59 | 0.004 |
| Femoral neck | 0.86 ± 0.15 | 0.87 ± 0.14 | 0.86 ± 0.16 | 0.96 ± 0.16* | 4.75 | 0.003 |
| Total hip | 0.95 ± 0.15 | 0.97 ± 0.14 | 0.96 ± 0.15 | 1.06 ± 0.16** | 5.91 | 0.001 |
| 23–29 yr old | n = 86 | n = 225 | n = 123 | n = 14 | | |
| Lumbar spine | 1.00 ± 0.10 | 0.99 ± 0.12 | 1.02 ± 0.12 | 1.02 ± 0.12 | 2.23 | 0.084 |
| Femoral neck | 0.90 ± 0.13 | 0.89 ± 0.13** | 0.94 ± 0.14 | 0.98 ± 0.14 | 5.08 | 0.002 |
| Total hip | 1.02 ± 0.11 | 1.01 ± 0.12** | 1.05 ± 0.13 | 1.05 ± 0.11 | 4.01 | 0.008 |
| 30–40 yr old | n = 106 | n = 406 | n = 301 | n = 74 | | |
| Lumbar spine | 0.96 ± 0.11** | 0.99 ± 0.12 | 1.01 ± 0.12 | 1.00 ± 0.11 | 4.22 | 0.006 |
| Femoral neck | 0.82 ± 0.12** | 0.85 ± 0.12 | 0.87 ± 0.11 | 0.85 ± 0.13 | 3.74 | 0.011 |
| Total hip | 0.95 ± 0.12*** | 1.00 ± 0.12 | 1.02 ± 0.12 | 1.01 ± 0.12 | 6.53 | <0.001 |
| Geometric index[c] | | | | | | |
| FN cortical thickness (mm) | 2.00 ± 0.41 | 2.00 ± 0.35 | 2.00 ± 0.29 | 2.00 ± 0.36 | 1.50 | 0.214 |
| FN CSA (cm$^2$) | 2.56 ± 0.64 | 3.59 ± 0.56 | 3.62 ± 0.53 | 3.61 ± 0.61 | 2.96 | 0.032 |
| FN CSMI (cm$^4$) | 3.92 ± 0.86 | 3.98 ± 0.89 | 4.05 ± 0.86 | 4.02 ± 0.87 | 2.26 | 0.080 |
| FN buckling ratio | 10.27 ± 2.47 | 9.96 ± 2.05 | 9.94 ± 1.97 | 9.96 ± 2.21 | 2.51 | 0.057 |
| Women | | | | | | |
| 10–19 yr old[b] | n = 57 | n = 172 | n = 87 | n = 7 | | |
| Lumbar spine | 0.92 ± 0.13 | 0.87 ± 0.14 | 0.84 ± 0.15 | 0.77 ± 0.15 | 0.94 | 0.421 |
| Femoral neck | 0.79 ± 0.13 | 0.75 ± 0.12 | 0.73 ± 0.12 | 0.68 ± 0.14 | 0.49 | 0.693 |
| Total hip | 0.91 ± 0.13 | 0.88 ± 0.12 | 0.86 ± 0.13 | 0.80 ± 0.14 | 1.11 | 0.344 |
| 20–28 yr | n = 169 | n = 320 | n = 95 | n = 13 | | |
| Lumbar spine | 0.96 ± 0.11 | 0.96 ± 0.10 | 0.97 ± 0.11 | 0.98 ± 0.13 | 0.33 | 0.805 |
| Femoral neck | 0.77 ± 0.10 | 0.78 ± 0.10 | 0.79 ± 0.11 | 0.79 ± 0.12 | 1.99 | 0.115 |
| Total hip | 0.88 ± 0.11 | 0.90 ± 0.10 | 0.91 ± 0.11 | 0.91 ± 0.12 | 1.49 | 0.216 |
| 29–40 yr | n = 270 | n = 627 | n = 325 | n = 37 | | |
| Lumbar spine | 0.99 ± 0.11 | 1.00 ± 0.11 | 1.01 ± 0.12 | 1.00 ± 0.10 | 0.44 | 0.728 |
| Femoral neck | 0.76 ± 0.10 | 0.76 ± 0.10 | 0.77 ± 0.11 | 0.79 ± 0.10 | 1.41 | 0.237 |
| Total hip | 0.89 ± 0.11 | 0.90 ± 0.11 | 0.91 ± 0.11 | 0.93 ± 0.11 | 1.58 | 0.193 |
| Geometric index[c] | | | | | | |
| FN cortical thickness (mm) | 1.80 ± 0.26 | 1.80 ± 0.27 | 1.80 ± 0.26 | 1.80 ± 0.30 | 0.10 | 0.958 |
| FN CSA (cm$^2$) | 2.79 ± 0.36 | 2.82 ± 0.38 | 2.86 ± 0.41 | 2.87 ± 0.42 | 0.84 | 0.471 |
| FN CSMI (cm$^4$) | 2.32 ± 0.49 | 2.37 ± 0.55 | 2.42 ± 0.58 | 2.43 ± 0.52 | 0.36 | 0.784 |
| FN buckling ratio | 9.64 ± 1.96 | 9.68 ± 1.94 | 9.57 ± 1.97 | 9.47 ± 1.91 | 0.75 | 0.525 |

Data are expressed as mean ± SE. Geometric indices were available for 2876 participants. Season of vitamin D determination was defined four periods during the year: March to May, June to August, September to November, and December to February. Overall results were derived from the covariance analysis. FN, Femur neck.

[a] BMD was adjusted for age, body mass index, regular walking, regular exercise, and season, except men aged 10–22 yr and women aged 10–19 yr.

[b] In men aged 10–22 yr and women aged 10–19 yr, BMD was adjusted for age, body mass index, and season.

[c] Geometric index was adjusted for age, body mass index, regular walking, regular exercise, and season.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$, for comparison with the reference group with serum 25(OH)D of 50 to <75 nmol /liter.

Although mean 25(OH)D levels were significantly different between groups, most nonskeletal parameters were not associated with 25(OH)D level in men. Plasma triglyceride level showed a significant *P* value; however, the intergroup differences were not definite. In women, no significant parameters were observed. Figure 3 lists the odds ratio of concomitant diseases according to serum 25(OH)D level. Compared with the group with 25(OH)D levels greater than 50 nmol/liter, there were no statistically significant odds ratios in the less than 50 nmol/liter group. Although rheumatoid arthritis was more prevalent in the vitamin D-deficient group, the prevalence of other medical conditions was not associated with the concentration of serum 25(OH)D (Supplemental Table 3).

## Discussion

Recently, the significance of vitamin D has been emphasized in public health contexts because vitamin D deficiency, which is independently associated with an increased risk of mortality in the general population (9), is

**TABLE 3.** Nonskeletal characteristics of each group according to serum 25(OH)D level

| | Serum 25(OH)D (nmol/liter) | | | | |
|---|---|---|---|---|---|
| | <25 | 25 to <50 | 50 to <75 | ≥75 | *P* value |
| Men (n) | 273 | 925 | 606 | 122 | |
| Anthropometric parameters with age[a] | | | | | |
| Age (yr) | 27.09 ± 7.69 | 28.24 ± 8.20 | 29.25 ± 8.74 | 31.68 ± 7.69 | <0.001 |
| Height (cm) | 172.48 ± 7.07 | 172.78 ± 7.16 | 171.34 ± 8.24 | 172.36 ± 6.89 | 0.003 |
| Body weight (kg) | 68.76 ± 12.46 | 70.60 ± 13.15 | 70.27 ± 13.05 | 69.41 ± 10.45 | 0.192 |
| Waist circumference (cm) | 79.77 ± 10.41 | 80.99 ± 10.41 | 81.52 ± 10.26 | 80.81 ± 8.86 | 0.137 |
| Body mass index (kg/m$^2$) | 23.06 ± 3.71 | 23.55 ± 3.67 | 23.82 ± 3.62 | 23.31 ± 2.90 | 0.031 |
| Cardiopulmonary parameters | | | | | |
| Systolic blood pressure (mm Hg)[a] | 110.81 ± 13.45 | 112.13 ± 13.79 | 112.26 ± 13.70 | 112.54 ± 10.96 | 0.917 |
| Diastolic blood pressure (mm Hg)[a] | 75.07 ± 11.92 | 75.28 ± 12.47 | 75.60 ± 11.15 | 74.16 ± 9.43 | 0.829 |
| FEV1/FVC (%)[b] | 0.86 ± 0.05 | 0.83 ± 0.07 | 0.83 ± 0.06 | 0.82 ± 0.07 | 0.184 |
| Bone metabolic parameters | | | | | |
| Serum 25(OH)D (nmol/liter)[a] | 24.98 ± 3.55 | 39.90 ± 5.48 | 60.15 ± 6.99 | 85.40 ± 8.69 | <0.001 |
| Calcium intake per day (mg)[a] | 530.11 ± 353.12 | 538.49 ± 317.53 | 589.54 ± 366.34 | 571.06 ± 395.06 | 0.050 |
| Total ALP (U/liter)[c] | 230.43 ± 61.22 | 230.38 ± 58.05 | 224.14 ± 54.59 | 219.36 ± 59.48 | 0.362 |
| Metabolic parameters[c] | | | | | |
| Fasting glucose (mg/dl) | 91.09 ± 16.51 | 91.35 ± 10.97 | 93.19 ± 18.92 | 91.05 ± 7.59 | 0.388 |
| Insulin (μIU/ml) | 9.95 ± 4.51 | 10.64 ± 7.09 | 9.92 ± 4.71 | 9.20 ± 3.88 | 0.080 |
| HOMA-IR | 2.26 ± 1.17 | 2.46 ± 2.01 | 2.32 ± 1.37 | 2.09 ± 0.96 | 0.196 |
| Total cholesterol (mg/dl) | 177.65 ± 32.79 | 181.12 ± 34.55 | 182.64 ± 31.68 | 180.97 ± 29.27 | 0.820 |
| HDL-cholesterol (mg/dl) | 50.25 ± 10.81 | 49.92 ± 11.10 | 49.79 ± 11.19 | 49.19 ± 10.56 | 0.582 |
| Triglyceride (mg/dl) | 138.89 ± 119.55 | 151.67 ± 132.87 | 145.40 ± 113.77 | 127.38 ± 80.89 | 0.039 |
| Women (n) | 531 | 1212 | 548 | 59 | |
| Anthropometric parameters with age[a] | | | | | |
| Age (yr) | 29.22 ± 7.40 | 28.98 ± 7.99 | 29.77 ± 8.50 | 29.88 ± 7.71 | 0.252 |
| Height (cm) | 160.31 ± 5.48 | 160.06 ± 5.83 | 159.35 ± 6.02 | 160.09 ± 6.33 | 0.038 |
| Body weight (kg) | 55.73 ± 9.45 | 56.44 ± 9.94 | 55.95 ± 10.51 | 56.82 ± 10.56 | 0.489 |
| Waist circumference (cm) | 72.28 ± 9.06 | 73.42 ± 9.53 | 73.79 ± 9.97 | 75.09 ± 11.13 | 0.021 |
| Body mass index (kg/m$^2$) | 21.67 ± 3.44 | 22.00 ± 3.52 | 21.98 ± 3.70 | 22.16 ± 3.97 | 0.312 |
| Cardiopulmonary parameters | | | | | |
| Systolic blood pressure (mm Hg)[a] | 101.38 ± 10.91 | 101.22 ± 10.53 | 102.13 ± 10.85 | 103.04 ± 9.44 | 0.675 |
| Diastolic blood pressure (mm Hg)[a] | 66.94 ± 9.82 | 67.24 ± 9.41 | 66.61 ± 9.73 | 68.37 ± 9.11 | 0.765 |
| FEV1/FVC (%)[b] | 0.85 ± 0.07 | 0.83 ± 0.09 | 0.83 ± 0.07 | 0.84 ± 0.06 | 0.234 |
| Bone metabolic parameters | | | | | |
| Serum 25(OH)D (nmol/liter)[a] | 25.23 ± 3.61 | 39.28 ± 5.44 | 59.10 ± 6.70 | 81.85 ± 7.64 | <0.001 |
| Calcium intake per day (mg)[a] | 431.22 ± 289.76 | 441.07 ± 281.32 | 435.80 ± 262.81 | 484.60 ± 283.58 | 0.586 |
| Total ALP (U/liter)[c] | 185.11 ± 52.93 | 186.38 ± 55.41 | 189.26 ± 61.99 | 180.85 ± 45.65 | 0.689 |
| Metabolic parameters[c] | | | | | |
| Fasting glucose (mg/dl) | 88.75 ± 9.86 | 89.91 ± 13.44 | 90.61 ± 18.13 | 89.75 ± 8.83 | 0.861 |
| Insulin (μIU/ml) | 9.40 ± 5.00 | 9.60 ± 4.23 | 9.27 ± 3.45 | 9.20 ± 3.73 | 0.510 |
| HOMA-IR | 2.09 ± 1.32 | 2.15 ± 1.13 | 2.10 ± 1.07 | 2.07 ± 0.94 | 0.675 |
| Total cholesterol (mg/dl) | 166.76 ± 29.30 | 172.17 ± 29.92 | 174.03 ± 28.03 | 172.49 ± 25.88 | 0.050 |
| HDL-cholesterol (mg/dl) | 57.07 ± 12.88 | 57.62 ± 12.42 | 57.07 ± 12.35 | 54.86 ± 11.55 | 0.166 |
| Triglyceride (mg/dl) | 84.03 ± 56.11 | 87.92 ± 65.21 | 86.28 ± 53.30 | 83.76 ± 50.43 | 0.757 |

Data are expressed as mean ± SE. ANCOVA, adjusted for age, body mass index, season, regular walking, and regular exercise, was used. FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ALP, alkaline phosphatase.

[a] Variables were derived from ANOVA.

[b] FEV1/FVC (%) data were available for 289 men and 338 women.

[c] Reference ranges: total ALP, 38.0–115.0 U/liter; fasting glucose, 70–110 mg/dl; insulin, 4.2–5.0 μIU/ml; total cholesterol, 100–220 mg/dl; HDL-cholesterol, 40–400 mg/dl; triglyceride, 44–166 mg/dl.

a great threat to both young and elderly people (1, 6, 10–12). Previous studies have reported that vitamin D deficiency is related to a higher risk of metabolic bone diseases, cancers, autoimmune diseases, infection, diabetes mellitus, and cardiovascular disease (2, 13–19). Moreover, in children, vitamin D deficiency may increase adiposity and lower HDL cholesterol (20), and vitamin D supplementation can prevent asthma exacerbation caused by acute respiratory infection (21). However, there is a paucity of systemic data on the skeletal and nonskeletal effects of vitamin D deficiency in the youth.

In this study, the acquisition of PBM was achieved in women at the end of adolescence, and was delayed several years in men, as previously reported (5). Intriguingly, we observed a "spooning pattern" in femur neck and total hip BMD, indicating that after reaching PBM, BMD decreased

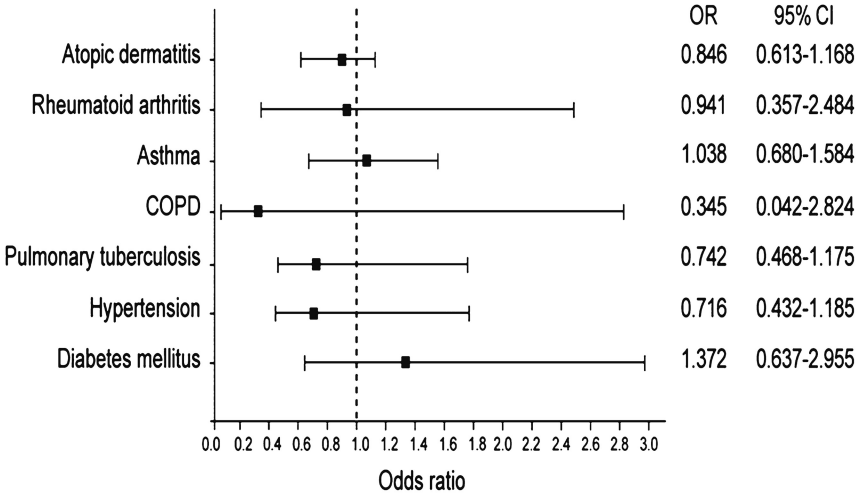


**FIG. 3.** Odds ratios (95% confidence interval) of concomitant diseases according to serum 25(OH)D level. Multivariate logistic regression analyses were used to examine the odds ratios of concomitant diseases between groups with 25(OH)D less than 50 and at least 50 nmol/liter, adjusted for age, sex, body mass index, and season. COPD, Chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

rapidly until the age of 28 or 29, then slightly increased or remained constant. This phenomenon appeared to be more prevalent in women than in men. Khosla *et al.* (22) previously mentioned such a spooning pattern at the distal radius and distal tibia using peripheral quantitative computed tomography, but this change was only found in young adult men. They suggested that it could be associated with hormonal changes such as declining serum IGF-I levels (22). In our study, changes in serum 25(OH)D with age were similar to that of BMD. Therefore, we hypothesized that vitamin D status is one of the major determinants in the spooning pattern of BMD in young adults and aimed to assess the relationship between vitamin D deficiency and BMD in this population.

Interestingly, there were gender differences in the skeletal effects of vitamin D in three phases. In young men, BMD in the modeling phase was higher in the vitamin D-sufficient group, but no linear relationship was found in spline plots, suggesting that multiple factors other than vitamin D may contribute to bone health during this phase. Although the Pearson correlation coefficient was low, BMD in the decelerating and consolidating phases had a positive correlation with 25(OH)D level and may be relatively more susceptible to vitamin D deficiency than that in the modeling phase. For young women, contrary to expectations, no meaningful differences in both BMD and geometric indices according to 25(OH)D level were observed in each of the three phases, although the prevalence of vitamin D deficiency was higher in women than in men. The next question was how to explain such gender differences.

According to the "unitary model" proposed by Riggs and Melton, estrogen deficiency is the predominant cause of both early, accelerated and late, slow phases of bone loss in postmenopausal women and is a contributing cause of the continuous phase of bone loss in aging men (23, 24). In both genders, there is a steady decline in bioavailable estrogen level with age, although the absolute value is different, superimposed on which is a marked decrease in estrogen level in women at menopause (25). Even in elderly men, estrogen is more important than androgen, and the yearly incidence of fractures increased remarkably at estradiol levels of less than 16 pg/ml (26). Estrogen directly or indirectly stimulates intestinal calcium absorption by enhancing expression of vitamin D receptors (VDR) or calbindin D in the mucosa, and also stimulates 1$\alpha$-hydroxylase activity in the kidneys (27). This study showed the possibility that estrogen has a major influence on BMD starting just after the formation of PBM, rather than after menopause. The gender differences in the skeletal effects of vitamin D might be attributed to some protective roles of estrogen that surpass the disadvantage of vitamin D deficiency commonly observed in young women.

Sclerostin, the secreted Wnt antagonist produced by osteocytes, regulates bone mass negatively by binding to low-density lipoprotein receptor-related protein 5 and 6 (28). PTH may suppress the expression of sclerostin through myocyte enhancer factor-2 transcription factors (29). Estrogen also decreases circulating sclerostin level, but not testosterone (28). Thus, elevated PTH caused by vitamin D deficiency and estrogen might synergistically decrease sclerostin. Meanwhile, we do not yet know whether the decelerating phase comes from accelerated bone resorption or inadequate bone formation. Ethnic differences should be considered to understand this interesting observation, and more research is needed on the effects of sex hormone or calciotropic hormone on sclerostin and the alteration of GH-IGF secretion patterns in both genders.

Regarding the nonskeletal effects of vitamin D, there were no differences in metabolic profiles, such as insulin resistance and lipids, or cardiopulmonary parameters in the three phases, except for plasma triglycerides in men. In our unpublished study, which looked at all ages of the general population, basal insulin level and HOMA-IR were elevated in the vitamin D-deficient group. There is no good explanation for this discrepancy, but we speculated that insulin resistance may be aggravated by vitamin D deficiency in elderly people who have a limited reserve capacity of $\beta$-cells. VDR is also expressed in $\beta$-cells, and

VDR expression has been thought to be a determinant of insulin secretory capacity (30). In an association study, only rheumatoid arthritis seemed to be more prevalent in the vitamin D-deficient group. However, further study is needed to examine the relationship between 25(OH)D level and concomitant diseases in this age group because the number of participants with underlying disease was insufficient to confirm the significance of this content.

The major strength of this study is that we analyzed data collected from a nationwide survey including more than 4000 participants aged 40 or younger in Korea, which is one of the most vitamin D deficiency-prone countries among young people (6). This is the first observational study to investigate skeletal and nonskeletal health extensively according to vitamin D status, focusing on the younger generation. However, this study also has some limitations. First, data were obtained from a questionnaire. Second, although occupational factor also could affect serum 25(OH)D level (6), we did not use occupation as an adjustment factor because more than 40% of all the participants were students or housewives, and those who worked outdoors only comprised 0.5% of the subjects 20–30 yr old. Third, we could not distinguish the age-related changes in trabecular bone from cortical bone due to the limitation of dual x-ray absorptiometry. Fourth, the relationship between serum 25(OH)D and PTH levels was not assessed. Lastly, we could not inquire into data regarding physical activity in the modeling phase, which might affect young people's vitamin D status. Hence, it is statistically probable that there were small significant differences, compared with most studies targeting the elderly. However, because the survey proceeded in detail, showing the prospective nature, our results are very reliable.

Vitamin D plays an important role in skeletal health of young people. Thus, serum 25(OH)D level should be maintained at 20–30 ng/ml or higher, especially during the modeling phase in men, to ensure BMD. We have little evidence to support the necessity of higher doses of vitamin D supplementation to maintain a serum 25(OH)D level of higher than 30 ng/ml consistently in this age group. In addition, young people tend to have indoor activities compared with other age groups (6). Therefore, we should not overlook the importance of lifestyle modification to encourage the younger generation to be adequately exposed to sunlight in a variety of ways, including regular use of a tanning bed (31). Further study is necessary to examine the gender-dependent skeletal effects of vitamin D in younger generations. Our results would be very helpful and informative to physicians and public healthcare officials.

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