Estimation of the dietary requirement for vitamin D in healthy adolescent white girls 1–3

Kevin D Cashman, Anthony P FitzGerald, Heli T Viljakainen, Jette Jakobsen, Kim F Michaelsen, Christel Lamberg-Allardt, and Christian Mølgaard

ABSTRACT

Background: Knowledge gaps have contributed to considerable variation (between 0 and 15 μg/d) in international dietary recommendations for vitamin D in adolescents.

Objective: We aimed to establish the distribution of dietary vitamin D required to maintain serum 25-hydroxyvitamin D [25(OH)D] concentrations above several proposed cutoffs (25, 37.5, 40, and 50 nmol/L) during wintertime in adolescent white girls.

Design: Data (baseline and 6 mo) from 2 randomized, placebo-controlled, double-blind, 12-mo intervention studies in Danish (55°N) and Finnish (60°N) girls (n = 144; mean age: 11.3 y; mean vitamin D intake: 3.7 μg/d) at vitamin D3 supplementation amounts of 0, 5, and 10 μg/d were used. Serum 25(OH)D was measured with an HPLC assay in a centralized laboratory.

Results: Clear dose-related increments (P < 0.0001) in serum 25(OH)D with increasing supplemental vitamin D3 were observed. The slope of the relation between vitamin D intake and serum 25(OH)D at the end of winter was 2.43 nmol/L·μg intake−1, and no difference in the slopes between Finnish and Danish girls was observed. The vitamin D intakes that maintained serum 25(OH)D concentrations at >25, >37.5, and >50 nmol/L in 97.5% of the sample were 8.3, 13.5, and 18.6 μg/d, respectively, whereas an intake of 6.3 μg/d maintained a serum 25(OH)D concentration >40 nmol/L in 50% of the sample.

Conclusion: The vitamin D intakes required to ensure that adequate vitamin D status (defined variably as serum 25(OH)D >25 and >50 nmol/L) is maintained during winter in the vast majority (>97.5%) of adolescent girls (mean age: 11.3 y) at northern latitudes (>55°N) are 8.3 and 18.6 μg/d, respectively. This trial was registered at clinicaltrials.gov as NCT00267540. Am J Clin Nutr 2011;93:549–55.

INTRODUCTION

It is well established that prolonged and severe clinical vitamin D deficiency (defined as serum 25-hydroxyvitamin D [25(OH)D] concentrations <10–25 nmol/L; to convert to ng/mL, divide by a quotient of 2.5) leads to rickets in children and osteomalacia in adults (1). Less severe vitamin D deficiency causes secondary hyperparathyroidism and increases bone turnover and bone loss (2–4). Currently in the United Kingdom, a plasma concentration of 25 nmol(μg)/L is used as the lower threshold for vitamin D status (1). There is, however, a lack of consensus on the cutoff values of plasma 25(OH)D that define the lower limit of adequacy and sufficientness, and values between 30 and 80 nmol/L have been suggested (5–9). The Dietary Reference Intake (DRI) committee for calcium and vitamin D in the United States recently suggested that a congruence of data links a serum 25(OH)D concentration <30 nmol/L with an increased risk of rickets, impaired fractional calcium absorption, and decreased bone mineral content in children and adolescents (5). With this in mind, it is of concern that a high prevalence of low vitamin D status has been reported in adolescents in Europe (10–17), the United States (18–21), and elsewhere [Lebanon (22), New Zealand (23, 24), and Tasmania (25)], especially during the winter months. For example, data from the National Diet and Nutrition Survey (NDNS) in the United Kingdom showed that up to 21% of adolescent girls and boys (11–18-y-old) had winter serum 25(OH)D concentrations <25 nmol/L, and up to 50% of adolescents had year-round serum 25(OH)D concentrations <50 nmol/L. (10)—a threshold that has been associated with poorer adolescent bone growth and strength (26, 27) and less than maximal calcium absorption (5, 28).

In children aged 1–18 y and most adults, vitamin D is obtained primarily through cutaneous biosynthesis in the presence of ultraviolet B (UVB) sunlight and also from the diet (1, 5). In the absence of sufficient UVB sunlight exposure for dermal synthesis, vitamin D becomes an essential nutrient. Considerable variation exists between authoritative dietary recommendations for vitamin D intakes (1, 5, 29–31). The UK Committee on Medical Aspects of Food and Nutrition Policy (COMA) in 1991 (29), endorsed by the later Nutrition and Bone Health Report in 1998 (1), did not set a reference nutrient intake (RNI) for vitamin D in children or adolescents. The American Academy of Pediatrics (2004) and the National Academy of Sciences, US National Academy of Medicine (2010) set RNI for vitamin D of 200 and 400 IU/d, respectively. In the United States recently suggested that a congruence of data links a serum 25(OH)D concentration <30 nmol/L with an increased risk of rickets, impaired fractional calcium absorption, and decreased bone mineral content in children and adolescents (5). With this in mind, it is of concern that a high prevalence of low vitamin D status has been reported in adolescents in Europe (10–17), the United States (18–21), and elsewhere [Lebanon (22), New Zealand (23, 24), and Tasmania (25)], especially during the winter months. For example, data from the National Diet and Nutrition Survey (NDNS) in the United Kingdom showed that up to 21% of adolescent girls and boys (11–18-y-old) had winter serum 25(OH)D concentrations <25 nmol/L, and up to 50% of adolescents had year-round serum 25(OH)D concentrations <50 nmol/L. (10)—a threshold that has been associated with poorer adolescent bone growth and strength (26, 27) and less than maximal calcium absorption (5, 28).

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individuals aged 4–64 y on the basis that skin synthesis of vitamin D would generally ensure adequacy, but did set an RNI of 10 µg/d (to convert to IU/d, multiply by a factor of 40) for those in this age group with very limited summer UBV sunshine. The European dietary recommendation for vitamin D for adolescents (aged 11–17 y) was set in 1993 as a range from 0 to 15 µg/d (30), whereas the Nordic recommendation was set in 2004 at 7.5 µg/d (31). Very recently, the US DRI committee set an estimated average requirement (EAR) and Recommended Dietary Allowance (RDA) for vitamin D of 10 and 15 µg/d, respectively, for adolescents (5).

The aim of this study was to establish the distribution of dietary requirements for the maintenance of nutritional adequacy of vitamin D in adolescent girls during late winter, as indicated by serum 25(OH)D concentrations ranging from ≥25 to ≥50 nmol/L. This was possible by using data available from 2 randomized, double-blind, placebo-controlled, 12-mo vitamin D3 intervention studies in adolescent Danish and Finnish girls (26, 32).

SUBJECTS AND METHODS

Subjects in the original 12-mo intervention trials

Full details of the subjects in both 12-mo vitamin D intervention trials, which had bone health as the primary outcome [as part of the European Commission (EC) Optimal Strategy for Vitamin D Fortification (OPTIFORD) project (contract no. QLK1-CT-2000-00623); www.optiford.org], are described elsewhere (26, 32). In brief, participants in the Danish intervention study were recruited by using information from the Danish National Central Offices of Civil Registrations, which allowed for the identification of the names and addresses of all appropriately aged girls born in Denmark with Danish citizenship living in the municipalities of Copenhagen and Frederiksberg, 55°N (n = 1755). To minimize age differences at inclusion, the oldest subjects were recruited first and recruitment continued until 225 (mean age: 11.4 y) had agreed to participate. The subjects included were healthy white girls who used no medicines known to affect calcium metabolism. The study was approved by the Research Ethical Committee of Copenhagen and Frederiksberg [J.nr (KF) 01–129/01] and registered at clinicaltrials.gov (NCT00267540). In the Finnish intervention study, a total of 228 healthy white adolescent girls (mean age: 11.4 y) were studied in the capital region of Helsinki (60°N) in southern Finland. Recruitment was conducted in primary schools. Ethical approval was obtained from the Ethical Committee of Helsinki and Uusimaa Hospital District. In both studies the subjects and their parents gave informed written consent in agreement with the Helsinki Declaration before entering the study. Girls were excluded on the basis of the following criteria: chronic diseases, intake of drugs that could influence bone metabolism, and daily intake of calcium supplements or vitamin-mineral supplements.

Design and conduct of the original 12-mo intervention trials

Both studies were double-blind, placebo-controlled trials in which the adolescent girls were randomly assigned to receive 0 (placebo), 5, or 10 µg vitamin D3/d for 12 mo, and bone health indexes were the primary outcome (26, 32). In the Danish study, subjects were commenced on the intervention on a rolling basis over 13 mo. To achieve an even distribution among intervention groups over the inclusion period from the middle of November 2001 to the beginning of December 2002, the 225 girls were randomly assigned in a double-blind fashion by using blocks of 15 subjects with 5 randomly assigned to each of the 3 groups: 0 (placebo), 5, or 10 µg vitamin D3/d for 12 mo. In the Finnish study, all 228 girls commenced the intervention within 6 mo between September 2001 and March 2002. A stratified randomization process was performed 3 times for equal size blocks. The stratification factor was pubertal development (Tanner stage). In each Tanner stage, an equal number of subjects was randomly assigned into 1 of 3 treatment groups: 0 (placebo), 5, or 10 µg vitamin D3/d for 12 mo. In both studies, the randomization was done by a person not involved in the project, and the allocation remained concealed until the final analyses, and all data were reported by persons who were masked to the allocation scheme. The vitamin D3 tablets and matching placebo tablets were produced by Scanpharm Ltd (Birkerød, Denmark) and were identical in appearance and taste. The vitamin D3 content of the tablets was confirmed by analysis performed at the Danish Institute for Food and Veterinary Research (now National Food Institute, Søborg, Denmark). Compliance was evaluated by tablet counting.

In both studies, subjects were sampled at baseline, 6 mo, and 12 mo. During each visit, height, weight, and pubertal development were assessed, as described in detail elsewhere (26, 32). Fasting blood samples were taken between 0800 and 1000 at baseline and after 6 and 12 mo of intervention. Fasting blood samples were processed to serum and were stored at −80°C until required for analysis. Dietary calcium and vitamin D intakes were estimated at baseline by using a country-specific food-frequency questionnaire (FFQ). In the Danish study, the girls filled in, together with their parents, a standardized FFQ that ascertained the foods (including fortified foods) contributing to 95% of the vitamin D intake and 75% of the calcium intake determined from the most recent dietary intake studies in Denmark. The questionnaire had 9 predefined possible frequencies (ranging from “less than one time per month” to “4–5 times per day or more”). The Danish Institute for Food and Veterinary Research (now National Food Institute) performed the intake calculations by using the General Intake Estimation System, which were reported earlier (15). In the Finnish study, the dietary vitamin D and calcium intakes were evaluated by using a validated semiquantitative FFQ covering >70 foods (13). The nutrient contents of the foods were calculated by using the Finnish National Food Composition Database, Fineli, version 2001, which is maintained by the National Public Health Institute of Finland, Nutrition Unit. All forms were checked by the researchers, and additional information was requested if needed.

Selection of a subgroup of trial subjects for estimation of dietary requirement for vitamin D

To establish the distribution of dietary vitamin D required to maintain serum 25(OH)D concentrations above the proposed cutoffs during wintertime in adolescent girls, we needed to identify those girls whose baseline sampling was in late summer
(September and October) and would be after receiving 6 mo of vitamin D₃ supplementation by the following March to April, representing late winter and during which period of time vitamin D status would be expected to decline to a nadir in non-supplemented individuals (33). This time frame is similar to that used recently in our vitamin D intervention studies, which estimated vitamin D requirements in adults and older adults (34, 35) and is in line with the approach used by the US DRI committee of prioritizing the response of serum 25(OH)D concentrations to total intake of vitamin D in northern latitudes in Europe and Antarctica during their respective winter seasons when effective UVB sun exposure for endogenous vitamin D synthesis is minimal (5). Of the 221 girls (corresponding to 98%) who completed the Danish study (32) and 212 girls (corresponding to 93%) who completed the Finnish study (26), 47 and 97 Danish and Finnish girls, respectively, commenced the 12-mo intervention studies between September and October, had a midpoint (6 mo) assessment between March and April (in 2001 or 2002), and did not take a winter sun vacation (during the 6 mo). The mean compliance was 90% in this subgroup of girls (mean age: 11.3 y). Serum 25(OH)D and calcium data at baseline and after 6 mo of supplementation were used in the present analysis.

Laboratory analysis

Serum 25(OH)D

Concentrations of 25(OH)D were measured centrally in all samples at the Danish Institute for Food and Veterinary Research (now National Food Institute), Søborg, Denmark, by using an HPLC-based assay, as described in detail elsewhere (36). Participation in the International Vitamin D External Quality Assessment Scheme (DEQAS; Charing Cross Hospital, London, United Kingdom) ensured that the HPLC method was in agreement with commercially available assays. The intra- and interassay CVs were 4.3% and 6.3%, respectively. Serum calcium was analyzed centrally in all samples at the Calcium Research Unit, Department of Food and Environmental Sciences, University of Helsinki, Finland, by using an automated KoneLab spectrophotometer (Thermo Clinical Labsystems, Espoo, Finland) following a routine method. The intra- and interassay CV for this analysis was <7.5%.

Mathematical modeling of the relation between vitamin D intake and status

The aim of the modeling was to describe the conditional distribution of serum 25(OH)D at specific values of vitamin D intake. The mean serum 25(OH)D concentration was modeled as a linear function of vitamin D intake. The linear model was chosen after a series of models were assessed for best fit. A regression model was used to estimate the variation in 25(OH)D concentrations about the mean, and Q-Q plots were used to examine the assumption that variation about the predicted value was normally distributed. The distribution of serum 25(OH)D as a function of total vitamin D intake was obtained. Finally, we estimated the dietary requirements for vitamin D to maintain selected percentages of the population above 4 specific serum 25(OH)D concentrations. The 95% CIs of required vitamin D intakes were calculated by using a bias-corrected bootstrap based on 10,000 replications. Results were verified by using robust regression models that minimized the effect of outliers and heteroscedasticity.

Statistical analysis

Post hoc power calculations showed that a study design incorporating 150 volunteers—50 subjects to each of 3 dose levels (0, 5, or 10 µg vitamin D/d)—had 90% power to show a dose-response relation at α = 0.05. This was based on many assumptions, as outlined in our previous studies (34, 35). In brief, because of the relative paucity of data on the relation between habitual vitamin D intake and serum 25(OH)D concentrations, power calculations were performed under relatively pessimistic assumptions concerning the magnitude of any relation and the residual variation in serum 25(OH)D concentration after the effect of background dietary intake was removed. Specifically, a P value of 0.5 was assumed to represent the minimum clinically important slope, and that the residual variation of serum 25(OH)D concentrations around the mean line was normal. On the basis of the distribution of data from adolescent European girls from our previous study (15), it was assumed that the distribution of dietary intakes in the current study would be similar.

Statistical analysis of the data was conducted by using SPSS for Windows (version 12.0; SPSS Inc, Chicago, IL) and Stat 11 (StataCorp LP, College Station, TX). The distributions of all variables were tested with Kolmogorov-Smirnov tests. Descriptive statistics (mean and SD) were determined for all variables. Baseline characteristics of the girls in both study centers were compared by using unpaired Student’s t tests or a chi-square test as appropriate. Baseline characteristics of the girls in the different intervention groups were compared by using one-factor analysis of variance or chi-square test as appropriate. Linear models of the response in a repeated-measures analysis for the differences in serum 25(OH)D and calcium concentrations were also constructed. The main effects included were dietary treatment and country. The linear models also included 2-factor interactions between the main effects. A P value of <0.05 was considered significant.

RESULTS

Baseline characteristics of subjects

Girls in Denmark were slightly, but significantly (P < 0.001–0.0001), older and taller than those in Finland (Table 1). No significant difference in mean weight or BMI at baseline were observed between subjects from the 2 countries (Table 1). Habitual vitamin D and calcium intake in girls in Denmark were significantly (P < 0.001–0.0001) lower than those in Finland at baseline (Table 1). No significant difference in baseline serum 25(OH)D or calcium concentration was observed between subjects from the 2 countries (Table 1). Significantly more Danish girls than Finnish girls were in the later stages of puberty (Tanner scores III–IV) (Table 1).

Effects of vitamin D intervention

No differences (P > 0.2) in mean age, weight, height, BMI, or distribution of Tanner scores at baseline were observed between the 3 treatment groups (data not shown). Similarly, no differences...
in mean habitual vitamin D or calcium intake or in mean preintervention serum 25(OH)D or calcium concentrations were observed between the treatment groups (Table 2). As expected, total vitamin D intake (diet plus supplemental vitamin D) increased in a dose-related manner with supplementation (mean ± SD: 3.7 ± 1.8, 8.7 ± 2.4, and 13.7 ± 1.8 μg/d for placebo and 5 and 10 μg vitamin D3/d, respectively; \( P < 0.0001 \)).

A significant (\( P < 0.0001 \)) effect of treatment on mean postintervention serum 25(OH)D concentrations was observed, as was a clear dose-related increment with increasing supplemental vitamin D3 (Table 2). The response of 25(OH)D concentrations to vitamin D3 supplementation was not influenced by whether baseline serum 25(OH)D concentrations in the girls was above or below the median (55.4 nmol/L; \( P = 0.663 \)). The seasonal decline in serum 25(OH)D concentration was less pronounced in those subjects in the placebo group who had baseline serum concentrations below the median than in those with concentrations above the median [mean (±SD) change in serum 25(OH)D over 6 mo: −19.3 ± 6.3 nmol/L and −32.0 ± 11.8 nmol/L, respectively; \( P = 0.001 \)]. No difference in mean postintervention serum calcium concentrations to vitamin D3 supplementation was not influenced by whether baseline serum 25(OH)D concentrations in the girls was above or below the median (55.4 nmol/L; \( P = 0.663 \)).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Habitual dietary intake and biochemical measure of vitamin D status in treatment groups before and after intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 46)</td>
</tr>
<tr>
<td>Habitual dietary vitamin D (μg/d)</td>
<td>3.7 ± 1.8</td>
</tr>
<tr>
<td>Habitual dietary calcium (mg/d)</td>
<td>1052 ± 517</td>
</tr>
<tr>
<td>Serum 25(OH)D (nmol/L)</td>
<td></td>
</tr>
<tr>
<td>Before intervention</td>
<td>54.5 ± 14.8</td>
</tr>
<tr>
<td>After intervention</td>
<td>31.0 ± 10.0</td>
</tr>
</tbody>
</table>

\( ^1 \) All values are means ± SDs. 25(OH)D, 25-hydroxyvitamin D. Values in the same row with different superscript letters are significantly different, \( P < 0.01 \) (one-factor ANOVA followed by Tukey’s test).

\( ^2 \) All baseline blood samples from girls (a subset of those in the original 12-mo intervention trials) were taken between September and October 2001 or 2002.

\( ^3 \) Repeated-measures ANOVA was also used to test the treatment \( \times \) time interaction, and the same trend was observed for serum 25(OH)D (\( P \leq 0.0001 \)). There was no significant interaction with country (\( P = 0.2 \)). All endpoint blood samples of girls (a subset of those in the original 12-mo intervention trials) were taken between March and April 2001 or 2002.

Relation between vitamin D intake and vitamin D status

The relation between serum 25(OH)D concentrations in late winter and total vitamin D intake (diet and supplemental) in adolescent girls (mean age: 11.3 y) is shown in Figure 1. The slope of the relation between total vitamin D intake and serum 25(OH)D in the entire group was 2.43 nmol \cdot L\(^{-1} \cdot \mu g\) intake\(^{-1} \). No significant difference between the slope estimates for Danish (2.04 nmol \cdot L\(^{-1} \cdot \mu g\) intake\(^{-1} \)) and Finnish (2.62 nmol \cdot L\(^{-1} \cdot \mu g\) intake\(^{-1} \)) girls was observed (\( P = 0.1 \)). When included in the model, no significant (\( P > 0.1 \)) interactions with country, BMI, or pubertal status (Tanner scores I–II or III–IV) were observed.

Using mathematical modeling of the vitamin D intake–status data, we estimated that the vitamin D intakes that maintained serum 25(OH)D concentrations >25 nmol/L in 90%, 95%, and 97.5% of the adolescent girls (mean age: 11.3 y) were 5.5, 7.0, and 8.3 μg/d, respectively (Table 3). The EAR [the vitamin D intake required to maintain serum 25(OH)D concentrations >25 nmol/L in 50% of the adolescents] was 0.2 μg/d. The Institute of Medicine’s new dietary reference intake values for

### Table 1
Baseline characteristics of the subjects in the 2 intervention studies

<table>
<thead>
<tr>
<th></th>
<th>All girls (n = 144)</th>
<th>Danish girls (n = 47)</th>
<th>Finnish girls (n = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>11.3 ± 0.3 (^1)</td>
<td>11.6 ± 0.1</td>
<td>11.2 ± 0.3 (^2)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>42.1 ± 8.5</td>
<td>44.0 ± 10.3</td>
<td>41.4 ± 9.0</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.50 ± 0.07</td>
<td>1.53 ± 0.07</td>
<td>1.48 ± 0.07 (^3)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>18.6 ± 3.0</td>
<td>18.5 ± 3.0</td>
<td>18.7 ± 3.0</td>
</tr>
<tr>
<td>Dietary calcium (mg/d)</td>
<td>1122 ± 382</td>
<td>921 ± 461</td>
<td>1219 ± 611 (^4)</td>
</tr>
<tr>
<td>Dietary vitamin D (μg/d)</td>
<td>3.7 ± 2.0</td>
<td>2.6 ± 1.2</td>
<td>4.2 ± 2.1 (^5)</td>
</tr>
<tr>
<td>Serum 25-hydroxyvitamin D (nmol/L)</td>
<td>56.6 ± 13.9</td>
<td>57.2 ± 13.5</td>
<td>56.2 ± 14.1</td>
</tr>
<tr>
<td>Serum calcium (nmol/L)</td>
<td>2.61 ± 0.11</td>
<td>2.59 ± 0.10</td>
<td>2.62 ± 0.09</td>
</tr>
<tr>
<td>Tanner stage (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I and II (early puberty)</td>
<td>54.8</td>
<td>37.5</td>
<td>62.3</td>
</tr>
<tr>
<td>III–IV (midpuberty)</td>
<td>45.2</td>
<td>62.5</td>
<td>36.7</td>
</tr>
</tbody>
</table>

\(^1\) Mean ± SD (all such values).

\(^2,3\) Significantly different from Danish girls (unpaired Student’s \( t \) tests): \( ^2 P \leq 0.0001, ^3 P \leq 0.001 \).

\(^4\) The distribution between Finnish and Danish girls was significantly different, \( P < 0.01 \) (chi-square test).
vitamin D suggest an EAR of 10 \( \mu \)g/d [to achieve a serum 25(OH)D concentration of 40 nmol/L] and an RDA of 15 \( \mu \)g/d [to achieve a serum 25(OH)D concentration of 50 nmol/L] for persons aged 1–18 y (5). Our data suggest that the dietary EAR [on the basis of the 40 nmol serum 25(OH)D/L cutoff] and RDA [on the basis of the 50 nmol serum 25(OH)D/L cutoff] for vitamin D for adolescent Danish and Finnish girls (mean age: 11.3 y) is 6.3 and 18.6 \( \mu \)g/d, respectively (Table 3).

The 50th, 90th, 95th, and 97.5th percentile estimates for vitamin D intake per the various indicators of adequacy for vitamin D status (<25, <37.5, <40, and <50 nmol/L) are shown in Table 3.

DISCUSSION

The EAR and RDA for nutrients are generally established as the average daily intakes that are sufficient to meet the nutrient requirements for 50% and nearly all (97–98%) individuals, respectively, in a life-stage and sex group (1, 5). Adolescents are a life-stage group that together with pregnant women, the elderly, and immigrants appear to be at risk of vitamin D deficiency (37, 38), which is of concern in light of the fact that adolescence is a time of accelerated skeletal growth, and adequate vitamin D status is required to enhance intestinal calcium absorption. Uncertainty and gaps in the available data about the relative contribution of exposure of skin to UVB radiation from sunshine and diet to vitamin D status and vitamin D requirements for health maintenance have presented international authorities with considerable difficulty in setting dietary requirements for vitamin D. An approach that prioritizes identifying the intakes that will maintain serum 25(OH)D concentrations above chosen cutoffs when dermal production of vitamin D is absent or markedly diminished was recently endorsed by the US DRI committee (5).

Using data from the first 6 mo (September–October to March–April) of two 12-mo, randomized, controlled, 3-dose vitamin D intervention trials as part of the EC OPTIFORD project, we examined the relation between total vitamin D intake and serum 25(OH)D concentrations in late winter in 144 healthy white adolescent girls (mean age: 11.3 y) living at 55 and 60°N. We found that a daily intake of 6.3 \( \mu \)g vitamin D/d would have maintained serum 25(OH)D concentrations >40 nmol/L in 50% of the sample, and intakes of 8.3 and 18.6 \( \mu \)g/d vitamin D would have maintained serum 25(OH)D concentrations >25 and 50 nmol/L, respectively, in 97.5% of the sample.

When it was establishing the EAR and RDA for vitamin D for children and adolescents aged 1–18 y, the US DRI committee for calcium and vitamin D used evidence of serum 25(OH)D concentrations that benefited bone health, such as the prevention of rickets, maximizing calcium absorption and the positive effects on bone mineral content (5). Using an approach that approximated a median value for serum 25(OH)D, above which approximately half the population might meet requirements for bone health and below which one-half might not, the committee concluded that such a value lies between 30 and 50 nmol/L. For children and adolescents, a serum 25(OH)D concentration of 40 nmol/L (from the middle of the range of 30–50 nmol/L and at which risk of adverse bone health outcomes increases) and 50 nmol/L (which includes an additional 30% to cover nearly all the population, ie, 97.5%) were selected to serve as the target concentrations for a median dietary requirement (EAR) and RDA, respectively, to be established for persons aged 1–18 y (5). The DRI committee then used data from 9 vitamin D intervention

### Table 3

<table>
<thead>
<tr>
<th>Serum 25(OH)D cutoff</th>
<th>50th</th>
<th>90th</th>
<th>95th</th>
<th>97.5th</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;25 nmol/L</td>
<td>0.2</td>
<td>5.5</td>
<td>7.0</td>
<td>8.3</td>
</tr>
<tr>
<td>&gt;37.5 nmol/L</td>
<td>5.3</td>
<td>10.6</td>
<td>12.1</td>
<td>13.5</td>
</tr>
<tr>
<td>&gt;40 nmol/L</td>
<td>6.3</td>
<td>11.7</td>
<td>13.2</td>
<td>14.5</td>
</tr>
<tr>
<td>&gt;50 nmol/L</td>
<td>10.4</td>
<td>15.8</td>
<td>17.3</td>
<td>18.6</td>
</tr>
</tbody>
</table>

1 All values are estimates; 95% CIs in parentheses. The results are based on a log-linear model of serum 25(OH)D as a function of vitamin D intake, and 95% CIs were calculated by using a bias-corrected bootstrap based on 10,000 replications.

2 The vitamin D intake that will maintain serum 25(OH)D concentrations in 50% of adolescent girls (mean age: 11.3 y) above the indicated cutoff concentration during winter.
studies of individuals aged 6 to >60 y performed at northern latitudes in Europe and Antarctica during their respective winter seasons (with minimal UVB sun exposure) to establish regression equations of the simulated response of serum 25(OH)D concentrations to total vitamin D intake. The EAR and RDA for vitamin D of 10 and 15 μg/d, respectively, were derived from this regression analysis (5). The slightly lower and higher estimates of the EAR (5.3 μg/d) and RDA (18.6 μg/d) values, respectively, in the present study may reflect our use of a regression equation based on individual data from a cohort of adolescent girls supplemented with vitamin D compared with that used by the DRI committee, which was based on mean responses in vitamin D treatment groups arising from the 9 intervention studies, only one of which was in children and adolescents (39). Whereas no age effect on the response of serum 25(OH)D to total vitamin D intake was found in their combined regression analysis, the committee did indicate that there was considerable uncertainty in this simulated dose-response relation that needs to be taken into account, in particular in relation to the CIs of the relation (5).

The US DRI committee suggested that it would be ideal if the relative contribution made by UVB sunlight to the overall serum 25(OH)D concentration could be quantified, thereby clearing the path to better estimate the total intake of vitamin D needed to maintain a specified serum 25(OH)D concentration associated with the health outcome (5). However, because much of the data related to dietary recommendations about vitamin D is complicated by the confounding effect of UVB sunlight exposure, the DRI panel set the EAR and RDA assuming minimal cutaneous synthesis of vitamin D through sun exposure (5). Furthermore, the committee suggested that vitamin D requirements cannot be based on an accepted or “recommended” level of sun exposure as a means to meet vitamin D requirements, because existing public health concerns about sun exposure and skin cancer preclude this possibility (5). Interestingly, the UK COMA subgroup on bone health (1) in their reevaluation of dietary vitamin D requirement suggested that the majority of the UK population can achieve adequate vitamin D status if the skin of the face and arms is exposed for ∼0.5 h/d between April and October. However, some have argued that this level of surface exposure may not be sufficient (40), and it is worth noting that population levels of unprotected sun exposure may be rapidly declining as a consequence of public education campaigns in relation to skin cancer (41). Moreover, the UK COMA subgroup concluded that there was no evidence on which to base a recommendation to establish an RNI for individuals aged 4–64 y on the basis that skin synthesis of vitamin D would generally ensure adequacy, except for those in this age group with very limited UVB sun exposure (and for whom an RNI of 10 μg/d was set) (1).

Our data show that 50% of adolescent girls would be able to maintain winter serum 25(OH)D concentrations ≥25.0 nmol/L with intakes as low as 0.2 μg/d, which lends support to the concept that cutaneous vitamin D synthesis during the summer months (and resulting tissue stores of vitamin D) probably offsets the dietary requirement for vitamin D for many in the population. It could be that those adolescents who do not maintain serum 25(OH)D concentrations ≥25.0 nmol/L in winter have low tissue stores of vitamin D arising from limited dermal synthesis during summer. The DRI committee suggest that the kinetics of vitamin D turnover or mobilization from stores may differ in those with lower baseline serum 25(OH)D concentrations and also that the potential contribution from body stores remains unknown and thus introduces uncertainty (5). Our data on the dietary requirement for vitamin D could provide a basis for reconsidering the establishment of an RNI for vitamin D by the authoritative bodies responsible for devising nutrition policy in the United Kingdom should they question the rationale that skin synthesis of vitamin D (and tissues stores) during summer will generally ensure adequacy in winter time for most adolescent populations, except those at risk of limited UVB sunshine exposure. Survey data from the UK NDNS show that up to 21% and 50% of UK free-living adolescents (age: 11–18 y; whose mean vitamin D intake was 2.6 μg/d) have plasma 25(OH)D concentrations <25 and <50 nmol/L, respectively, in winter (10), which might suggest that low vitamin D status is evident in significant numbers of certain population subgroups. Furthermore, should the UK authoritative bodies decide to retain a serum 25(OH)D concentration <25 nmol/L as the threshold, our data support the choice of the UK COMA subgroup in setting 10 μg/d as the RNI for at-risk individual’s (aged 4–64 y) with limited UVB exposure to achieve adequacy on the basis of the <25 nmol/L criterion (1).

Establishment of dietary reference intakes for vitamin D is complicated by the seasonal variation in serum 25(OH)D arising from the contribution of UVB sunshine to vitamin D status. In particular, it is not known how much of a risk is posed by the decline in winter serum 25(OH)D concentrations below a specified threshold, compared with chronically low concentrations, which warrants urgent research emphasis.

Whereas the data for the present analysis came from 2 different studies that could be viewed as a limitation, these studies were part of the same project, had very similar designs, and used the same supplements and centralised analysis of serum 25(OH)D. The dietary vitamin D estimate data build on the very limited evidence base for adolescents.

In conclusion, the vitamin D intakes required to maintain wintertime serum 25(OH)D concentrations above the most conservative threshold of adequacy [ie, 25 nmol/L; and that used traditionally by several UK and European Union authorities (1, 29–31)] and the more recently suggested concentration of 50 nmol/L by the Institute of Medicine (5) in >97.5% of adolescent girls are 8.3 and 18.6 μg/d, respectively.

The authors’ responsibilities were as follows—CM, CL-A, KFM, JJ, and KDC: involved in the conception of work and are grant holders; KFM, HTV, CM, and CL-A: contributed to the execution of the study; JJ: contributed to the sample analysis; APF and KDC: contributed to the data analysis; and KDC: drafted the manuscript. All authors approved the final manuscript. None of the authors had a conflict of interest.

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