Estimation of the dietary requirement for vitamin D in healthy adults[1–3]

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ABSTRACT

Background: Knowledge gaps have contributed to considerable variation among international dietary recommendations for vitamin D.

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 (ie, 25, 37.5, 50, and 80 nmol/L) during wintertime after adjustment for the effect of summer sunshine exposure and diet.

Design: A randomized, placebo-controlled, double-blind 22-wk intervention study was conducted in men and women aged 20–40 y ($n = 238$) by using different supplemental doses (0, 5, 10, and 15 μg/d) of vitamin D_3 throughout the winter. Serum 25(OH)D concentrations were measured by using enzyme-linked immunoassay at baseline (October 2006) and endpoint (March 2007).

Results: There were clear dose-related increments ($P < 0.0001$) in serum 25(OH)D with increasing supplemental vitamin D_3. The slope of the relation between vitamin D intake and serum 25(OH)D was 1.96 nmol $\cdot$ L^{-1} $\cdot$ μg^{-1} intake. The vitamin D intake that maintained serum 25(OH)D concentrations of >25 nmol/L in 97.5% of the sample was 8.7 μg/d. This intake ranged from 7.2 μg/d in those who enjoyed sunshine exposure, 8.8 μg/d in those who sometimes had sun exposure, and 12.3 μg/d in those who avoided sunshine. Vitamin D intakes required to maintain serum 25(OH)D concentrations of >37.5, >50, and >80 nmol/L in 97.5% of the sample were 19.9, 28.0, and 41.1 μg/d, respectively.

Conclusion: The range of vitamin D intakes required to ensure maintenance of wintertime vitamin D status [as defined by incremental cutoffs of serum 25(OH)D] in the vast majority (>97.5%) of 20–40-y-old adults, considering a variety of sun exposure preferences, is between 7.2 and 41.1 μg/d. *Am J Clin Nutr* 2008;88:1535–42.

INTRODUCTION

It is well established that prolonged and severe clinical vitamin D deficiency, represented as serum or plasma 25-hydroxyvitamin D [25(OH)D] concentrations of <10–25 nmol/L, 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 25(OH)D/L is used as the lower threshold for vitamin D status (1). There is, however, a lack of consensus on the cutoffs of plasma 25(OH)D that define the lower limit of adequacy or sufficiency, and values between 30 and 80 nmol/L have been suggested (5–7). In addition, a growing body of evidence suggests that serum 25(OH)D concentrations of <50 nmol/L may be associated with greater risk of a wide range of other nonskeletal chronic diseases (8, 9). With this in mind, it is of concern that a high prevalence of low vitamin D status has been reported in adults from many countries, as reviewed in several reports (10–13). In addition, the age profile of those with low vitamin D status is contrary to previously accepted wisdom; for example, younger adults in the United Kingdom are more likely to have serum 25(OH)D values of <25 nmol/L than are older adults (20.2% and 11.7% of adults aged 19–34 y and 35–64 y, respectively) (14).

In humans, 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 sun exposure for dermal synthesis, vitamin D becomes an essential nutrient. Considerable variation exists between authoritative dietary recommendations for vitamin D intakes (1, 5, 15, 16). The UK Committee on Medical Aspects of Food and Nutrition Policy (COMA) chose in 1991 not to set a reference nutrient intake (RNI) for persons aged 4–64 y on the basis of the expectation that skin synthesis of vitamin D would generally ensure adequacy (15), a recommendation upheld in 1998 by the UK COMA subgroup on bone health (1).

In contrast, the US Dietary Reference Intake (DRI) panel for calcium and related nutrients set adequate intakes (AIs) for vitamin D in 1997 (5). The US DRI panel concluded that there was insufficient evidence to set estimated average requirements [(EAR)], which are the foundation for setting recommended dietary allowances (RDA), for vitamin D, and the panel emphasized the fact that contributions from sunlight and food are difficult to measure (5). An AI for vitamin D was set on the basis of intakes necessary to achieve "normal" ranges of serum 25(OH)D concentrations. However, in establishing the AI, the US DRI

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panel assumed that there was no cutaneous synthesis of vitamin D through sun exposure (5). The European Union (EU) dietary recommendation [population reference intake (PRI)] for vitamin D in adults ranges from 0 to 10 μg/d to account for the widely varying latitudes in which EU citizens live (35–70 °N) (16).

The aim of the present study was to perform a randomized controlled intervention study in adults (aged 20–40 y) by using supplemental intakes (0, 5, 10, and 15 μg/d) of vitamin D_3 throughout the winter to establish the distribution of dietary requirements for the maintenance of nutritional adequacy of vitamin D during late winter, as indicated by serum 25(OH)D concentrations ranging from ≥25 nmol/L to ≥80 nmol/L. In addition, the effect of summer sunshine exposure (and the resulting tissue vitamin D stores) on these dietary requirements was assessed.

SUBJECTS AND METHODS

Subjects

A total of 245 apparently healthy adults were recruited to this 2-center 22-wk vitamin D intervention trial. Subjects were recruited in Cork, Ireland (n = 123), and Coleraine, Northern Ireland (United Kingdom) (n = 122), with the use of advertisements placed around the universities, at shopping centers, and at various workplaces. We aimed to recruit equal numbers of men and women and equal numbers of participants aged from 20 to 30 y and from >30 to 40 y. Inclusion criteria were consenting white men and women aged 20–40 y. Volunteers were excluded if they consumed vitamin D–containing supplements for 12 wk before initiation of the study or if they planned to take a winter vacation (during the course of the 22-wk intervention) to a location at which either the altitude or the latitude would be predicted to result in significant cutaneous vitamin D synthesis from solar radiation (eg, a mountain ski resort or a sunny winter coastal resort). Severe medical illness, hypercalcemia, known intestinal malabsorption syndrome, excessive alcohol use, current medications known to interfere with vitamin D metabolism, and pregnancy or plans to become pregnant during the 22-wk intervention also were reasons for exclusion.

All participants gave written informed consent according to the Helsinki Declaration. The study was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, University College Cork, and by the Research Ethics Committee of the University of Ulster, Coleraine. The study was also registered on the Current Controlled Trials Register (ISRCTN Reg. no. ISRCTN20236112; Internet: http://www.controlled-trials.com/ISRCTN20236112).

Design and conduct of study

The present study was a double-blind, placebo-controlled trial in which adult subjects at 2 centers were randomly assigned to receive 0 (placebo), 5, 10, or 15 μg vitamin D_3/d for 22 wk. This range of supplemental vitamin D was estimated to provide a range of intakes of vitamin D that fit closely within the 2.5th and 97.5th percentiles of intakes for UK adults (data from the National Diet and Nutrition Survey [NDNS (14)]. The upper end of the estimated range of daily total intake was well below the tolerable upper intake level (UL) for vitamin D (50 μg/d) established by the EU Scientific Committee on Food (16) and the US DRI panel (5). Randomization was centralized, computer-generated, stratified by center, and adjusted for age (20–30 or >30–40 y) and sex. The vitamin D_3 capsules and matching placebo capsules were produced by Banner Pharmacaps (Tilburg, Netherlands) and were identical in appearance and taste. The vitamin D_3 content of the capsules was independently confirmed by laboratory analysis (Consultus Ltd, Glanmire, Ireland). Compliance was assessed by capsule counting. An a priori decision was made to include only those subjects whose compliance exceeded 85%. The allocation remained concealed until the final analyses, and all data were reported by persons who were blinded to the allocation scheme.

The study was carried out in 2 locations: Cork, Ireland (latitude 51 °N), and Coleraine, Northern Ireland, United Kingdom (latitude 55 °N). A 2-center approach was chosen because of the differences in summer weather patterns and cloud cover between the 2 centers and because the 2 centers, which are separated by 4 ° of latitude, provide a geographic spread that covers a sizeable area of Ireland and the United Kingdom. [Data from the NDNS show that mean serum 25(OH)D concentrations in older adults were ≈10 nmol/L lower in the northern part of the United Kingdom (55–57 °N) than in London and the Southeast (51 °N) (17)].

All subjects were recruited between March 2006 and June 2006, and they were asked to keep a sunshine-exposure diary and answer a sunshine-exposure questionnaire during a defined period in July 2006. Instructions on recording and completing the sunshine diary were provided during a screening visit to the study centers. The 7-d diary was developed as part of the EU Framework V–funded OPTIFORD project (18). Variables recorded included time spent outdoors, weather conditions, and manner of dress.

All subjects commenced the intervention study between October 2 and November 2, 2006, and they finished the study 22 wk later, between February 27 and April 7, 2007; this timespan represents a period during which vitamin D status would be expected to decline to a nadir (19). During the intervention phase, each participant made 2 further visits to the study centers, at baseline (week 0) and endpoint (week 22). At each visit, an overnight fasting blood sample was taken from each participant by a trained phlebotomist between 0830 and 1030. Blood was collected by venipuncture into an evacuated tube without an additive and processed to serum, which was immediately stored at −80 °C until required for analysis. Anthropometric measurements including height, weight, waist circumference, and biceps, triceps, subscapular and suprailiac skinfold thicknesses were taken as described previously (20). Habitual intakes of calcium and vitamin D were estimated by using a validated food-frequency questionnaire (FFQ) (21, 22), which was administered by a research nutritionist; a health and lifestyle questionnaire, which assessed physical activity, general health, smoking status, and alcohol consumption, also was completed. Participants were contacted monthly by phone, E-mail, or both to promote compliance and encourage completion of the study protocol.

Laboratory analysis

Serum 25-hydroxyvitamin D

25(OH)D concentrations were measured in serum samples by using an enzyme-linked immunosorbent assay [(ELISA) OCTEIA 25-Hydroxy Vitamin D; Immuno Diagnostic Systems Ltd, Boldon, United Kingdom]. The intraassay and interassay CV for

the ELISA method was 5.9% and 6.6%, respectively. This ELISA is used for the quantitative measurement of 25(OH)D, further details of which have been described previously (23). The quality and accuracy of serum 25(OH)D analysis in our laboratory are ensured on an ongoing basis by participation in the Vitamin D External Quality Assessment Scheme [(DEQAS) Charing Cross Hospital, London, United Kingdom].

Serum intact parathyroid hormone

Serum intact parathyroid hormone (iPTH) concentrations were measured in serum with the use of an ELISA (MD Biosciences Inc, St Paul, MN). The intraassay and interassay CV was 3.4% and 3.8%, respectively.

Serum total calcium

Total calcium and albumin concentrations in serum were measured by using an automated system (Instrumentation Laboratories UK Ltd, Warrington, United Kingdom). Serum calcium concentrations were adjusted for albumin concentration.

Mathematical modeling of the relation of 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. Given the skewed distribution of serum 25(OH)D, the mean value of log-transformed serum 25(OH)D 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 around the mean, and *Q-Q* plots were used to examine the assumption that variation around the predicted value was normally distributed. The distribution of log serum 25(OH)D was transformed to obtain the distribution for serum 25(OH)D as a function of total vitamin D intake. Finally, we estimated the dietary requirements for vitamin D to maintain selected percentages of the population above 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. A more complex model that included sun preference as a categorical variable allowed the mean concentrations of log serum 25(OH)D to vary with sun preference. Sun preference and total vitamin D intake were independent predictors of serum 25(OH)D concentrations. There was no evidence that the association between serum 25(OH)D and vitamin D intake depended on sun preference. Results were verified by using robust regression models that minimized the effect of outliers and heteroscedasticity.

Statistical analysis

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 about the magnitude of any relation and the residual variation in serum 25(OH)D concentration, after the effect of background dietary intake has been removed. Specifically, a value of 0.5 was assumed to represent the minimum clinically important slope, and the residual variation of serum concentration of 25(OH)D around the mean line was assumed to be normal. On the basis of the distribution of data from older women from our group's previous study (22), it was assumed that the distribution of dietary intakes in the current study would be similar. With these assumptions, a study design recruiting 240 volunteers, 60 of whom were assigned to 1 of 4 dose levels (0, 5, 10, and 15 μg vitamin D/d), and including 20% to cover potential dropouts, had 90% power to show a dose-response relation.

Statistical analysis of the data were conducted by using SPSS for WINDOWS software (version 12.0; SPSS Inc, Chicago, IL) and STATA software (version 10.0; StataCorp LP, College Station, TX). The distributions of all variables were tested with the use of Kolmogorov-Smirnov tests. Descriptive statistics ($\bar{x} \pm$ SD or median and interquartile range, where appropriate) were determined for all variables. Serum concentrations of 25(OH)D and PTH, as well as baseline dietary vitamin D and calcium, were not normally distributed and thus were log transformed to achieve near-normal distributions. Serum concentrations of albumin-corrected calcium, endpoint dietary calcium and total vitamin D concentrations, and age, weight, height, and body mass index (BMI; in kg/m^2) were normally distributed. Baseline characteristics of subjects in both study centers were compared by using chi-square (for male-to-female ratio and sun preference) or unpaired Student's *t* tests. Baseline characteristics of subjects in the different intervention groups were compared by using chi-square tests (for male-to-female ratio and sun preference) and one-factor analysis of variance (ANOVA). Changes in calcium and vitamin D intake from baseline to endpoint were tested by using ANOVA and Tukey's test. Linear models of the response in a repeated-measures ANOVA for the differences in serum 25(OH)D and PTH concentrations were also constructed. The main effects included were dietary treatment and sex. The linear models also included 2-way interactions between the main effects. $P < 0.05$ was considered to be statistically significant.

RESULTS

Baseline characteristics of subjects

Of the 245 subjects recruited into the study, 238 returned for the intervention phase, and 221 completed the intervention phase. The progress of these subjects through the trial is shown in **Figure 1**. Subjects in Cork were slightly but significantly ($P < 0.01$) younger than those in Coleraine (**Table 1**), but there was no significant ($P = 0.5$) difference in mean age between males and females (data not shown). There was no significant difference in mean weight, height, or BMI at baseline between subjects from the 2 centers (Table 1).

Two-factor ANOVA showed that, whereas baseline serum 25(OH)D concentrations did not differ by sex ($P = 0.5$), they differed significantly ($P = 0.001$) by center (Table 1). There was no significant interaction ($P = 0.2$) between these 2 main factors. Baseline serum PTH concentrations were similar in subjects from both centers ($P = 0.7$; Table 1) but were significantly higher in women than in men [median (interquartile range); 49.2 (35.3–63.7) and 40.7 (30.1–54) ng/mL, respectively; $P < 0.05$). Mean $\pm$ SD baseline serum albumin–corrected calcium concentrations were significantly lower in subjects from Cork than in those from Coleraine ($P = 0.001$; Table 1) and significantly higher in men than in women (8.8 $\pm$ 0.3 and 8.7 $\pm$ 0.2 nmol/L, respectively; $P < 0.01$).

There was no significant between-center difference in habitual vitamin D or calcium intake in subjects at baseline (Table 1);

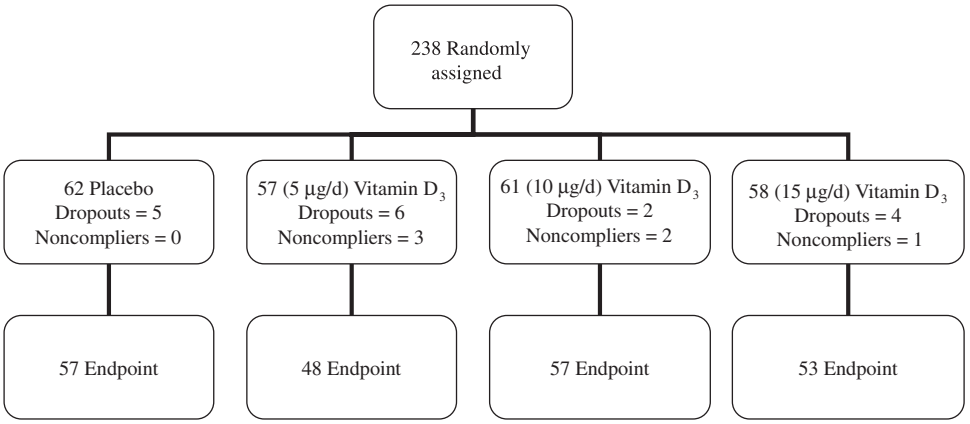

FIGURE 1. Flow of subjects through the study.

however, men had significantly ($P < 0.006$) higher intakes of vitamin D and calcium than did women [3.8 (2.4–5.8) and 3.3 (1.7–5.0) μg/d, respectively, for vitamin D; 1128 (857–1485) and 803 (587–1045) mg/d, respectively, for calcium), which was expected, because men typically have higher food and nutrient intakes than do women.

Baseline serum 25(OH)D concentrations in subjects who described themselves as often having exposure to summer sunshine ($n = 84$) were significantly ($P < 0.01$) higher than those in subjects who described themselves as avoiding ($n = 27$) or sometimes having exposure to summer sunshine ($n = 107$) [82.4 (61.6–105.9), 50.5 (43.7–78.2), and 65.2 (51.0–86.3) nmol/L, respectively]. The difference between the latter 2 groups was not significant ($P = 0.3$).

Effects of vitamin D intervention

There difference in mean age, weight, height or BMI at baseline among the 4 treatment groups was not significant ($P = 0.7$; data not shown). Similarly, there was no significant difference in the proportion of men to women, in sun exposure preferences, in mean habitual dietary vitamin D or calcium intake, or in mean preintervention serum 25(OH)D, PTH, or albumin-corrected calcium concentrations among the treatment groups (**Table 2**).

No adverse events were reported during the study. Of the 17 dropouts, 5, 6, 2, and 4 were from the placebo and 5, 10, and 15 μg vitamin D/d groups, respectively. Subjects dropped out for a variety of reasons (eg, pregnancy, loss of interest, illness unrelated to the intervention, or desire to take sun holiday), and in no instance was dropping out related to the intervention. Six subjects failed to exceed the minimum 85% compliance, and they were excluded from the main analysis. In the remaining subjects, there was good supplement adherence based on pill count [100% (97.4–100%)], and compliance did not differ significantly among the 4 treatment groups ($P = 0.7$).

As expected, total vitamin D intake (diet plus supplemental vitamin D) increased in a dose-related manner with supplementation (4.4 ± 3.6, 9.1 ± 2.4, 13.9 ± 2.0, and 19.2 ± 3.1 μg/d in the placebo and 5, 10, and 15 μg vitamin D/d groups,

TABLE 1
Baseline characteristics of the subjects who entered the intervention study[1]

	All subjects ($n = 221$)	Cork ($n = 108$)	Coleraine ($n = 113$)
Male:female (n)	111:111	54:54	57:56
Age (y)	29.9 ± 6.2[2]	28.7 ± 6.0	31.1 ± 6.3[3]
Weight (kg)	77.0 ± 15.8	76.6 ± 15.9	77.3 ± 15.7
Height (m)	1.71 ± 0.09	1.72 ± 0.10	1.71 ± 0.08
BMI (kg/m^2)	26.1 ± 4.3	25.8 ± 4.0	26.3 ± 4.5
Dietary calcium (mg/d)	976 (682–1301)[4]	955 (676–1301)	990 (718–1307)
Dietary vitamin D (μg/d)	3.6 (2.1–5.4)	3.4 (2.1–5.1)	3.6 (2.3–5.7)
Serum 25(OH)D (nmol/L)	70.3 (53.4–90.3)	76.2 (57.4–104.1)	64.9 (48.5–84.9)[4]
Serum PTH (ng/mL)	43.8 (32.3–59.3)	43.6 (31.5–57.6)	44.1 (34.4–60.1)
Serum calcium (mmol/L)[5]	8.8 ± 0.3	8.7 ± 0.3	8.9 ± 0.3[4]
Summer sun exposure preferences (%)			
Sun avoiders	12.7	13.0	12.4
Some exposure	48.8	54.0	44.2
Frequent exposure	38.5	33.0	43.4

[1] PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.
[2] $\bar{x}$ ± SD (all such values).
[3] Significantly different from subjects in Cork, $P \leq 0.001$ (unpaired Student's t tests).
[4] Median; interquartile range in parentheses (all such values); used in the case of nonnormally distributed variables.
[5] Albumin corrected.

TABLE 2
Habitual dietary intake, summer sunshine exposure preference, and biochemical measures of vitamin D status among treatment groups before and after intervention[1]

	Treatment group				
	Placebo ($n = 57$)	5 μg vitamin D/d ($n = 48$)	10 μg vitamin D/d ($n = 57$)	15 μg vitamin D/d ($n = 53$)	P^2
Habitual dietary vitamin D (μg/d)	3.4 (2.0–5.0)[3]	4.3 (2.2–5.7)	3.5 (2.3–4.7)	3.6 (1.8–5.8)	0.856
Habitual dietary calcium (mg/d)	924 (694–1197)	905 (655–1314)	976 (681–1286)	1014 (744–1387)	0.600
Summer sun exposure preferences (%)					
Sun avoider	12.5	12.5	8.9	17.0	
Some sun exposure	50.0	50.0	46.4	49.1	
Frequent sun exposure	37.5	37.5	44.6	34.0	0.885
Serum 25(OH)D (nmol/L)					
Before intervention[4]	65.7 (58.4–94.1)	60.0 (50.0–89.7)	72.2 (55.7–91.9)	75.9 (55.9–89.3)	0.623
After intervention[5,6]	37.4 (31.4–47.9)[a]	49.7 (44.6–60.0)[b]	60.0 (51.0–69.1)[c]	69.0 (59.1–84.2)[d]	<0.0001
Serum PTH (ng/mL)					
Before intervention[4]	49.7 (32.9–62.1)	46.9 (34.0–70.3)	43.1 (35.6–57.9)	38.4 (29.0–50.3)	0.145
After intervention[5,6]	56.2 (41.3–67.8)[a]	52.0 (35.9–67.9)[a]	50.5 (41.1–69.4)[a]	43.0 (33.1–62.0)[b]	0.060

[1] PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D. Values in a row with different superscript letters are significantly different, $P < 0.05$.
[2] One-factor ANOVA followed by Tukey's test.
[3] Median; interquartile range in parentheses (all such values), used in the case of nonnormally distributed variables.
[4] All baseline blood samples were taken between October 2 and November 7, 2006.
[5] Repeated-measures ANOVA was used to test the treatment × time interaction; and the same trend was observed for serum 25(OH)D ($P \leq 0.0001$), but the treatment × time interaction was not significant for serum PTH ($P = 0.274$).
[6] All endpoint blood samples were taken between February 27 and April 7, 2007.

respectively; $P < 0.0001$). In contrast, calcium intake at endpoint did not differ significantly ($P = 0.5$) among the 4 groups (data not shown).

There was a significant ($P < 0.0001$) effect of treatment on mean postintervention serum 25(OH)D concentrations, with clear dose-related increments with increasing supplemental vitamin D_3 (Table 2). There was no significant difference in mean postintervention serum albumin–corrected calcium concentrations among the treatment groups (8.6 ± 0.3, 8.7 ± 0.3, 8.6 ± 0.3, and 8.6 ± 0.3 mmol/L in the placebo and 5, 10, and 15 μg vitamin D/d groups, respectively; $P = 0.526$) and no significant change over time (P for time × treatment = 0.336). None of the subjects had hypercalcemia. There was a trend ($P = 0.06$) for postintervention serum PTH concentration to be affected by treatment, and post hoc analysis showed a significantly ($P = 0.009$) lower mean concentration in the group receiving 15 μg/d than in the group receiving placebo (Table 2). However, the treatment × time interaction in repeated-measures ANOVA was not significant ($P = 0.274$) for the effect of vitamin D supplementation on serum PTH concentrations.

Relation between vitamin D intake and vitamin D status

The relation between serum 25(OH)D concentrations in late winter 2007 and the total vitamin D intake (diet and supplemental) in the 20–40-y-old subjects is shown in **Figure 2**. The slope of the relation between total vitamin D intake and serum 25(OH)D concentrations in the entire group was 1.96 nmol/L·μg intake. There was no significant difference between the slope estimates for men and women (1.82 and 2.15 nmol·L^{-1}·μg^{-1} intake, respectively; $P = 0.26$).

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 20–40-y-old adults were 2.7, 5.9, and 8.7 μg/d, respectively. An EAR [the vitamin D intake required to maintain serum 25(OH)D concentrations >25 nmol/L in 50% of the adults] could not be estimated because, at the lowest vitamin D intake (0.1 μg), the serum 25(OH)D concentrations in the 50th percentile were 34.5 nmol/L. Data on sun preference also were incorporated into the model; the vitamin D intakes that maintained serum 25(OH)D concentrations of ≥25 nmol/L in 97.5% of the sample were 7.2, 8.8, and 12.3 μg/d in those who reported often having sunshine exposure, those who sometimes had sunshine exposure, and sunshine avoiders, respectively. The vitamin D intakes that maintained serum 25(OH)D concentrations above 2 other commonly suggested cutoffs in 97.5% of the sample were 26.1, 27.7, and 31.0 μg/d (for ≥50 nmol/L) and 38.9, 40.6, and 43.9 μg/d (for ≥80 nmol/L) in those who reported often having

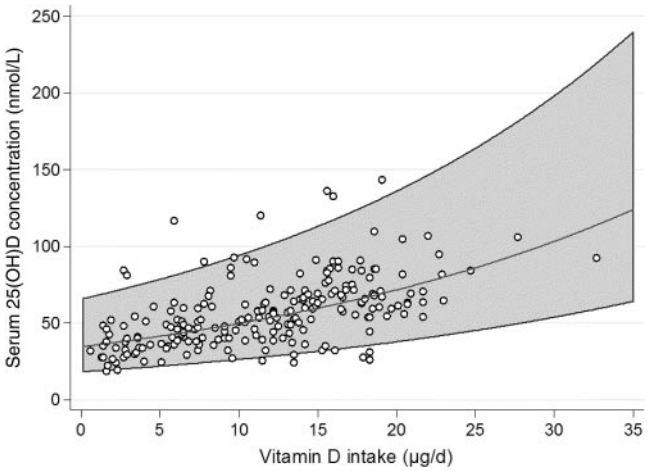

FIGURE 2. The relation between serum 25-hydroxyvitamin D [25(OH)D] concentrations (in late winter 2007) and total vitamin D intake (diet and supplemental) in 20–40-y-old healthy persons ($n = 215$) living at northerly latitudes (51 and 55 °N). Mean response and 95% CIs in the shaded area.

sunshine exposure, those who sometimes had sunshine exposure, and sunshine avoiders, respectively.

Whereas a serum 25(OH)D concentration of <25 nmol/L has been used by several authorities as the traditional indicator of adequacy for vitamin D (1, 5, 15, 16), several other biochemical cutoffs for serum 25(OH)D, ranging from 37.5 to 80 nmol/L, have been suggested (6–9, 24). The 50th, 90th, 95th, and 97.5th percentile estimates for vitamin D intake, obtained by using a range of alternative indicators of adequacy for vitamin D status, are shown in **Table 3**.

DISCUSSION

The RDA for nutrients is generally established as the average daily intake level that is sufficient to meet the nutrient requirement for nearly all (97–98%) persons in a life-stage and sex group (1, 5). Uncertainty and gaps in the available data about the relative contribution of 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 the identification of the intake values that will maintain serum 25(OH)D concentrations above chosen cutoffs when dermal production of vitamin D is absent or markedly diminished is urgently required. We examined the relation between vitamin D intake and serum 25(OH)D concentrations in late winter, after a 4-dose vitamin D intervention study that lasted 22 wk (from October 2006 to March 2007) in 221 healthy 20–40-y-old whites living at 51 °N and 55 °N. We found that a daily intake of 8.7 μg vitamin D/d would have maintained serum 25(OH)D concentrations >25 nmol/L in 97.5% of the sample. Because the thresholds for vitamin D adequacy are widely disputed, we also reported the 50th, 90th, 95th, and 97.5th percentiles of vitamin D intakes required to maintain serum 25(OH)D concentrations in excess of 37.5, 50, and 80 nmol/L (6, 7).

These data could provide a basis for reconsideration of the establishment of an RNI for vitamin D by the authoritative bodies responsible for devising nutrition policy. In the United Kingdom, COMA concluded in 1998 that there was no evidence on which to base a recommendation to establish an RNI (1). When it was establishing the AI for vitamin D for persons aged 19–50 y (5), the US DRI panel for calcium and related nutrients relied heavily on data from a study by Kinyamu et al (25), which showed that an average intake of 3.3–3.4 μg vitamin D/d was sufficient to keep serum 25(OH)D concentrations above 30 nmol/L during winter months in most (94%) women 25–35 y old (n = 52) in Nebraska (latitude: 41 °N). The panel rounded down this intake value to 2.5 μg/d and then doubled it to achieve an AI of 5.0 μg/d (5). Working from a lack of data in men, the panel also made an assumption that the AI for men would be similar to that for women (5). The findings of the present study suggest that a vitamin D intake of approximately twice the AI is required by healthy white men and women at latitudes of ≈50 °N to maintain 25(OH)D at these concentrations (≈30 nmol/L).

In setting the AI, the US DRI panel also assumed that there was no cutaneous synthesis of vitamin D through sun exposure (5). This is true in winter, and, whereas summertime dermal synthesis can be viewed as a supplement ("top-up") to help generate wintertime tissue stores of vitamin D, individual variation is likely to be high, which makes summertime dermal synthesis an unreliable contributor to vitamin D status. In the current study, sun exposure preference was assessed as a surrogate for tissue stores; as expected, whereas most people liked some (≈50%) or a lot (≈38%) of sun, ≈12% of subjects were sun avoiders. One might expect this minority of subjects to have the highest dietary requirement for vitamin D in winter as a consequence of their low tissue stores. In fact, the vitamin D intake required to maintain serum 25(OH)D concentrations in late winter above 25 nmol/L was 12.3, 8.8, and 7.2 μg/d for sunshine avoiders, those who get some sunshine, and those who enjoy the sun, respectively. This analysis, although perhaps limited by the relatively small number of sunshine avoiders, serves to illustrate not only the greater dietary requirement for vitamin D in persons who steer clear of the sun but also the potential importance of high vitamin D stores from sun exposure during summer in offsetting potentially deleterious effects of low dietary intakes of vitamin D during winter.

It is interesting that the UK COMA subgroup on bone health, in their re-evaluation of dietary vitamin D requirement (1), took an approach completely opposite to that of the US authority (5) in terms of contribution of sun exposure to vitamin D requirement. The COMA subgroup suggested that most of the adult population in the United Kingdom can achieve adequate vitamin D status if the skin of the face and arms is exposed for ≈30 min/d between April and October. Some have argued, however, that this degree of surface exposure may not be sufficient (26). Moreover, the COMA subgroup concluded there had been no new evidence to suggest that persons aged 4–64 y rely on dietary intake for adequate vitamin D status. The data from the present study clearly show that vitamin D tissue stores, developed during summer via exposure of skin to sunshine, were not sufficient to maintain serum 25(OH)D concentrations of ≥25 nmol/L in most of the population, and that dietary vitamin D is an absolute requirement to maintain status above this minimum threshold.

TABLE 3
Estimated dietary requirements for vitamin D at selected percentiles in 215 men and women aged 20–40 y to maintain serum 25-hydroxyvitamin D [25(OH)D] concentrations above selected biochemical cutoffs during winter[1]

Cutoff	50th percentile[2]	90th percentile	95th percentile	97.5th percentile
		μg/d		
Serum 25(OH)D >25 nmol/L	—	2.7 (0.0, 4.7)	5.9 (3.6, 8.0)	8.7 (6.5, 11.1)
Serum 25(OH)D >37.5 nmol/L	2.3 (0.0, 4.2)	13.8 (12.1, 15.9)	17.0 (14.8, 19.9)	19.9 (17.2, 23.5)
Serum 25(OH)D >50 nmol/L	10.2 (8.9, 11.4)	21.7 (19.3, 25.0)	25.0 (21.9, 29.1)	28.0 (24.2, 32.8)
Serum 25(OH)D >80 nmol/L	23.1 (21.0, 26.0)	34.8 (30.4, 40.6)	38.3 (33.0, 44.8)	41.1 (35.4, 48.7)

[1] All values are estimate; 95% CI in parentheses. Results were based on a log-linear model of serum 25(OH)D as a function of vitamin D intake; the 95% CIs were calculated by using a bias-corrected bootstrap based on 10 000 replications.

[2] The vitamin D intake value that will maintain serum 25(OH)D concentrations in 50% of 20–40-y-old adults above the indicated cutoff during winter.

Survey data from the UK NDNS showed that up to 20% of UK adults 19–34 y old (whose median vitamin D intake was 2.5 μg/d) have plasma 25(OH)D concentrations of <25 nmol/L (14), which underscores our findings. We acknowledge that cutaneous vitamin D synthesis during summer months probably offsets the dietary requirement for vitamin D that would ensure adequacy during wintertime. However, it is worth noting that the percentage of the population with unprotected sun exposure may be rapidly declining, as a consequence of public education campaigns in relation to skin cancer (27).

In the current analysis, we placed strong emphasis on using a cutoff of 25 nmol/L for serum 25(OH)D on the basis that concentrations of ≈20–27.5 nmol/L are considered to be consistent with vitamin D deficiency and rickets or osteomalacia (1, 28), and the 25 nmol/L threshold has been in use to date by various important authorities (1, 5, 15, 16). However, we also reported dietary requirements for vitamin D in the current sample of white 20–40-y-old persons by using several other serum 25(OH)D cutoffs (37.5, 50, and 80 nmol/L) (6, 7). The rationale for these alternative definitions of adequacy for vitamin D in relation to skeletal and nonskeletal health benefits has been detailed elsewhere (8, 9). In an extended vitamin D supplementation study (supplementation range: 0–250 μg/d) in adult males ($\bar{x}$ age: 38.7 y) in Omaha, NE (latitude: 41.2 °N), Heaney et al (29) used pharmacokinetic modeling to estimate the vitamin D intake required to maintain prewinter serum 25(OH)D concentrations, to reach concentrations of 80 nmol/L during winter, or both. They reported a slope estimate of 0.70 nmol · L^{-1} · μg^{-1} intake (29), a figure that has been used widely to predict dietary requirements for the US adult population (27, 30). Although derived by a different means, the slope estimate in our study was 1.96 nmol/L·μg intake. It is not clear why there is a large variation between these estimates, because both studies were in young adults and both were conducted throughout winter. Despite similar concentrations of 25(OH)D (≈70 nmol/L) at baseline (October), the placebo group in the study by Heaney et al (29) experienced a mean decline in serum 25(OH)D of only 11.4 nmol/L between October and March, whereas the concentration in our placebo group decreased by 28.3 nmol/L over the same period. The men in the study by Heaney et al (29) may have had higher tissue stores after a summer at 41 °N in the United States, whereas our subjects presumably had less sun at latitudes of 51–54 °N in Ireland. It is interesting that our slope estimate agrees well with the estimates ranging from 1.6–2.2 nmol · L^{-1} · μg^{-1} intake derived in several studies in older adults (31–34). Heaney et al (29) suggested that tissue stores in the subjects in those studies may have made a lower contribution to serum 25(OH)D concentrations than did the tissue stores in the younger men in their own study. Our estimate of the dietary vitamin D requirement needed to maintain serum 25(OH)D concentrations above 80 nmol/L in 97.5% of our sample of 20–40-y-olds was 41 μg/d, which is considerably less than the 114 μg/d suggested by Heaney et al (29). Our data also show that, even for the lower cutoff of 50 nmol/L serum 25(OH)D, which may be associated with a lower risk of a wide range of nonskeletal chronic diseases (8, 9), the dietary requirement (28.0 μg/d) is still much higher than the amount currently being consumed by adult populations (14, 22, 35). A potential limitation of the present study was that relatively few subjects (17%) achieved winter serum 25(OH)D concentrations of ≥80 nmol/L, because of our use of a maximum of 15 μg supplemental vitamin D/d. This fact may have influenced the accuracy with which we can estimate the dietary requirement to achieve such high serum 25(OH)D concentrations. To absolutely confirm that our recommended intakes can achieve 25(OH)D concentrations in the range of 50 to 80 nmol/L, a wintertime intervention study using higher doses of vitamin D (at least 20–40 μg/d) would be required.

In conclusion, to ensure that the needs of >97.5% of 20–40-y-old persons are met in relation to vitamin D status during winter, 8.7 μg vitamin D/d is required to maintain serum 25(OH)D concentrations above the most conservative threshold of adequacy (ie, 25 nmol/L).

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