Estimation of the dietary requirement for vitamin D in free-living adults ≥64 y of age[1–3]

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ABSTRACT

Background: Older adults may be more prone to developing vitamin D deficiency than younger adults. Dietary requirements for vitamin D in older adults are based on limited evidence.

Objective: The objective was to establish the dietary intake of vitamin D required to maintain serum 25-hydroxyvitamin D [25(OH)D] concentrations above various cutoffs between 25 and 80 nmol/L during wintertime, which accounted for the effect of summer sunshine exposure and diet.

Design: A randomized, placebo-controlled, double-blind, 22-wk intervention was conducted in men and women aged ≥64 y ($n = 225$) at supplemental levels of 0, 5, 10, and 15 μg vitamin D_3/d from October 2007 to March 2008.

Results: Clear dose-related increments ($P < 0.0001$) in serum 25(OH)D were observed with increasing supplemental vitamin D_3 intakes. The slope of the relation between total vitamin D intake and serum 25(OH)D was 1.97 nmol · L^{-1} · μg $intake^{-1}$. The vitamin D intake that maintained serum 25(OH)D concentrations >25 nmol/L in 97.5% of the sample was 8.6 μg/d. Intakes were 7.9 and 11.4 μg/d in those who reported a minimum of 15 min daily summer sunshine exposure or less, respectively. The intakes required to maintain serum 25(OH)D concentrations of >37.5, >50, and >80 nmol/L in 97.5% of the sample were 17.2, 24.7, and 38.7 μg/d, respectively.

Conclusion: To ensure that the vitamin D requirement is met by the vast majority (>97.5%) of adults aged ≥64 y during winter, between 7.9 and 42.8 μg vitamin D/d is required, depending on summer sun exposure and the threshold of adequacy of 25(OH)D. This trial was registered at http://www.controlled-trials.com/ISRCTN20236112 as ISRCTN registration no. ISRCTN20236112. *Am J Clin Nutr* 2009;89:1366–74.

INTRODUCTION

In adults, prolonged and severe clinical vitamin D deficiency, defined as a serum or plasma 25-hydroxyvitamin D [25(OH)D]) concentration <10–25 nmol/L, leads to a mineralization defect in the skeleton causing osteomalacia (1). Less severe vitamin D deficiency causes secondary hyperparathyroidism and increases bone turnover and bone loss (2–4). Currently in the United Kingdom, the lower threshold for vitamin D status is a plasma concentration of 25 nmol/L 25(OH)D (1). There is, however, a lack of consensus on the cutoff values of plasma 25(OH)D that defines the lower limit of adequacy or sufficiency; values between 30 and 80 nmol/L have been suggested (5–7).

In common with most population subgroups, except infants, adults aged >65 y depend on sunlight for most of their vitamin D requirement. However, this age group may be more prone to developing vitamin D deficiency because of a variety of factors that reduce the cutaneous production of vitamin D, including age itself (5, 8). The dermal capacity to produce vitamin D in persons aged >65 y is ≈25% of that in persons aged 20–30 y exposed to the same amount of sunlight (9, 10). The wearing of more concealing clothing (11), an increased use of sunscreen (12), and a general lack of sun exposure arising from less physical activity and time outdoors compared with younger age groups (13, 14) can also increase the risk of low vitamin D status. Indeed, vitamin D deficiency is now a significant concern in adults aged >50 y in northern industrialized regions of the world (15–19).

In the absence of sufficient sun exposure and/or a reduced physiologic efficiency of dermal biosynthesis, vitamin D becomes an essential nutrient (1, 5). This dietary requirement is reflected in authoritative dietary recommendations for vitamin D intakes for older adults (1, 5, 13, 20). The UK and European Union (EU) dietary recommendations for vitamin D in older adults are both set at 10 μg/d (1, 13, 20). Whereas the US Dietary Reference Intake (DRI) panel for calcium and related nutrients in 1997 set an Adequate Intake (AI) for vitamin D of 10 μg/d for adults aged 51–70 y, they set a value of 15 μg/d for those aged >70 y (5). Recently, Dawson-Hughes (21) suggested that a mean serum 25(OH)D concentration of ≥75 nmol/L may be required in older adults to reduce the risk of fracture, necessitating daily vitamin D intakes of ≥20–25 μg/d.

We recently showed that the vitamin D intakes that maintained winter serum 25(OH)D concentrations above 25, 50, and 80

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nmol/L in 97.5% of young adults (20–40 y) were 8.7, 28.0, and 41.1 μg/d, respectively (22). These estimates were relatively high considering the age group, which would be expected to have a good capacity for dermal vitamin D synthesis and reasonably high peak serum 25(OH)D concentrations at the end of the summer. The aim of this study was to perform a randomized controlled intervention study in apparently healthy, free-living adults (aged ≥64 y) at supplemental levels (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 serum 25(OH)D concentrations at ranges from ≥25 to ≥80 nmol/L. In addition, the effect of summer sunshine exposure (and thus tissue vitamin D stores) on these dietary requirements was assessed.

SUBJECTS AND METHODS

Subjects

A total of 225 apparently healthy, free-living adults aged ≥64 y were recruited to this 2-center 22-wk vitamin D intervention trial. Subjects were recruited in Cork ($n = 103$) and Coleraine ($n = 122$) through senior citizens groups, active retirement groups, and day care centers as well as through advertisements across the 2 locations. Because we predicted that it would be more difficult to recruit men than women, we aimed to recruit a ratio of ≈55:45 females to males. Consenting white men and women aged ≥64 y were included to the study. Volunteers were excluded if they consumed vitamin D–containing supplements for 12 wk before initiation of the study. Volunteers were also excluded 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 winter sun coastal resort or a mountain ski resort) or if they used tanning facilities of any type. Severe medical illness, hypercalcemia, known intestinal malabsorption syndrome, excessive alcohol use, and use of medications known to interfere with vitamin D metabolism were also reasons for exclusion. The study was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, University College Cork and the Research Ethics Committee of the University of Ulster, Coleraine. All participants gave their written consent according to the Helsinki Declaration.

Design and conduct of the study

This was a double-blind, placebo-controlled trial in which elderly subjects at 2 centers were randomly assigned to receive 0 (placebo) or 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 older adults in the United Kingdom [data from the National Diet and Nutrition Survey (NDNS); 23]. 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 (24) and US DRI panel (5). Randomization was centralized, computer-generated, stratified by center, and accounted for sex. The vitamin D_3 capsules and matching placebo capsules were produced by Banner Pharmacaps (Tilburg, Netherlands). The placebo tablet and active (5, 10, or 15 μg vitamin D_3) tablets were identical in appearance and taste. The vitamin D_3 content of the capsules was independently confirmed by laboratory analysis (Consultus Ltd, Glanmire, Co, Cork, Ireland). Compliance was assessed by capsule counting. An a priori decision was made to include only those subjects who exceeded 85% compliance. The allocation remained concealed until the final analyses, and all outcomes were reported by people who were masked to the allocation scheme.

The study was carried out in 2 locations: Cork, Republic of Ireland (latitude 51°N), and Coleraine, Northern Ireland (latitude 55°N). A 2-center approach was chosen on the basis that there are differences in summer weather patterns and cloud cover between the 2 centers and that the 2 centers, which are separated by 4 degrees of latitude, provide a good geographic spread that sits well within a sizeable area in Ireland and the United Kingdom (data from the NDNS show that mean serum 25(OH)D concentrations in adults aged ≥65 y were ≈10 nmol/L lower in the northern region of United Kingdom (55–57°N) than in London and the southeast (51°N; 23).

All subjects were recruited between April and July 2007 and were requested to keep a sunshine exposure diary and answer a sunshine exposure questionnaire during a defined period in July and August 2007. Instructions on recording and completing the sunshine diary were provided to each participant during their screening visit, either at the study centers or day care or retirement centers. Both the 7-d diary and sun exposure questionnaire were developed as part of the EU Framework V-funded Toward a Strategy for Optimal Vitamin D Fortification (OPTIFORD) project; contract no. QLK1-CT-2000–00623. Diary variables included time spent outdoors, weather conditions, clothing, and skin sites exposed (eg, face only, hands and face, hands and face plus arms). The sun exposure questionnaire, which was piloted in-house ($n = 100$) and validated against ultraviolet exposure estimates using a polysulfone ultraviolet dosimeter badge (B Cullen and M Kully, unpublished observations, 2007), is capable of distinguishing between people with different levels of ultraviolet exposure and has the additional benefit of identifying the behaviors that predict exposure. The questionnaire is interviewer administered and contains categorical data on 70 items, including time spent outdoors during working hours and in recreational pursuits, vacations to sunny or ski resorts and habitual practice with respect to sun- versus shade-seeking behavior, clothing worn in the sun, sunscreen use and use of tanning facilities.

All subjects commenced the intervention study between 28 September and 16 November 2007 and finished 22 wk later between 21 February and 5 April, 2008, during which time vitamin D status would be expected to decline to a nadir (25). During the intervention phase, each participant was met by researchers on 2 occasions, either at the study centers or day care/retirement centers, at baseline (week 0) and the endpoint (week 22). At each visit, an overnight fasting blood sample was collected from each participant between 0830 and 1030 by a trained phlebotomist. Blood was collected by venipuncture into an evacuated tube with no additive and processed to serum, which was immediately stored at −80°C until required for analysis. Anthropometric measures, including height, weight, waist circumference, and biceps, triceps, subscapular, and suprailiac skinfold thickness, were taken as described previously (26). Habitual intake of calcium and vitamin D was estimated via a validated

food-frequency questionnaire (FFQ) (27, 28), which was administered by a research nutritionist, and a health and lifestyle questionnaire, which assessed physical activity, general health, smoking status, and alcohol consumption was completed. Participants were contacted monthly by phone and/or by correspondence to promote compliance and encourage completion of the study protocol.

Serum 25-hydroxyvitamin D

25(OH)D concentrations were measured at University College Cork in all serum samples by using an enzyme-linked immunosorbent assay (ELISA) (OCTEIA 25-Hydroxy Vitamin D; Immuno Diagnostic Systems, Ltd, Boldon, United Kingdom). The intra- and interassay CVs for the ELISA method were 5.9% and 6.6%, respectively. This ELISA assay was used for the quantitative determination of 25(OH)D, further details of which were described previously (29). The quality and accuracy of serum 25(OH)D analysis in our laboratory is ensured on an ongoing basis by participation in the Vitamin D External Quality Assessment Scheme (DEQAS, Charing Cross Hospital, London, United Kingdom). A comparison of the performance of our ELISA assay with that of liquid chromatography mass spectroscopy (LC-MS) in relation to DEQAS ($n = 20$) samples for 2008 showed a high correlation (ELISA $= 1.0258 \times$ LC-MS $- 3.0351$; $r = 0.96$).

Serum intact parathyroid hormone

Serum intact parathyroid hormone (PTH) concentrations were measured at University College Cork in all serum samples by using an ELISA (intact PTH; MD Biosciences Inc, St Paul, MN). The intra- and interassay CVs were 3.4% and 3.8%, respectively.

Serum total calcium

Total calcium and albumin concentrations in all serum samples were measured at University of Ulster, Coleraine, with an automated system (Instrumentation Laboratories UK Ltd, Cheshire, United Kingdom). Serum calcium concentrations were adjusted for albumin concentrations.

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 total intakes of vitamin D (including habitual diet and intervention dose). Given the skewed distribution of serum 25(OH)D, the mean value of square root–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 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 square root 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 as a categorical variable whether an individual reported receiving a minimum of 15 min summer sun exposure per day (13) allowed the mean levels of square root serum 25(OH)D to vary with sun exposure. Minimal sun exposure during the previous summer and total vitamin D intake were independent predictors of serum 25(OH)D. There was no evidence that the association between serum 25(OH)D and vitamin D intake depended on sun exposure. Results were verified by using robust regression models that minimized the effect of outliers and heteroskedasticity.

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 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 value of 0.5 was assumed to represent the minimum clinically important slope, and that the residual variation of serum concentration of 25(OH)D around the mean line was normal. On the basis of the distribution of data from older women from our previous study (28), it was assumed that the distribution of dietary intakes in the current study would be similar. With these assumptions, a study design recruiting 200 volunteers, 50 subjects to each of 4 dose levels (0, 5, 10, and 15 μg vitamin D/d), and which included 10% to cover potential dropouts, had 90% power to demonstrate a dose-response relation.

Statistical analysis of the data was conducted by using SPSS for Windows version 12.0 (SPSS Inc, Chicago, IL) and Stata 10 (StataCorp LP, College Station, TX). The distributions of all variables were tested with Kolmogorov-Smirnov tests. Descriptive statistics (means $\pm$ SDs and medians and interquartile ranges, where appropriate) were determined for all variables. Serum concentrations of 25(OH)D and PTH as well as baseline and endpoint dietary vitamin D and calcium were not normally distributed and thus were log transformed [except for serum 25(OH)D, which was square root transformed] to achieve near-normal distributions. Serum concentrations of albumin-corrected calcium as well as age, weight, height, and BMI were normally distributed. Baseline characteristics of subjects in both study centers were compared by using a chi-square test (for male-to-female ratio and proportion of subjects achieving minimum summer sun exposure) or unpaired Student's t test. Baseline characteristics of subjects in the different intervention groups were compared by using a chi-square (for male-to-female ratio and proportion of subjects achieving minimum summer sun exposure), one-factor analysis of variance (ANOVA), and 2-factor ANOVA to investigate sex-interactions. Changes in calcium and vitamin D intakes from baseline to the endpoint were tested by ANOVA and Tukey's test. Serum 25(OH)D concentrations at baseline in subjects stratified by age ($>$ or $<$70 y) and sun exposure ($>$ or $<$15 min of daily summer sunshine) were compared by using unpaired Student's t tests. Linear models of the response in a repeated-measures analysis 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-factor interactions

between the main effects. A P value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of subjects

Of the 225 subjects recruited into the study, all returned for the intervention phase and 216 completed the intervention. The progress of these subjects throughout the trial is shown in **Figure 1**. Subjects in Cork were slightly, but significantly ($P = 0.025$), older than those in Coleraine (**Table 1**), but there was no difference ($P = 0.2$) in mean age between men and women (data not shown). There was no significant difference in mean weight, height, or BMI at baseline between subjects from the 2 centers (Table 1) or in mean BMI between males and females (mean ± SD: 28.4 ± 4.0 and 29.3 ± 5.2, respectively; $P = 0.2$).

Two-factor ANOVA showed that baseline serum 25(OH)D concentrations significantly differed by center ($P = 0.0005$; Table 1) and sex [median (interquartile range): 62.6 (44.6, 79.3) nmol/L for men and 50.7 (39.7, 65.9) nmol/L for women; $P = 0.001$]. There was no significant interaction ($P = 0.12$) between these 2 main factors. The baseline serum 25(OH)D concentration was significantly higher in subjects aged 64–70 y ($n = 108$) than in those aged >70 y ($n = 96$) [median (interquartile range): 56.8 (44.5, 75.1) nmol/L and 50.8 (36.7, 67.8) nmol/L, respectively; $P = 0.021$]. There was no significant difference in habitual vitamin D or calcium intake in subjects between centers at baseline (Table 1); however, men had significantly ($P < 0.03$) higher intakes of vitamin D [median (interquartile range): 4.8 (3.2, 7.0) μg/d and 4.0 (2.3, 5.6) μg/d] and calcium [median (interquartile range): 960 (776, 1210) mg/d and 804 (638, 1056) mg/d] than did women, which was expected because men typically have higher food and nutrient intakes than do women.

Stratification of subjects by their self-reported daily summer sun exposure showed that the baseline serum 25(OH)D concentrations of subjects who habitually had <15 min/d of exposure ($n = 40$) were significantly ($P < 0.0001$) lower than those who achieved or exceeded this exposure level ($n = 151$) [median (interquartile range): 41.8 (33.1, 54.5) nmol/L and 63 (44.2, 74.8) nmol/L, respectively]. A greater proportion ($P = 0.001$) of elderly women (29.5%) than men (8.9%) had a self-reported daily summer sun exposure that failed to meet the 15 min/d.

Effects of vitamin D intervention

There was no difference ($P > 0.1$) in mean age, weight, height, or BMI at baseline between the 4 treatment groups (data not shown). Similarly, there was no difference in the proportion of men to women, the proportion of subjects achieving a minimum of 15 min summer sun exposure, in mean habitual dietary vitamin D or calcium intake, or in mean preintervention serum 25(OH)D, PTH, or albumin-corrected calcium concentrations between the treatment groups (**Table 2**).

There were no adverse events reported during the study. Of the 9 dropouts, 4, 4, and 1 were from the placebo and 5 and 10 μg vitamin D/d groups, respectively. Dropouts during the intervention phase occurred for a number of reasons (eg, death, illness unrelated to intervention, and loss of interest) and in no instance was the dropout rate related to the intervention. Twelve subjects failed to exceed our minimum 85% compliance rate and were thus excluded from the main analysis. In the remaining subjects, there was good supplement compliance on the basis of pill counts [overall median (interquartile range): 100% (98.7%, 100%], and compliance was similar between the 4 treatment groups ($P = 0.9$).

As expected, total vitamin D intake (diet plus supplemental vitamin D) increased in a dose-related manner with supplementation (mean ± SD: 4.9 ± 3.4, 10.1 ± 3.3, 14.6 ± 2.7, and 20.4 ± 4.1 μg/d in the placebo and 5, 10, and 15 μg vitamin D/d groups, respectively; $P \leq 0.0001$). In contrast, calcium intake at the endpoint did not differ ($P = 0.08$) between the 4 groups (data not shown).

There was a significant ($P \leq 0.0001$) effect of treatment on mean postintervention serum 25(OH)D concentrations, with clear dose-related increments with increasing supplemental vitamin D_3 up to 10 μg vitamin D/d (Table 2). Postintervention serum 25(OH)D concentrations were similar ($P = 0.085$) in the groups who received 10 and 15 μg/d (Table 2). However, the change in mean serum 25(OH)D from before to after the intervention increased in a dose-related manner with supplementation (Table 2). There was no significant interaction between treatment and sex in any of the serum 25(OH)D statistical analyses (Table 2). None of the subjects exhibited hypercalcemia. There was no difference in mean postintervention serum albumin–corrected calcium or PTH concentrations between the treatment groups (Table 2). However, there was a significant treatment × time interaction ($P = 0.004$) in the repeated-measures analysis for the effect of vitamin D supplementation on serum PTH concentration (Table 2), which was not affected by adjustment for sex. Furthermore, the increase in serum PTH

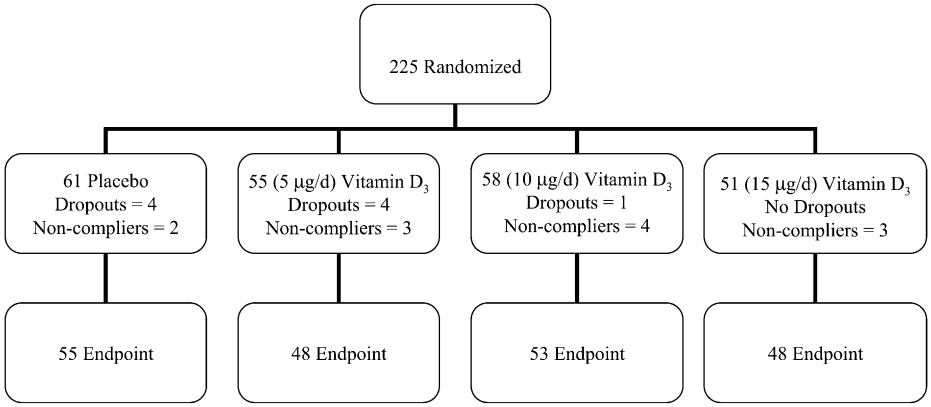

FIGURE 1. Flow of subjects throughout the study.

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

	All subjects ($n = 216$)	Cork ($n = 97$)	Coleraine ($n = 119$)
Sex (male:female)	86:130	38:59	48:71
Age (y)	70.7 ± 5.4[2]	71.6 ± 6.0	70.0 ± 4.7[3]
Weight (kg)	76.9 ± 14.3	78.7 ± 14.9	75.4 ± 13.7
Height (m)	1.62 ± 0.09	1.63 ± 0.09	1.62 ± 0.09
BMI (kg/m^2)	28.9 ± 4.8	29.3 ± 4.9	28.6 ± 4.7
Dietary calcium (mg/d)	874 (678, 1174)[4]	890 (681, 1162)	867 (677, 1183)
Dietary vitamin D (μg/d)	4.4 (2.7, 5.9)	3.7 (2.6, 5.6)	4.6 (2.9, 6.3)
Serum 25(OH)D (nmol/L)	55.0 (41.4, 71.7)	62.5 (43.3, 79.6)	50.8 (38.7, 65.7)[5]
Serum PTH (ng/mL)	51.6 (40.3, 67.1)	54.1 (40.8, 70.3)	50.8 (39.5, 64.0)
Serum calcium (mmol/L)[6]	9.2 ± 0.4	9.0 ± 0.4	9.3 ± 0.4[7]
Achieving 15 min summer sun exposure/d (%)	79.1	89.6	71.9[8]

[1] PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.
[2] Mean ± SD (all such values).
[4] Median; interquartile range in parentheses (all such values for nonnormally distributed variables).
[3,5,7] Significantly different from Cork subjects (Student's t test): [3]$P < 0.05$, [5]$P < 0.0006$, [7]$P < 0.0001$.
[6] Corrected for albumin.
[8] Significantly different from Cork subjects, $P < 0.002$ (chi-square test).

from before to after intervention in the placebo group was significantly ($P < 0.006$) different from that in the 3 vitamin D–supplemented groups, and there was no difference in the change between these latter 3 groups ($P > 0.6$) (Table 2).

Relation between vitamin D intake and vitamin D status

The relation between serum 25(OH)D concentrations in late winter, 2008, and total vitamin D intake (diet and supplemental) in the men and women aged ≥64 y is shown in **Figure 2**. The slope of the relation between total vitamin D intake and serum 25(OH)D in the entire group was 1.97 nmol · L^{-1} · μg intake^{-1}. There was a significant difference between the slope estimates for men and women (1.39 and 2.42 nmol · L^{-1} · μg intake^{-1}, respectively; $P = 0.008$). The significant difference between slope estimates for men and women persisted when adjusted for BMI, baseline serum 25(OH)D, separately and together ($P = 0.005$, $P = 0.02$, and $P = 0.02$, respectively). Similarly, the

TABLE 2
Habitual dietary intakes of vitamin D and calcium, summer sunshine exposure levels, and serum 25-hydroxyvitamin D [25(OH)D] concentrations in the treatment groups before and after intervention[1]

	Placebo ($n = 55$)	5 μg vitamin D/d ($n = 48$)	10 μg vitamin D/d ($n = 53$)	15 μg vitamin D/d ($n = 48$)	P value[2]
Sex (male:female)	24:31	17:31	22:31	19:29	0.820
Dietary vitamin D (μg/d)	4.7 (2.7, 6.2)[3]	4.1 (2.9, 5.4)	4.2 (2.9, 6.3)	4.8 (2.6, 6.5)	0.729
Dietary calcium (mg/d)	976 (719, 1140)	866 (740, 1266)	751 (622, 1000)	936 (626, 1176)	0.080
Achieving 15 min summer sun exposure/d (%)	82.0	71.1	79.6	81.8	0.810
Serum 25(OH)D (nmol/L)					
Before intervention[4]	58.8 (43.6, 78.5)	51.8 (41.3, 71.1)	54.3 (42.6, 72.0)	55.1 (39.6, 70.4)	0.767
After intervention[5,6]	41.6 (28.0, 55.4)[a]	53.2 (45.6, 68.7)[b]	69.5 (58.0, 81.4)[c]	73.8 (62.0, 89.2)[c]	<0.0001
Change	−16.2 ± 17.0[a,7]	0.7 ± 14.9[b]	11.8 ± 20.1[c]	22.8 ± 19.0[d]	<0.0001
Serum parathyroid hormone (ng/mL)					
Before intervention[4]	47.3 (40.1, 67.1)	54.3 (39.9, 64.5)	50.3 (38.9, 68.5)	53.8 (41.8, 68.5)	0.436
After intervention[5,6]	62.4 (49.8, 83.3)	58.1 (42.9, 74.8)	54.8 (40.1, 74.0)	57.8 (43.2, 79.2)	0.116
Change	16.6 ± 19.5[a]	6.3 ± 16.5[b]	5.8 ± 20.2[b]	4.4 ± 16.3[b]	0.002
Serum calcium (mmol/L)					
Before intervention[4,8]	9.2 ± 0.4	9.3 ± 0.5	9.1 ± 0.5	9.2 ± 0.4	0.399
After intervention[5,6,8]	9.0 ± 0.4	9.1 ± 0.5	9.1 ± 0.4	9.1 ± 0.4	0.604
Change	−0.2 ± 0.4	−0.2 ± 0.5	0.0 ± 0.4	−0.1 ± 0.3	0.095

[1] Values in a row with different superscript letters are significantly different, $P < 0.001$. There was no significant sex × treatment interaction for serum 25(OH)D, parathyroid hormone, or calcium ($P > 0.2$).
[2] One-factor ANOVA followed by Tukey's, 2-factor ANOVA (treatment, sex), or chi-square test for achieving 15 min summer sun exposure/d.
[3] Median; interquartile range in parentheses (all such values for nonnormally distributed variables).
[4] All baseline blood samples were collected between 28 September and 16 November 2007.
[5] Repeated-measures ANOVA was used to test the treatment × time interaction, and the same trends were observed for serum 25(OH)D and calcium ($P \leq 0.0001$ and 0.095, respectively); however, the treatment × time interaction was significant for serum parathyroid hormone ($P = 0.003$). There was no significant sex × treatment interaction for serum 25(OH)D, parathyroid hormone, or calcium ($P > 0.1$).
[6] All endpoint blood samples were collected between 21 February and 5 April 2008.
[7] Mean ± SD (all such values).
[8] Albumin corrected.

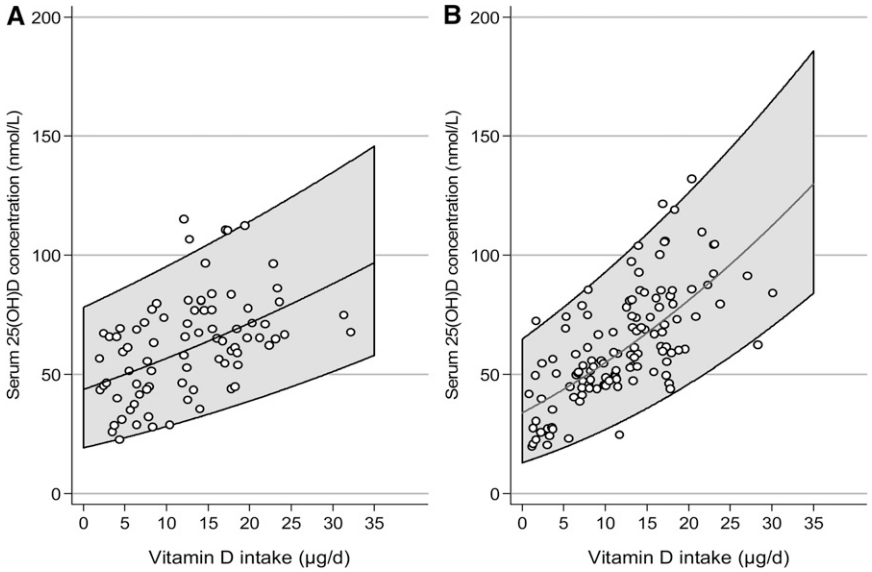

FIGURE 2. Relation between mean serum 25-hydroxyvitamin D [25(OH)D] concentrations (in late winter, 2008) and total vitamin D intake (diet and supplemental) in healthy men (A; $n = 82$) and women (B; $n = 122$) aged ≥64 y living at northerly latitudes (51 and 55°N). The shaded areas represent 95% CIs.

significant difference between slope estimates for men and women persisted when adjusted for body weight, baseline serum 25(OH)D, separately and together ($P < 0.001$, $P = 0.02$, and $P = 0.02$, respectively). When included in the model, age-group (> or <70 y) was not significant ($P = 0.7$).

Using mathematical modeling of the vitamin D intake–status data, we estimated that the vitamin D intakes that maintained serum 25(OH)D concentrations above 25 nmol/L in 90%, 95%, and 97.5% of the men and women combined were 2.6, 5.8, and 8.6 μg/d, respectively. The vitamin D intakes that maintained serum 25(OH)D concentrations above 25 nmol/L in 90%, 95%, and 97.5% of the subjects stratified by sex were 0, 2.9 and 6.8 μg/d, respectively, for men and 4.0, 6.6, and 8.9 μg/d, respectively, for women. An Estimated Average Requirement (the vitamin D intake required to maintain serum 25(OH)D concentrations above 25 nmol/L in 50% of the elderly 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 43.7 and 34.0 nmol/L for men and women, respectively. Whereas a serum 25(OH)D concentration <25 nmol/L has been used by several authorities as the traditional indicator of inadequacy for vitamin D (1, 5, 13, 20), several other biochemical cutoffs of serum 25(OH)D have been suggested ranging from 37.5 to 80 nmol/L (6, 7, 21, 30–32). The 50th, 90th, 95th, and 97.5th percentile estimates for vitamin D intake using a range of alternative indicators of adequacy for vitamin D status in adults aged ≥64 y (men and women separately and combined) are shown in **Table 3**.

Self-reported data on summer sun exposure were also incorporated into the model and the vitamin D intakes that maintained serum 25(OH)D concentrations ≥25 nmol/L in 97.5% of the sample were 7.9 μg/d in those who were exposed to a minimum of 15 min/d of summer sunshine and 11.4 μg/d in those who were not. Similarly, the vitamin D intakes that maintained serum 25(OH)D concentrations above 2 other commonly suggested cutoffs in 97.5% of the sample were 24.0 and 27.6 μg/d (for ≥50 nmol/L) and 39.0 and 42.8 μg/d (for ≥80 nmol/L) in those who were exposed to ≥15 min of summer sunshine daily and those who were not, respectively.

DISCUSSION

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 in different population subgroups 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 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 over 22 wk from October 2007 to March 2008 in 216 apparently healthy, free-living white adults aged ≥64 y living at latitudes of 51 and 55°N. We found that a daily intake of 8.6 μg/d vitamin D would have maintained serum 25(OH)D above 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 reconsidering vitamin D requirements. In 1998, the UK Committee on Medical Aspects of Food and Nutrition Policy (COMA) concluded that a prudent public health approach to safeguard against vitamin D deficiency and its adverse effect on bone health would be to retain the Reference Nutrient Intake set in 1991 (10 μg/d for those aged ≥65 y) (1). The US DRI panel for calcium and related nutrients (5) relied heavily on data from a small number of vitamin D supplementation studies in older women (15, 33, 34), which suggested that dietary intakes of vitamin D >2.5 μg/d (and possibly as high as 17.5 μg/d) were necessary to prevent higher

TABLE 3
Estimated dietary vitamin D requirements at selected percentiles in the entire group of free-living elderly (age ≥64 y) subjects, stratified by sex, to maintain serum 25-hydroxyvitamin D [25(OH)D] concentrations above selected biochemical cutoffs during winter[1]

Serum 25(OH)D cutoff	50th Percentile[2]	90th Percentile	95th Percentile	97.5th Percentile
	μg/d	*μg/d*	*μg/d*	*μg/d*
>25 nmol/L				
All	—	2.6 (0.0, 4.9)	5.8 (3.3, 7.6)	8.6 (6.4, 10.4)
Men	—	—	2.9 (0.0, 6.9)	6.8 (1.3, 10.4)
Women	—	4.0 (1.5, 5.8)	6.6 (4.6, 8.3)	8.9 (7.2, 10.7)
>37.5 nmol/L				
All	—	11.2 (9.7, 12.7)	14.4 (12.9, 16.2)	17.2 (15.4, 19.4)
Men	—	10.6 (6.8, 13.6)	15.0 (12.1, 18.5)	18.9 (15.9, 23.4)
Women	1.9 (0, 4.0)	11.1 (9.8, 12.6)	13.7 (12.3, 15.6)	15.9 (14.3, 18.3)
>50 nmol/L				
All	7.1 (5.2, 8.5)	18.4 (16.8, 20.5)	21.8 (19.5, 24.3)	24.7 (21.9, 27.7)
Men	5.0 (0.0, 8.4)	20.8 (17.6, 25.4)	25.3 (21.2, 31.5)	29.1 (24.1, 37.1)
Women	7.9 (6.1, 9.2)	17.0 (15.4, 19.2)	19.6 (17.6, 22.5)	21.9 (19.5, 25.3)
>80 nmol/L				
All	21.5 (19.5, 24.0)	33.2 (29.1, 37.7)	36.6 (31.8, 41.7)	38.7 (34.1, 45.1)
Men	25.3 (21.0, 31.5)	41.0 (32.7, 54.2)	45.5 (36.0, 60.9)	49.4 (38.8, 66.6)
Women	19.6 (17.8, 22.1)	28.8 (25.4, 33.7)	31.4 (27.5, 37.1)	33.6 (29.4, 40.0)

[1] All values are estimates (95% CIs). Results are based on a square root linear model of serum 25(OH)D as a function of vitamin D intake; 95% CIs were calculated by using a bias-corrected bootstrap based on 10,000 replications.

[2] Defined as the vitamin D intake needed to maintain serum 25(OH)D concentrations in 50% of adults aged ≥64 y above the indicated cutoff during winter.

rates of bone loss in those aged 51–70 y during periods of low sun exposure. The panel acknowledged that there were few data from individuals with limited and uncertain sun exposure and stores to precisely determine a value between 2.5 and 17.5 μg/d, so it chose 5 μg/d and doubled it to cover the needs of all adults aged 51–70 y (5). For adults aged >70 y, the panel suggested that 7.5 μg/d may be prudent for individuals with limited sun exposure and stores and doubled this value to cover the needs of all older adults (5). In particular, the panel relied heavily on data from studies of older adults who were either nursing home residents or those confined indoors (16, 35, 36). The findings of our study suggest that the AI for older adults (10 μg/d) is appropriate for apparently healthy, free-living, white-skinned men and women aged ≥64 y at latitudes of up to ≈55°N to maintain serum 25(OH)D concentrations >25–30 nmol/L. There was no evidence that the dietary vitamin D requirement differed for those aged 64–70 y and >70 y. It should be noted, however, that our sample was entirely free-living, which may have had a positive effect on vitamin D status (23).

Note that the intake required to maintain serum 25(OH)D above 25 nmol/L in 97.5% of the present sample (8.6 μg/d) was close to the 8.7 μg/d that we recently reported for adults aged 20–40 y (22), which suggests a similar dietary requirement throughout adulthood. Although it was not our primary research question and given that the study was not designed to explore potential sex-specific differences, we found different estimates of vitamin D requirements in women and men of 9.0 and 7.0 μg/d, respectively. The US DRI panel, given a lack of evidence to the contrary, assumed no sex differences in setting AIs for calcium and related nutrients (5) and it is not clear why a sex difference emerged in the current subjects and not in the 20–40-y-old adults in our previous study (22). In contrast with the 20–40-y-old women, who had baseline (October) 25(OH)D values similar to the 20–40-y-old men, the baseline serum 25(OH)D concentrations in the current group of women were ≈12 nmol/L lower than their male counterparts on average, in close agreement with survey data from the UK NDNS of older free-living adults. In addition to differences in basal 25(OH)D concentrations, differences in BMI have been suggested as possible determinants of the response of serum 25(OH)D to a given dose of vitamin D_3 (37, 38). However, the sex differences in dose-response slopes in the present study remained after adjustment for BMI, body weight, and baseline serum 25(OH)D concentration. Thus, further investigation is required to investigate the underlying reasons for a sex-specific difference in dietary vitamin D requirement.

In setting the AIs, the US DRI panel assumed that there was no cutaneous synthesis of vitamin D (5). This is true in winter, and while summertime dermal synthesis can be viewed as a top-up to help generate winter-time tissue stores of vitamin D, individual variation is likely to be high, making this an unreliable contributor to status. In the present study, 40 subjects did not obtain a minimum of 15 min/d sun exposure in summer and their dietary requirement for vitamin D in winter [using serum 25(OH)D >25 nmol/L as the cutoff] was 11.4 μg/d, compared with 7.9 μg/d in subjects who did have a minimum of 15 min sun/d in summer. This analysis, although perhaps limited by the small number of subjects in the low sun exposure group, serves to illustrate not only the increased dietary requirement for vitamin D in subjects who do not obtain minimal sun exposure in summer, but also the potential importance of vitamin D stores from that minimal summertime exposure in offsetting the potentially deleterious effects of low dietary intakes of vitamin D during winter.

In the current analysis, we strongly emphasized using a cutoff for serum 25(OH)D of 25 nmol/L on the basis that concentrations

of ≈20–27.5 nmol/L are consistent with vitamin D deficiency and osteomalacia (1), and the 25 nmol/L threshold has been used by various important authorities at least until now (1, 5, 13, 20). However, we also reported vitamin D requirements for the current sample of white-skinned adults aged ≥64 y using a number of other serum 25(OH)D cutoff values (37.5, 50, and 80 nmol/L) (6, 7, 21, 30, 32). The rationale for these alternative definitions of adequacy for vitamin D in relation to skeletal and nonskeletal health benefits has been detailed elsewhere (30–32). The slope estimate in the present study (1.97 nmol $\cdot$ L^{-1} $\cdot$ μg intake^{-1}) was almost identical to that recently reported by us for 20–40-y-old adults (1.96 nmol $\cdot$ L^{-1} $\cdot$ μg intake^{-1}) (22) and was similar to estimates ranging from 1.6 to 2.2 nmol $\cdot$ L^{-1} $\cdot$ μg intake^{-1} obtained in many studies of older adults (34, 39–41). Our estimate of the vitamin D requirement to maintain serum 25(OH)D concentrations >80 nmol/L in 97.5% of the current sample was 38.7 μg/d, which again is in close agreement with our estimate of 41 μg/d in 20–40-y-olds (22). Dawson-Hughes (21) suggested that the average older man and woman will need intakes of ≥20–25 μg/d of vitamin D_3 to reach a serum 25(OH)D concentration of 75 nmol/L. Our data show that, even at the lower cutoff of 50 nmol/L serum 25(OH)D, which may be associated with a reduced risk of a wide range of nonskeletal chronic diseases (30–32), the dietary requirement (24.7 μg/d) is still much higher than current intakes by elderly populations (23, 42, 43). A potential limitation of our study was that relatively few subjects (20%) achieved winter serum 25(OH)D concentrations ≥80 nmol/L because of our maximum dose of 15 μg/d of supplemental vitamin D. This may have influenced the accuracy with which we were able to estimate the dietary requirement needed to achieve such high serum 25(OH)D concentrations. To absolutely confirm our recommended intakes needed to achieve 25(OH)D concentrations in the 50–80 nmol/L range, a wintertime intervention study using higher doses of vitamin D (at least between 20 and 40 μg/d) would be required.

In conclusion, to ensure that the vitamin D needs of >97.5% of adults aged ≥64 y are met during winter, 8.6 μg/d of vitamin D are required to maintain serum 25(OH)D concentrations above the most conservative threshold of adequacy (ie, 25 nmol/L).

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