Plasma 25-hydroxyvitamin D and its determinants in an elderly population sample\(^1\)–\(^4\)

Paul F Jacques, David T Felson, Katherine L Tucker, Brenda Mahnken, Peter WF Wilson, Irwin H Rosenberg, and David Rush

ABSTRACT This study describes the distribution and determinants of plasma 25-hydroxyvitamin D [25(OH)D] concentrations and risk factors for low 25(OH)D (≤ 37.5 nmol/L) in 290 men and 469 women aged 67–95 y who were in the Framingham Heart Study cohort. Mean (± SD) 25(OH)D concentrations were 82 ± 29 nmol/L in men and 71 ± 29 nmol/L in women. 25(OH)D was lower in 6.2% of men and 14.5% of women. 25(OH)D concentrations were strongly associated with season of examination, inversely associated with time spent indoors and body mass index, and positively associated with dietary vitamin D intake. In women, concentrations were also inversely associated with age and positively associated with supplemental vitamin D intake and residence for ≥ 3 mo/y in Florida, California, or Arizona, and in men were positively associated with serum creatinine concentrations. Similar amounts of variance in 25(OH)D concentrations were explained by vitamin D intake and sunlight exposure, the former being more important in women and the latter in men. None of the known or suspected determinants of vitamin D status could explain the lower 25(OH)D concentrations in women, but the sex difference was not seen for individuals examined during the winter. Results from this population-based sample of elderly individuals suggest that inadequate vitamin D status is an important public health problem, which could be readily addressed by adequate vitamin D intake or sunlight exposure. Am J Clin Nutr 1997;66:929–36.

KEY WORDS Vitamin D, age, elderly individuals, 25-hydroxyvitamin D, Framingham Heart Study, sunlight exposure

INTRODUCTION

Vitamin D is unique among vitamins because in addition to its availability from the diet, it can be formed in the skin as a result of sunlight exposure (1). The major circulating form of this vitamin, 25-hydroxyvitamin D [25(OH)D], is the most sensitive measure of vitamin D stores in humans (1). Elderly individuals may be at risk of inadequate circulating 25(OH)D concentrations because of reduced sunlight exposure, possibly reflecting reduced mobility and activity (2), lessened capacity of the skin to produce vitamin D (3, 4), and lower dietary vitamin D intake as a consequence of lower energy intakes (5).

Omdahl et al (6) first documented a high prevalence of inadequate vitamin D concentrations in a sample of healthy older Americans from the New Mexico Aging Process Study. They observed that plasma 25(OH)D concentrations were significantly lower in elderly (mean: 38 nmol/L) than in younger (mean: 73 nmol/L) subjects, and that almost 15% of the elderly sampled had 25(OH)D concentrations < 20 nmol/L. Vitamin D concentrations were not lower with increasing age among another large sample of noninstitutionalized elderly Americans from the Baltimore Longitudinal Study of Aging (7). Only 1% of men and 4% of women had 25(OH)D concentrations < 35 nmol/L. Neither sample was population based, and each was composed of highly selected healthy elderly individuals who were free of serious medical conditions and not taking prescription medications. No differences in 25(OH)D concentrations were observed with increasing age in a population-based sample of women from Iowa who were aged 30–80 y (8).

Inadequate vitamin D intake might be expected to be less frequent in the United States, where milk is supplemented with vitamin D, than in countries where milk is not supplemented. In fact, inadequate vitamin D concentrations were found to be common among older populations in Britain (9–11), Ireland (12), Switzerland (13), the Netherlands (14), Denmark (15), France (16), and Spain (17). A study of older individuals from 11 European countries found that 36% of men and 47% of women had 25(OH)D concentrations < 30 nmol/L (18). 25(OH)D concentrations are strongly related to sunlight exposure (2, 8, 11, 13, 15, 19–21) and dietary and supplemental

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\(^3\) The contents of this publication do not necessarily reflect the views or policies of the US Department of Agriculture, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government.

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vitamin D intakes (6, 8, 13, 14, 18, 20–23). However, no previous study has considered their relative importance in a population-based, elderly US sample. Other factors may also influence 25(OH)D concentrations. Various studies have indicated lower 25(OH)D concentrations in women than in men (6, 7, 16–18, 21) whereas others report no sex differences (11, 13, 14). There have been few attempts to explain the sex differences in circulating vitamin D concentrations. Other behavioral, biochemical, and physiologic factors may influence 25(OH)D concentrations, but none of these relations are well established. Associations have been reported with weight and obesity (19, 21, 24), physical activity (6, 25), and other factors (8, 18, 25, 26).

We used data from elderly survivors of the population-based Framingham Heart Study cohort to (1) describe the distribution of plasma 25(OH)D concentrations and identify the prevalence of plasma 25(OH)D concentrations that are low and indicating deficiency in older individuals, 2) examine the independent determinants of mean plasma 25(OH)D concentrations and low circulating vitamin D concentrations, 3) determine the relative importance of established determinants of 25(OH)D concentrations, and 4) investigate possible reasons for lower 25(OH)D concentrations in women.

SUBJECTS AND METHODS

Subjects

The Framingham Heart Study cohort of 5209 men and women aged 30–62 y was established between 1948 and 1950 (27). The cohort was examined every 2 y, and in 1988–1989 ~1300 survivors participated in the 20th examination. All data presented in this paper are from the 20th examination. The protocols for this study were approved by the Institutional Review Board for Human Research at Boston University Medical Center and the Human Investigations Review Committee at New England Medical Center.

Sample collection and plasma 25(OH)D determination

Nonfasting blood samples were collected in EDTA-containing tubes and were centrifuged promptly at 4 °C for 15 min at 2000 × g. Plasma was stored at −70 °C for ≤3 y. 25(OH)D was determined by a competitive protein-binding assay (28). Inter- and intraassay CVs for this assay were 10% and 7%, respectively. We defined low 25(OH)D concentrations as ≤37.5 nmol/L and concentrations indicating deficiency as ≤25 nmol/L (1, 2). 25(OH)D concentrations ≤25 nmol/L are consistent with impending or frank vitamin D deficiency (1), and among the elderly, plasma 25(OH)D concentrations > 37.5 nmol/L are required to maintain normal circulating intact parathyroid hormone (2), which suggests that concentrations ≤37.5 nmol/L are inadequate in elderly individuals.

Nutrient intake

Dietary vitamin D intake and use of supplements containing vitamin D were assessed with a semiquantitative food-frequency questionnaire (FFQ) (29). Vitamin D intake from this FFQ was shown to be strongly related to plasma 25(OH)D under conditions of low sunlight exposure (30). Participants whose dietary information was judged to be unreliable on the basis of the number of missing items (> 12) and reported energy intake (<2500 or >16 700 kJ) were excluded from these analyses (n = 71). We defined regular vitamin D supplement use as daily supplemental intake of ≥267 IU vitamin D [ie, an average intake from supplements of more than two-thirds of the recommended daily value of 400 IU (31), the amount most commonly found in multivitamin supplements].

Sunlight exposure

We had no direct measure of sunlight exposure. Rather, we used season of examination and questions on place of residence and time spent outside to characterize sunlight exposure. Summer was defined as June through August, autumn as September through November, winter as December through February, and spring as March through May. Participants were asked about their current and seasonal residences, and there were 59 participants who spent ≥3 mo in Florida, Arizona, or California during the year preceding the examination. Participants were also asked, “In the summer, on average, are you outside in the sunlight at least one-half hour a day, or at least 3–4 h a week?” and “Do you stay indoors most or all of the day (on average)?”

Other information

Additional data used in these analyses included age, smoking status (never, past, or current), a physical activity score (32), body mass index, serum albumin (33; as modified by using a Roche Diagnostics clinical chemistry analyzer and reagents (Montclair, NJ)), and creatinine (34; also as modified by using Roche Diagnostics products).

Statistical analyses

Our sample consisted of all individuals for whom we had a plasma 25(OH)D value and a valid FFQ. Because of sex interactions, we analyzed the data separately for men and women. To examine factors related to 25(OH)D concentrations, we created quintile categories for dietary vitamin D, physical activity score, body mass index, and creatinine. Regular vitamin D supplement use was defined as daily supplemental intake of ≥267 IU. We classified albumin concentration as normal (≥40 g/L) or low (<40 g/L). For all variables, we calculated the age-adjusted mean plasma 25(OH)D concentrations in each variable category and tested for linear trends with linear regression. To examine the independent contribution of the known or potential determinants of mean 25(OH)D concentration, factors that were significantly related (P < 0.05) to 25(OH)D in either men or women after adjustment for age were included in a multiple-regression model, and then removed by using a backward selection procedure. Age was included in the model to see whether the determinants of 25(OH)D could explain any association between 25(OH)D and age.

To explore the reasons for the observed difference in 25(OH)D concentrations between men and women, we entered those factors that were significantly related (P < 0.05) to 25(OH)D in either men or women after adjustment for age into a multiple-regression model including both men and women. We developed a model with a sex term and then used a forward selection procedure to determine whether the sex difference was reduced or became nonsignificant as variables entered, and if so, which variables explained the observed difference. Be-
cause of interactions between sex and season, this model was considered by season of examination.

To examine the relation between age and prevalence of concentrations of 25(OH)D that are low and indicating deficiency, we calculated exact binomial CIs (35). Age-adjusted odds ratios for low 25(OH)D were estimated by quintile of vitamin D intake by using logistic regression. To identify factors related to inadequate vitamin D concentrations (≤ 37.5 nmol/L) we used an analytic approach similar to that described above for correlates of 25(OH)D concentrations, but with logistic, rather than linear, regression. We did not present results of these analyses because mean 25(OH)D concentrations and prevalence of low 25(OH)D had similar determinants.

We used SAS statistical software for these analyses (36). If not otherwise noted, statistical significance refers to \( P < 0.05 \).

**RESULTS**

Complete plasma 25(OH)D concentrations and vitamin D intake data were available for 759 subjects. The mean ages of the 290 men and 469 women were 75 (median: 74) and 75 (median: 75) y, respectively. Participants ranged in age from 67 to 95 y. Distribution of 25(OH)D concentrations for men and women are shown in Figure 1. Mean (± SD) 25(OH)D concentrations for men and women were 82 ± 29 and 71 ± 29 nmol/L, respectively.

The prevalence of plasma 25(OH)D concentrations that are low (≤ 37.5 nmol/L) and indicating deficiency (≥ 25 nmol/L) by age and sex are shown in Table 1. The overall prevalence of low vitamin D concentrations and those indicating deficiency was 6.2% and 2.4% in men and 14.5% and 4.1% in women, respectively. The overall prevalence of low (but not those indicating deficiency) vitamin D concentrations was significantly greater in women than in men. The oldest women had a 3.5-fold higher prevalence of 25(OH)D concentrations indicating deficiency than the youngest women (\( P < 0.05 \)), but there was no consistent trend with age in men.

![Figure 1. Distribution of plasma 25-hydroxyvitamin D concentrations in 469 women (---) and 290 men (--) aged 67-95 y from the Framingham Heart Study cohort.](https://academic.oup.com/ajcn/article-abstract/66/4/929/4655989)

**Figure 1.** Distribution of plasma 25-hydroxyvitamin D concentrations in 469 women (---) and 290 men (--) aged 67-95 y from the Framingham Heart Study cohort.

![Figure 2. Age-adjusted mean (± SD) plasma 25-hydroxyvitamin D concentrations and odds ratios for low 25-hydroxyvitamin D concentrations (≤ 37.5 nmol/L) in 469 women (●) and 290 men (○) aged 67-95 y from the Framingham Heart Study cohort according to quintile category of vitamin D intake. (The upper two categories had to be combined to get stable odds ratio estimates because only one man and one woman in the highest intake quintile category had low 25-hydroxyvitamin D concentrations. Mean plasma 25-hydroxyvitamin D concentrations are plotted at the median intake within each quintile category.)](https://academic.oup.com/ajcn/article-abstract/66/4/929/4655989)

**Figure 2.** Age-adjusted mean (± SD) plasma 25-hydroxyvitamin D concentrations and odds ratios for low 25-hydroxyvitamin D concentrations (≤ 37.5 nmol/L) in 469 women (●) and 290 men (○) aged 67-95 y from the Framingham Heart Study cohort according to quintile category of vitamin D intake. (The upper two categories had to be combined to get stable odds ratio estimates because only one man and one woman in the highest intake quintile category had low 25-hydroxyvitamin D concentrations. Mean plasma 25-hydroxyvitamin D concentrations are plotted at the median intake within each quintile category.)

### Table 1

Prevalence of plasma 25-hydroxyvitamin D concentrations that are low (≤ 37.5 nmol/L) or indicating deficiency (≥ 25.0 nmol/L)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Low (≤ 37.5 nmol/L)</th>
<th>Indicating deficiency (≥ 25.0 nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>14.5 (11.4, 18.0)</td>
<td>6.2 (3.7, 9.6)</td>
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<tr>
<td>67–74 y</td>
<td>12.6 (8.6, 17.6)</td>
<td>3.9 (1.5, 8.3)</td>
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<tr>
<td>75–79 y</td>
<td>15.0 (9.6, 21.8)</td>
<td>10.3 (4.5, 19.2)</td>
</tr>
<tr>
<td>80–95 y</td>
<td>18.5 (11.1, 27.9)</td>
<td>6.8 (1.9, 16.5)</td>
</tr>
</tbody>
</table>

| P for trend | 0.18 | 0.25 | 0.03 | 0.13 |

1 Percentage of individuals and CIs in parentheses.
2,3 Significantly different from women (chi-square test): \( P < 0.01, P < 0.05 \).
4 Based on logistic regression coefficient for age.
TABLE 2
Age-adjusted mean plasma 25-hydroxyvitamin D concentrations by category of its known and potential determinants

| Variable | Women | | | Men | | |
|----------|-------|---------------------------------|--|---------------------------------|--|
| n Group  | 95% CI | P  | n Group  | 95% CI | P  |
| Age (y)  |      | | |      | | |
| 67–74    | 230   | 74.1 (70.4, 77.8) | 0.30 | 153   | 81.9 (77.3, 86.5) | 0.92 |
| 75–79    | 147   | 70.9 (66.2, 75.6) | 0.003 | 78    | 82.3 (75.8, 88.7) | 0.98 |
| 80–95    | 92    | 63.2 (57.3, 69.1) | 0.004 | 59    | 82.0 (74.6, 89.4) | 0.56 |

Known determinants
Dietary variables
Dietary vitamin D intake (IU)
<101 | 93 | 62.8 (57.1, 68.6) | 59 | 76.7 (69.4, 81.4) |
101–158 | 104 | 68.1 (62.6, 73.5) | 48 | 80.4 (72.3, 88.6) | 0.52 |
159–221 | 96 | 71.8 (66.2, 77.5) | 56 | 77.0 (69.4, 84.5) | 0.97 |
222–315 | 85 | 70.9 (64.9, 76.9) | 67 | 86.1 (79.2, 93.0) | 0.07 |
≥316 | 91 | 81.7 (75.9, 87.5) | < 0.001 | 60 | 88.5 (81.2, 95.8) | 0.03 |

Supplemental vitamin D > 66% of RDV<sup>3</sup>
No | 353 | 64.4 (61.7, 67.2) | < 0.001 | 232 | 80.4 (76.7, 84.1) |
Yes | 116 | 90.8 (86.0, 95.7) | 58 | 88.5 (81.0, 95.9) | 0.06 |

Sunlight exposure variables
Season
Winter (January–March) | 122 | 61.1 (56.1, 66.1) | 72 | 63.6 (57.6, 69.7) |
Spring (April–June) | 133 | 72.6 (67.9, 77.4) | 90 | 79.3 (73.9, 84.8) | < 0.001 |
Summer (July–September) | 98 | 79.0 (73.4, 84.6) | < 0.001 | 65 | 97.7 (91.3, 104.1) | < 0.001 |
Fall (October–December) | 116 | 72.7 (67.5, 77.8) | 63 | 90.5 (84.1, 97.0) | < 0.001 |
Reside in FL, AZ, or CA for ≥ 3 mo/y
No | 410 | 68.8 (66.0, 71.5) | 256 | 80.1 (76.6, 83.6) |
Yes | 59 | 86.2 (79.0, 93.4) | < 0.001 | 34 | 96.2 (86.6, 105.8) | 0.002 |
Stay indoors most of day
No | 259 | 74.6 (71.1, 78.1) | 192 | 86.7 (82.7, 90.7) |
Yes | 210 | 66.5 (62.6, 70.4) | 98 | 72.8 (67.2, 78.4) | < 0.001 |
3–4 h/wk in summer sun
No | 79 | 69.6 (63.2, 76.0) | 11 | 68.4 (51.3, 85.6) |
Yes | 390 | 71.2 (68.4, 74.1) | 0.65 | 279 | 82.5 (79.1, 85.9) | 0.12 |

Potential determinants
Smoking status
Never | 213 | 69.6 (65.7, 73.5) | 93 | 84.3 (78.4, 90.1) |
Past | 185 | 74.2 (70.1, 78.4) | 154 | 80.4 (75.9, 85.0) | 0.32 |
Current | 48 | 65.4 (57.2, 73.5) | 30 | 82.4 (72.0, 92.8) | 0.77 |
Alcohol intake (g/d)
< 2 | 302 | 68.4 (65.2, 71.6) | 121 | 80.7 (75.6, 85.8) |
2–9 | 61 | 71.4 (64.2, 78.6) | 43 | 75.3 (66.7, 83.9) | 0.30 |
10–14 | 29 | 79.6 (69.2, 90.0) | 0.05 | 30 | 78.9 (68.6, 89.2) | 0.76 |
≥15 | 77 | 77.4 (71.0, 83.7) | 96 | 87.6 (81.8, 93.4) | 0.09 |
Physical activity score
< 29.1 | 91 | 72.3 (66.3, 78.2) | 64 | 79.1 (71.9, 86.3) |
29.1–31.3 | 98 | 65.7 (60.0, 71.4) | 43 | 78.0 (69.3, 86.7) | 0.85 |
31.4–33.7 | 100 | 72.7 (67.1, 78.3) | 53 | 86.7 (78.9, 94.6) | 0.16 |
33.8–37.2 | 90 | 75.4 (69.4, 81.3) | 54 | 83.4 (75.6, 91.2) | 0.44 |
≥ 37.3 | 82 | 68.9 (62.7, 75.1) | 65 | 83.6 (76.4, 90.7) | 0.40 |
Body mass index (kg/m²)
< 25.9 | 111 | 78.5 (73.2, 83.7) | 40 | 87.1 (78.1, 96.0) |
25.9–28.5 | 94 | 78.7 (73.0, 84.4) | 56 | 87.8 (80.2, 95.4) | 0.90 |
28.6–30.5 | 82 | 67.6 (61.5, 73.7) | 69 | 83.3 (76.5, 90.2) | 0.52 |
30.6–33.6 | 86 | 65.3 (59.4, 71.3) | 64 | 78.7 (71.6, 85.8) | 0.16 |
≥ 33.7 | 92 | 63.1 (57.3, 68.8) | < 0.001 | 58 | 75.1 (67.6, 82.5) | 0.05 |
Albumin (g/L)
< 40 | 104 | 66.2 (60.7, 71.9) | 44 | 80.4 (71.9, 88.8) |
≥ 40 | 324 | 73.2 (70.5, 76.3) | 221 | 84.2 (80.5, 88.0) | 0.42 |
TABLE 2
Continued.

<table>
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<th>Variable</th>
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<th>P</th>
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<td>Group</td>
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<td>n</td>
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<td>111</td>
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<td>84–97</td>
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<td>≥ 98</td>
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1 P values for individual comparisons to referent category are based on a test of difference between least-squares means.
2 P value for trend based on linear-regression coefficient.
3 Recommended daily value (31).

The age-adjusted relation between 25(OH)D concentrations and quintile categories of vitamin D intake from food and supplements are shown in Figure 2. Men with higher intakes had higher 25(OH)D concentrations until intakes reached ~400 IU/d. Intakes above this value were not associated with higher 25(OH)D concentrations. In women, however, 25(OH)D concentrations appeared to increase even at intakes > 400 IU/d. The age-adjusted relation between low vitamin D concentrations and vitamin D intake is shown in the bottom panel of Figure 2. Odds ratios for low 25(OH)D concentrations (≤ 37.5 nmol/L) and their 95% CIs were estimated in the lowest three intake quintile categories relative to the upper two quintile categories. The upper two categories were combined to get stable odds ratio estimates because there was only one man and one woman in the highest intake quintile category with low 25(OH)D. The prevalence of low vitamin D was > 11 times greater for women (odds ratio: 11.8; 95% CI: 5.1, 27.1) and almost 9 times greater for men (odds ratio: 8.9; 95% CI: 1.8, 45.3) in the lowest vitamin D intake quintile category compared with those in the upper two quintile categories.

The age-adjusted relations between 25(OH)D and known and potential determinants of 25(OH)D in this elderly population-based sample are given in Table 2. We observed that 25(OH)D concentrations were significantly lower in the oldest women (80–96 y) than in women aged 67–74 y. Dietary vitamin D intake and regular vitamin D supplement use were both related to 25(OH)D in men and women, but both were stronger determinants in women. Season of examination was very strongly associated in both men and women, but in contrast with the dietary variables, the sunlight exposure variables were more strongly related to vitamin D concentrations in men. There was a striking inverse relation between BMI and plasma vitamin D concentrations. 25(OH)D concentrations were also positively associated with alcohol consumption in both men and women and serum albumin concentration in women, and inversely associated with serum creatinine in men.

Factors that were significantly associated (P < 0.05) with 25(OH)D concentrations in Table 2 were entered into a linear-regression model and the independent determinants of 25(OH)D concentration were identified by using a backward selection procedure (Table 3). Age and supplemental vitamin D intake were retained in the regression model for men even though they were not significant. The parameter estimates in Table 3 represent the difference in 25(OH)D concentrations over the specified range for continuous variables or the difference in 25(OH)D concentrations between each group and the specified reference group for categorical variables.

For women, age, dietary and supplemental vitamin D intake, three of the sunlight exposure variables, and body mass index were independently related to 25(OH)D concentrations. Plasma 25(OH)D concentrations were 0.7 nmol/L lower for each year of age (or 7.0 nmol/L lower for a 10-y age difference) (P < 0.004), indicating that the other determinants included in this model did not explain the age-related change in 25(OH)D. Plasma 25(OH)D concentrations were 1.7 nmol/L higher for each 50-IU difference in dietary vitamin D (P < 0.001) and women who regularly used vitamin D supplements had 25(OH)D concentrations that were 24.2 nmol/L higher than those who did not (P < 0.001). Women examined in the winter and spring had 25(OH)D concentrations that were 14.8 nmol/L (P < 0.001) and 8.9 nmol/L (P = 0.007) lower than women examined during the summer months. Women who resided in Florida, Arizona, or California for ≥ 3 mo during the year preceding the examination had 25(OH)D concentrations that were 11.2 nmol/L higher than women who did not (P = 0.002) and women who reported that they spent most of their day indoors had 25(OH)D concentrations that were 7.4 nmol/L lower (P = 0.002) than women who did not. For each difference of one unit of body mass index among women, plasma 25(OH)D concentrations were 0.8 nmol/L lower (P < 0.001). Based on the coefficient of determination (ie, the squared model correlation coefficient), these factors explained 31% of the observed variance in 25(OH)D concentrations in this sample of women. Sixteen percent of the variance in 25(OH)D (or more than one-half the explained variance) was associated with vitamin D intake from diet and supplements whereas season of examination and the other sunlight exposure variables were associated with only 7% of the variability in 25(OH)D concentrations.

For men, dietary vitamin D intake, two of the sunlight exposure variables, body mass index, and serum creatinine concentration were independent determinants of 25(OH)D concentration. Age was unrelated to vitamin D status. The association between dietary vitamin D intake and 25(OH)D, a 1.6-nmol/L difference in 25(OH)D for each 50-IU difference (P < 0.002), was similar in magnitude to that seen in women. However, unlike women, the difference in 25(OH)D between male vitamin D supplement users and nonusers (5.2 nmol/L) was not significant (P < 0.17). Only two of the sunlight exposure variables were related to 25(OH)D concentrations in...
men, but the associations between these variables and 25(OH)D concentrations were stronger in women. Men examined in the autumn, winter, and spring had 25(OH)D concentrations that were 8.7, 30.1, and 21.0 nmol/L lower than the concentrations in men examined during the summer months (P < 0.001 for each difference). Men who reported that they spent most of their day indoors had 25(OH)D concentrations that were 12.9 nmol/L lower than those who did not (P < 0.001), almost twice the difference in women. 25(OH)D concentrations in men were 1.1 nmol/L lower for a one-unit increase in body mass index. A 90-μmol/L (1-mg/dL) increment in serum creatinine concentration was associated with a 13.2-nmol/L difference in 25(OH)D (P = 0.003) in men after adjustment for other determinants. For men, these variables accounted for 30% of the observed variance in 25(OH)D in this elderly population. Vitamin D intake was associated with only 3% of the variability in 25(OH)D concentrations whereas the sunlight exposure variables accounted for 19% of the variance.

To determine whether any of the identified determinants might explain the large difference in vitamin D status between men and women, factors that were associated (P < 0.05) with 25(OH)D concentrations in Table 3 for either men or women were entered into a linear-regression model that included both men and women. Factors influencing the sex difference were screened by a forward selection procedure after sex was entered into the regression model. After entry of all factors, the plasma 25(OH)D concentrations in women remained 10.5 nmol/L lower than concentrations in men (P < 0.001). We further explored the relation with sex by stratifying participants by the season in which they were examined because of interactions between sex and season (Table 4). Significant differences in 25(OH)D concentrations between women and men were seen in each season except during the winter months when the difference between women and men was only −1.4 nmol/L (P = 0.79). We also observed other seasonal differences. Age was most strongly associated with 25(OH)D during the winter whereas BMI was related to 25(OH)D in all seasons except winter. Residence in Florida, Arizona, or California for ≥ 3 mo/y was most strongly associated with 25(OH)D concentrations during the winter and unrelated to concentrations during the summer. Creatinine was related to 25(OH)D in all seasons except spring. Supplemental vitamin D was associated

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women (n = 425)</th>
<th>Men (n = 262)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>144.6</td>
<td>138.0</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>−0.7</td>
<td>−8.9</td>
</tr>
<tr>
<td>Dietary vitamin D intake (per 50 IU)</td>
<td>1.7</td>
<td>24.2</td>
</tr>
<tr>
<td>Supplemental vitamin D &gt; 66% of RDV2</td>
<td>24.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Season (versus Summer)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autumn</td>
<td>−3.9</td>
<td>−8.7</td>
</tr>
<tr>
<td>Winter</td>
<td>−14.8</td>
<td>−30.1</td>
</tr>
<tr>
<td>Spring</td>
<td>−8.9</td>
<td>−21.0</td>
</tr>
<tr>
<td>Stay indoors most of day</td>
<td>−7.4</td>
<td>−12.9</td>
</tr>
<tr>
<td>Body mass index (per 1 kg/m²)</td>
<td>−0.8</td>
<td>−1.1</td>
</tr>
<tr>
<td>Serum creatinine (per 90 μmol/L)</td>
<td>13.2</td>
<td>13.2</td>
</tr>
</tbody>
</table>

1 Data from 28 men were missing for BMI (n = 3) or creatinine concentration (n = 25) and data from 44 women were missing for BMI (n = 4) or creatinine concentration (n = 40). n = 262 men, 425 women.

Recommended daily value (31).

TABLE 4
Determinants of plasma 25-hydroxyvitamin D concentration by season of examination: multiple linear regression'
with plasma 25(OH)D concentrations in all seasons, and dietary vitamin D intake was significantly associated with 25(OH)D concentrations in all seasons except winter.

**DISCUSSION**

We found a high prevalence of low vitamin D concentrations, but not of those indicating deficiency, in a population-based elderly sample of Americans. Approximately 15% of women and 6% of men had concentrations of 25(OH)D that were low (≤ 37.5 nmol/L) and ~4% of women and 2% of men had concentrations consistent with deficiency (≤ 25 nmol/L). The concentrations of 25(OH)D observed in the Framingham Heart Study cohort are much higher than those observed for men and women in the New Mexico Aging Process Study cohort (6). Concentrations for men in the Framingham Heart Study cohort were comparable with those for men in the Baltimore Longitudinal Study of Aging (7), whereas concentrations for women in the Framingham cohort were intermediate between the higher concentrations in women from the Baltimore Longitudinal Study of Aging (7) and lower concentrations in women from Iowa (8). 25(OH)D concentrations for both men and women from Framingham were nearly identical to those for a comparably aged sample from the Boston area (21). The basis for the differences in 25(OH)D between these samples of older Americans is not known.

This study also confirms the importance of sunlight exposure and vitamin D intake as the major determinants of circulating 25(OH)D in elderly individuals (2, 6, 10, 13, 15, 18–21, 23). Although vitamin D intake and sunlight exposure variables were predictive of 25(OH)D concentrations in both elderly women and men in this cohort, intake appeared to be a more important determinant in women and sunlight exposure was a more important determinant in men. Both the measures of intake and sunlight likely result in misclassification of individuals with respect to these determinants, and the observed relations are likely to underestimate the strength of the true relations.

We were limited in our ability to examine the relation between vitamin D status and age because the entire cohort was elderly, but we found a weak inverse association between age and vitamin D concentrations in women, which was not explained by other determinants of 25(OH)D. However, age and plasma 25(OH)D were more strongly correlated during the winter than during other seasons. This suggests that the effect of age on 25(OH)D concentrations may be mediated through either impaired absorption that is masked by biosynthesis, a reduced efficiency of skin biosynthesis under conditions of minimal sunlight exposure, or a diminished capacity for storage. Previous studies on impaired absorption of vitamin D from the intestine with age were equivocal (37, 38), but some earlier work does support the possibility of impaired skin biosynthesis with advancing age (3, 4).

Like others (6, 7, 16–18), we observed substantially lower 25(OH)D concentrations in women than in men, and this difference could not be explained by age, intake, or any other known or suspected determinant of vitamin D status. The lack of difference between men and women during the winter was also reported by Dawson-Hughes et al (21) in an elderly sample from the same geographic location as the Framingham cohort. The seasonal and sunlight exposure differences in the relation between vitamin D and sex could relate to the capacity of the skin to produce vitamin D, but there is no direct evidence that older men have a greater capacity to produce vitamin D from sunlight than do older women. Also, the sunlight questions we used, although strongly associated with vitamin D status, are obviously crude and might result in some misclassification of sunlight exposure, which might, for example, be responsible for the weaker association in women. [For example, we had no information on factors such as sunscreen use or extent of clothing cover, which affect cutaneous exposure to ultraviolet radiation and 25(OH)D concentrations (17, 39, 40).]

Dietary vitamin D intake was similarly related to 25(OH)D in both men and women although 25(OH)D appeared to plateau at intakes of ~400 IU/d in men, but not in women. Regular use of supplements containing vitamin D was strongly associated with 25(OH)D concentrations in women but not in men. This could not be explained by a higher dietary intake in male supplement users, which might conceivably lower the effect of supplementation on 25(OH)D concentrations. The dietary vitamin D intakes in men and women who regularly consumed vitamin D-containing supplements were 225 and 215 IU/d, respectively. Caution is recommended in the interpretation of the reported intake levels. Although vitamin D intake from the FFQ appears to correlate reasonably well with 25(OH)D when the contribution from sunlight is minimal (30), the accuracy of this FFQ for assignment of quantitative levels of intake, as we have presented in Figure 2, is unknown.

Both men and women with higher body mass indexes had lower 25(OH)D concentrations after adjustment for age, intake, and sunlight measures. Need et al (19) reported a similar observation in a sample of postmenopausal women and Dawson-Hughes et al (21) reported that weight was inversely associated with 25(OH)D in a sample of older men and women after adjusting for age, vitamin D intake, and indirect measures of sunlight exposure. Bell et al (24) observed lower circulating 25(OH)D concentrations in younger obese subjects, but Scragg et al (25) reported that body mass index was unrelated to 25(OH)D in younger men. Need et al (19) postulated that the inverse relation with body mass index might result from the larger body pool size and slower saturation of these stores in obese individuals, which is consistent with an inverse association between body mass index and 25(OH)D concentrations in all seasons except winter. We also observed that the circulating creatinine concentration was positively associated with 25(OH)D in men. We do not feel that the relation with creatinine is a consequence of renal function because the association was observed across the range of creatinine, not just at high or abnormal concentrations. It is possible that creatinine acts as a marker of muscle mass in this sample of elderly individuals, and there is evidence that vitamin D might have a subtle effect on muscle function (41, 42).

The high prevalence of low 25(OH)D concentrations in this population-based sample suggests an important public health problem in older Americans. These data also suggest that low 25(OH)D concentrations should be responsive to increased consumption of foods that are good sources of vitamin D or to supplemental vitamin D. For example, only 1% of individuals with reported vitamin D intakes ≥ 400 IU/d had 25(OH)D concentrations ≤ 25 nmol/L and only 2.5% had concentrations ≤ 37.5 nmol/L. Moreover, no one who regularly consumed supplements containing vitamin D had 25(OH)D concentrations ≤ 25 nmol/L and only 1% had concentrations ≤ 37.5 nmol/L. This confirms the observations of Webb et al (2) that elderly individuals who took a
vitamin supplement or drank two to three glasses of milk per day were vitamin D sufficient. However, 75% of women and 80% of men in our population-based sample of elderly individuals did not regularly take vitamin D supplements, and among these unsupple-
mented individuals, 68% of women and 64% of men consumed < 8 oz milk (240 mL)/d. Obvious dietary improvements could readily increase circulating 25(OH)D concentrations in elderly Americans.

REFERENCES