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Low serum concentrations of 25-hydroxyvitamin D in older persons and the risk of nursing home admission^{1–3}

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ABSTRACT

Background: The prevalence of vitamin D deficiency in nursing home patients is high.

Objective: We aimed to ascertain whether lower serum 25-hydroxyvitamin D [25(OH)D] concentrations increase the risk of future nursing home admission and early death.

Design: We included 1260 independent, community-dwelling persons aged ≥ 65 y who were participating in the Longitudinal Aging Study Amsterdam (1995–1996). Study outcomes were time to nursing home admission during 6 y of follow-up and time to death until 1 April 2003.

Results: Vitamin D deficiency [25(OH)D < 25 nmol/L] and insufficiency [25(OH)D = 25–49.9 nmol/L] were present in 127 (10.1%) and 462 (36.7%) subjects, respectively. During follow-up, 138 subjects (11.0%) were admitted to nursing homes, and 380 subjects (30.2%) died. The risk of nursing home admission for participants with 25(OH)D deficiency was 53 cases per 1000 person-years higher than that for those with high 25(OH)D (≥ 75 nmol/L) concentrations (58 compared with 5 cases). After adjustment for potential confounders, the hazard ratio (95% CI) of nursing home admission was 3.48 (1.39, 8.75) for vitamin D-deficient, 2.77 (1.17, 6.55) for vitamin D-insufficient, and 1.92 (0.79, 4.66) for vitamin D–borderline persons as compared with persons with high 25(OH)D (P for trend = 0.002). The results remained after additional adjustment for frailty indicators. Lower 25(OH)D was associated with higher mortality risk, but this association was not significant after adjustment for frailty indicators.

Conclusion: Lower serum 25(OH)D concentrations in older persons are associated with a greater risk of future nursing home admission and may be associated with mortality. *Am J Clin Nutr* 2006;84:616–22.

KEY WORDS Vitamin D deficiency, nursing home admission, mortality, nutrition, prospective study, elderly

INTRODUCTION

Vitamin D deficiency is common in older persons; it has a reported prevalence of 30% to 90%, depending on the definition used (1, 2). This frequency in older persons is partly due to their lower sunshine exposure and the reduced capacity of older skin to synthesize vitamin D₃ under the influence of ultraviolet light (3). A poor nutritional intake also contributes to a lower vitamin D status in older persons (4). The high prevalence of vitamin D deficiency in nursing home patients may thus be the consequence

of their poor physical health and functioning. However, a reverse pathway could also be hypothesized.

It is well known that low 25-hydroxyvitamin D [25(OH)D] concentrations and low 1,25-hydroxyvitamin D [1,25(OH)D] concentrations accelerate bone loss with aging and increase the risk of falling (5) and, possibly, of fractures (1, 6, 7). Several cross-sectional studies have shown that low 25(OH)D is also related to lower muscle strength and poorer physical performance in older persons (8–11), and a prospective study by our group reported that low 25(OH)D concentrations in older men and women were associated with greater loss of muscle strength (12). Although not all intervention studies support these findings (13, 14), several intervention studies have shown improvements of muscle strength, body sway, fall risk, and physical performance after vitamin D supplementation in older persons (15–19).

The results of most of the studies referenced above suggest that low vitamin D concentrations may accelerate the age-related decline in physical health and functioning. We therefore hypothesized that low vitamin D concentrations increase the risk of nursing home admission. To our knowledge, this hypothesis has never been tested. Even among community-dwelling older persons, vitamin D deficiency is common (1, 2), which shows the dramatic effect of a potential association on chronic care of older persons. Thus, the aim of this prospective, population-based study was to investigate whether lower 25(OH)D concentrations increase the risk of nursing home admission and mortality in independent, community-dwelling older men and women.

SUBJECTS AND METHODS

Study participants

Data for this study were collected in the Longitudinal Aging Study Amsterdam (LASA), a prospective study of persons aged

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Received January 31, 2006.

Accepted for publication March 20, 2006.

55–85 y. The sampling and data collection procedures and the response rate were described in detail elsewhere (20). In summary, a random sample stratified by age, sex, and expected 5-y mortality was drawn from the population registers of 11 municipalities in 3 areas—the western, northeastern, and southern parts of the Netherlands. In total, 3107 subjects were enrolled in the baseline examination (1992–1993), and they were representative of the Dutch older population. Examinations, which were repeated after 3, 6, and 9 y of follow-up, consisted of general and medical interviews, conducted in each participant's home. The medical interviews were performed by trained nurses, and all interviews were recorded so that their quality could be monitored.

The sample for the current study comprised 1509 participants who participated in the medical interview at the first LASA follow-up (1995–1996) and who were born in or before 1930 (ie, were aged ≥ 65 y as of 1 January 1996). This follow-up examination was selected as the baseline of our study because of blood sample availability. We excluded participants who were not living independently at baseline ($n = 88$), who did not provide a blood sample or had no measurement of serum 25(OH)D ($n = 153$), or who had missing contact information during the 6-y follow-up ($n = 8$); these exclusions left a total of 1260 participants with complete data for the statistical analyses.

Compared with those who were included in the statistical analyses, those excluded ($n = 249$) were older, less educated, less physically active, and less likely to have a household partner; had poorer mobility performance, lower serum total cholesterol concentrations, poorer cognitive function, more depressive symptoms, and more diabetes mellitus, incontinence, and stroke; used less alcohol; and were more likely to smoke. Those excluded with available serum 25(OH)D concentrations ($n = 60$) had a lower median (interquartile range) concentration (28.3 nmol/L; 20.3–43.8 nmol/L) than did those included (51.8 nmol/L; 37.2–68.8 nmol/L; $P < 0.0001$). Finally, those excluded were more likely (59.4%) than were those included (30.2%) to die during follow-up.

Written informed consent was obtained from all participants. The study was approved by the Medical Ethics Committee of the Vrije University Medical Center.

Serum 25-hydroxyvitamin D

During an additional visit in a nearby hospital or health care center, fasting blood samples were obtained. The blood samples were collected in the morning and centrifuged at $1800 \times g$ for 5 min at room temperature, and the serum samples were stored at -20° until hormone measurement in 1997–1998. Serum 25(OH)D was measured by using a competitive protein-binding assay (Nichols Diagnostics, San Juan Capistrano, CA). The lower limit of functional detection was 10 nmol/L, and the interassay CV was $<15\%$. The analyses were carried out at the Endocrine Laboratory of the Vrije University Medical Center. To investigate the effect of storage at -20° on the 25(OH)D concentration, 25 serum samples were remeasured in 2004 by using a radioimmunoassay (DiaSorin SpA, Saluggia, Italy); the correlation between the 2 measurements was 0.94 (P Lips, unpublished observations, March 2006).

Serum 25(OH)D was categorized into 4 groups on the basis of published cutoffs: <25 nmol/L for deficiency, 25–49.9 nmol/L for insufficiency, 50–74.9 nmol/L for borderline status, and ≥ 75 nmol/L for normal status (ie, reference group) (1). Because the

lowest serum 25(OH)D concentration that allows optimal skeletal health varies between 50 and 80 nmol/L (21), the category of 50–74.9 nmol/L was labeled as “borderline.”

Nursing home admission

A nursing home was defined as a chronic care facility, mainly for older persons. In the Netherlands, admission to a nursing home is based on the level of care requested by a regional Center of Care Assessment, and expenses are covered by the Exceptional Medical Expenses Act (Dutch national insurance) so that long-term care is accessible for all citizens.

Time to nursing home admission was ascertained through the general interviews of the participant (69.2% of the study sample) or a proxy (3.0% of the study sample), information from the death certificate (24.4% of the study sample), and information obtained during the last study contact (3.3% of the study sample).

If the participant had moved to a nursing home, person-time (in this case, the time that elapsed during the study before a person moved to a nursing home) was set at the midpoint between the previous (pre-nursing home) interview and the next interview that took place after he or she went to the nursing home. For participants who died during follow-up, the last known residence, stated on the death certificate, was used to ascertain nursing home admission. If the deceased participant had moved to a nursing home before death, person-time was set at the midpoint between the last interview and the date of death. If the participant was contacted for a planned interview but refused or was physically or cognitively ineligible to participate further, information obtained from the participant (or a proxy) during this last study contact was used to assess nursing home admission. If the participant had moved to a nursing home, person-time was set at the midpoint between the last interview and the date of this final study contact. If no nursing home admission took place, person-time for each participant was calculated as the time between the date of the baseline interview (1995–1996) and the date of the follow-up interview 6 y later (2002–2003), the date of death, or the date of final study contact, whichever came first.

Mortality

Death certificates were traced through the registries of the municipalities in which the participants were living. Vital status ascertainment was 100% complete. All deaths that occurred between the baseline of our study (1995–1996) and 1 April 2003 were recorded. Survival time was calculated as the time between the date of the baseline interview and the date of death or 1 April 2003, whichever came first.

Potential confounders and effect modifiers

The following potential confounders measured at baseline were included in the statistical analyses: sex, age, education, household partner status (for nursing home admission outcome only), chronic diseases, the serum creatinine concentration, cognitive status, depressive symptoms, smoking status, alcohol consumption, body mass index, physical activity level, mobility performance, a low serum albumin concentration, and a low serum total cholesterol concentration. These confounders are known to be associated with 25(OH)D and the study outcomes nursing home admission, mortality, or both, and therefore they may confound the associations under study. Level of education was categorized as low (elementary school or less), moderate,

and high (higher vocational school, college, or university). A household partner was defined as a person whom the participant considered as a partner (spouse or other person) and with whom the participant was living and sharing a household. Participants were asked (yes or no) whether they currently had or had had any of the following conditions: chronic obstructive pulmonary disease (ie, asthma, chronic bronchitis, or pulmonary emphysema), cardiac disease, peripheral atherosclerosis, stroke, diabetes mellitus, arthritis (ie, rheumatoid arthritis and osteoarthritis), cancer, and incontinence. The serum creatinine concentration ($\mu\text{mol/L}$) was used as an indicator of renal function, which is known to influence 25(OH)D concentrations (22).

A Dutch version of the Center for Epidemiologic Studies Depression (CES-D) scale, a 20-item self-report scale, was used to measure depressive symptoms; a score ≥ 16 points was used to identify clinically relevant depression (23, 24). Cognitive function was measured with the Mini-Mental State Examination; and a score < 24 was used to identify poor cognitive function (25). Smoking (never, former, or current) and alcohol consumption (none, < 7 drinks/wk, or ≥ 7 drinks/wk) were based on self-report. Measured body weight and height were used to calculate the body mass index (BMI; in kg/m^2), which was categorized as < 25 , 25–29.9, or ≥ 30 . Information on physical activity in the previous 2 wk was obtained by using a validated interviewer-administered questionnaire (26). The total time spent in walking outdoors, bicycling, heavy household activities, and sports activities was categorized as < 30 , 30–59, or ≥ 60 min/d. Mobility performance was objectively assessed by using a timed walking test and a repeated chair stands test. Those completing a test were assigned scores of 1 to 4, corresponding to the quartiles of time needed to complete the test; the fastest times were scored as 4 (27). Those who could not complete a test were assigned a score of 0. Mobility performance scores could range from 0 (unable to perform both tests) to 8 (performance time in the fastest quartile for both tests). Serum albumin concentrations (g/L) were measured by using the bromocresol purple method. Low serum albumin was defined as a concentration < 38 g/L (28). Serum total cholesterol concentrations (mmol/L) were measured by using an enzymatic colorimetry assay with a Hitachi 747 analyzer (Roche Diagnostics, Basel, Switzerland). Low serum cholesterol was defined as a concentration < 5.2 mmol/L (< 200 mg/dL) (29).

Statistical analysis

All analyses were conducted by using SAS software (version 9.1.3; SAS Institute Inc, Cary, NC). Potential differences between 25(OH)D categories in continuous variables were tested by using linear regression analyses, and differences between those in categorical variables were tested by using the chi-square test. *P* values were based on 2-sided tests and were considered significant if $P < 0.05$. Kaplan-Meier curves were generated to investigate the associations of 25(OH)D categories with time to nursing home admission and mortality, which were tested by using the log-rank test. Cox proportional hazards analysis was used to investigate the association between 25(OH)D category (independent variable) and time to nursing home admission or time to death (dependent variables). In the first model, adjustment for age, sex, and education (and household partner status for nursing home admission outcome) was made. The second model added adjustment for chronic disease, serum creatinine concentrations, cognitive status, and depressive symptoms. The third model further added adjustment for lifestyle variables including

smoking status, alcohol consumption, BMI, and physical activity level. Poor mobility performance, a low serum albumin concentration, and a low serum total cholesterol concentration are known indicators of frailty and have been associated with nursing home admission and mortality (27, 30, 31) and with lower vitamin D concentrations (8–10, 32). These indicators may confound the associations but may also act as potential mediators. Therefore, the frailty indicators were adjusted for in a separate, final model (model 4). Results are presented as hazard ratios (HRs) with 95% CIs. Because of the controversy regarding cut-offs for 25(OH)D categories, we also used the 25(OH)D concentration as a continuous variable and expressed the HRs per 1-SD increase in 25(OH)D. Log(-log) plots and time interaction terms were used to check the proportional hazards model assumption, which was not violated in any of the models. Potential sex and age group differences in the relation of serum 25(OH)D to nursing home admission and mortality were tested by using product terms in additional analyses.

RESULTS

Vitamin D deficiency and insufficiency were present in 127 (10.1%) and 462 (36.7%) persons, respectively (Table 1). Persons with lower 25(OH)D concentrations were more likely to be female, older, less educated, obese, physically inactive, and never smokers; more likely to abstain from alcohol; and less likely to live with a partner. They were also more likely to be incontinent and cognitively impaired or depressed, to report arthritis, and to have a lower serum creatinine concentration. Finally, they had a poorer performance on the mobility performance tests and were more likely to have low serum albumin and total cholesterol concentrations.

Nursing home admission

During the 6 y of follow-up, 138 subjects (11.0%) were admitted to a nursing home. Lower 25(OH)D concentrations were associated with a greater probability of nursing home admission ($P < 0.0001$, log-rank test; Figure 1). The risk of nursing home admission for participants with 25(OH)D deficiency was 53 cases per 1000 person-years higher than that for those with high (ie, ≥ 75 nmol/L) 25(OH)D concentrations (58 compared with 5 cases). After adjustment for age, sex, education and household partner status, lower 25(OH)D concentrations were associated with a significantly (P for trend = 0.0006) higher risk of nursing home admission during the 6-y follow-up (Table 2). Additional adjustment for physical, cognitive, and emotional health (model 2) and lifestyle variables (model 3) only marginally attenuated the observed HRs. In a final model, additional adjustment was made for several frailty indicators. The HR for older persons with 25(OH)D deficiency (HR: 2.88; 95% CI: 1.15, 7.23) and 25(OH)D insufficiency (HR: 2.51; 95% CI: 1.06, 5.96) compared with those with high 25(OH)D (≥ 75 nmol/L) remained significant (P for trend = 0.010). When 25(OH)D was used as a continuous variable, the HR per 1-SD (ie, 23.9 nmol/L) increase in 25(OH)D was 0.70 (95% CI: 0.56, 0.87) for model 1, 0.74 (95% CI: 0.59, 0.93) for model 2, 0.74 (95% CI: 0.58, 0.93) for model 3, and 0.77 (95% CI: 0.61, 0.97) for model 4. The association between categories of 25(OH)D and nursing home admission did not differ significantly between men and women or between those subjects aged < 70 , 70–79, and ≥ 80 y ($P > 0.31$).



TABLE 1

Characteristics of the study sample by category of serum vitamin D concentration; the Longitudinal Aging Study Amsterdam

Characteristic	Serum 25-hydroxyvitamin D concentration (nmol/L)				P
	<25	25–49.9	50–74.9	≥75	
Study sample [n (%)]	127 (10.1)	462 (36.7)	440 (34.9)	231 (18.3)	
Female (%)	61.4	60.6	46.1	36.4	<0.0001
Age (%)					
<70 y	10.2	19.7	29.8	45.5	
70–79 y	32.3	45.0	51.6	42.9	<0.0001
≥ 80 y	57.5	35.3	18.6	11.7	
Education (%)					
Low	46.5	43.9	38.6	36.8	
Moderate	37.8	44.8	53.0	47.2	0.0039
High	15.7	11.3	8.4	16.0	
Partner in household (%)	35.4	47.6	63.0	79.2	<0.0001
BMI (%)					
<25 kg/m ²	33.1	32.2	34.6	48.5	
25–29.9 kg/m ²	44.1	44.2	47.9	39.8	0.0001
≥ 30 kg/m ²	22.8	23.6	17.5	11.7	
Smoking status (%)					
Never	48.0	39.6	31.2	29.9	
Former	27.6	42.4	52.7	51.9	<0.0001
Current	24.4	18.0	16.1	18.2	
Alcohol consumption					
0 glasses/wk	30.7	30.3	20.0	12.5	
1–6 glasses/wk	54.3	50.0	51.8	53.3	<0.0001
≥ 7 glasses/wk	15.0	19.7	28.2	34.2	
Physical activity (%)					
< 30 min/d	51.2	41.6	25.2	25.6	
30–59.9 min/d	22.8	26.0	25.7	24.2	<0.0001
≥ 60 min/d	26.0	32.4	49.1	50.2	
Chronic conditions (%)					
Lung disease	18.1	16.5	15.5	11.7	0.31
Cardiovascular disease	40.9	32.9	31.6	31.6	0.24
Diabetes mellitus	9.5	9.5	6.8	4.8	0.11
Incontinence	37.0	27.5	19.8	16.9	<0.0001
Stroke	9.5	7.8	7.7	4.8	0.35
Arthritis	59.1	47.8	43.6	45.0	0.02
Cancer	17.3	12.6	12.1	9.1	0.15
Serum creatinine (μmol/L)	84 (74–99) ¹	88 (77–101)	90 (81–103)	94 (83–105)	<0.0001
Cognitively impaired (%)	19.7	11.0	7.5	6.1	<0.0001
Depressive symptoms (%)	20.5	16.7	11.4	10.8	0.0092
Mobility score (%)					
0–2	41.7	26.2	14.6	8.7	
3–5	51.2	42.9	42.7	38.5	<0.0001
6–8	7.1	31.0	42.7	52.8	
Low serum albumin (%) ²	23.6	17.8	13.2	5.6	<0.0001
Low serum cholesterol (%) ³	33.1	23.6	22.5	16.5	0.0045

¹ \bar{x} ; interquartile range in parentheses (all such values).² < 38 g/L.³ < 5.2 mmol/L.

Mortality

During the study follow-up, 380 persons (30.2%) died. The Kaplan-Meier curves in **Figure 2** show a lower survival in those with lower 25(OH)D concentrations ($P < 0.0001$, log-rank test). After adjustment for age, sex, and education, 25(OH)D deficiency was associated with a higher mortality risk (HR: 1.61; 95% CI: 1.09, 2.37) than were high (≥ 75 nmol/L) 25(OH)D concentrations (**Table 3**). However, after additional adjustment

for health and lifestyle variables and several frailty indicators, the relation between 25(OH)D concentration and mortality was no longer statistically significant (P for trend = 0.19). When 25(OH)D was used as a continuous variable, the HR per 1-SD increase in 25(OH)D was 0.84 (95% CI: 0.75, 0.95) for model 1, 0.86 (95% CI: 0.77, 0.97) for model 2, and 0.88 (95% CI: 0.78, 0.99) for model 3. After additional adjustment for the frailty indicators (model 4), the association was no longer statistically

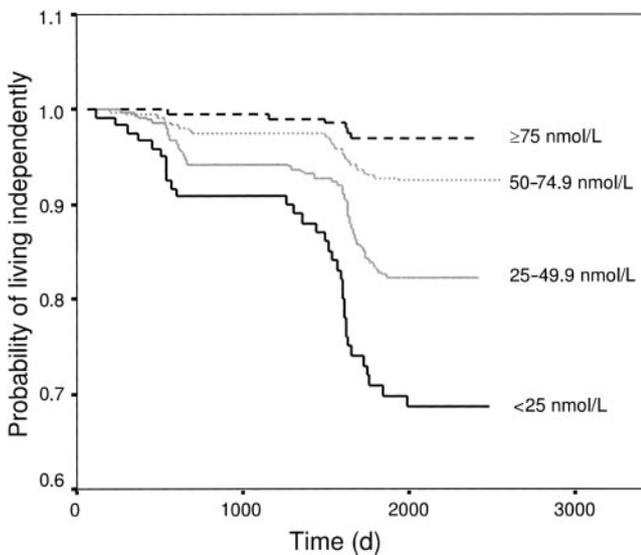


FIGURE 1. Kaplan-Meier curves for nursing home admission according to categories of serum 25-hydroxyvitamin D [25(OH)D] concentration from the Longitudinal Aging Study Amsterdam.

significant (HR: 0.91; 95% CI: 0.81, 1.02). The association between categories of 25(OH)D and mortality did not differ significantly between men and women or between those subjects aged < 70, 70–79, and ≥ 80 y ($P > 0.33$).

DISCUSSION

To our knowledge, this is the first population-based study investigating the association of serum 25(OH)D concentrations with nursing home admission and mortality in older persons by using a longitudinal design. The results suggest that deficient and insufficient 25(OH)D concentrations (ie, those <50 nmol/L) are associated with a higher risk of nursing home admission in older men and women. These relations were present after careful adjustment for health and lifestyle factors, age, sex, education, and household partner status. More important, the relations were maintained after adjustment for indicators of frailty, including poor mobility performance and low serum albumin and total cholesterol concentrations.

TABLE 2

Adjusted hazard ratios (HRs) for nursing home admission during 6-y follow-up by category of serum 25-hydroxyvitamin D [25(OH)D] concentration: the Longitudinal Aging Study Amsterdam¹

	<i>n</i>	Event rate ²	Model 1	Model 2	Model 3	Model 4
			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
25(OH)D						
<25 nmol/L	127	58	3.76 (1.53, 9.29)	3.26 (1.31, 8.12)	3.48 (1.39, 8.75)	2.88 (1.15, 7.23)
25–49.9 nmol/L	462	31	3.01 (1.29, 7.06)	2.74 (1.16, 6.47)	2.77 (1.17, 6.55)	2.51 (1.06, 5.96)
50–74.9 nmol/L	440	13	1.96 (0.81, 4.73)	1.87 (0.77, 4.54)	1.92 (0.79, 4.66)	1.78 (0.73, 4.33)
≥ 75 nmol/L	231	5	1.0	1.0	1.0	1.0
<i>P</i> for trend			0.0006	0.0033	0.0023	0.011

¹ Model 1: adjusted for sex, age, education, and partner status; model 2: adjusted for as in model 1 and for chronic diseases, serum creatinine concentration, cognitive status, and depressive symptoms; model 3: adjusted for as in model 2 and for lifestyle variables including BMI, smoking status, alcohol consumption, and physical activity; model 4: adjusted for as in model 3 and for frailty indicators: mobility performance, low serum albumin concentration, and low serum total cholesterol concentration.

² Events/1000 person-years.

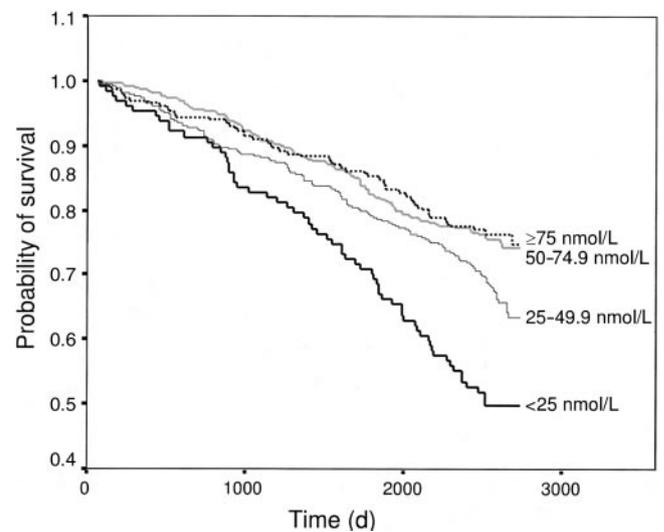


FIGURE 2. Kaplan-Meier curves for mortality according to categories of serum 25-hydroxyvitamin D [25(OH)D] concentration from the Longitudinal Aging Study Amsterdam.

An association between lower 25(OH)D concentrations and higher mortality risk was also observed. However, this association was no longer significant after adjustment for the frailty indicators. Because the frailty indicators may act as mediators of the association between lower 25(OH)D and mortality risk, adjustment for these indicators could be considered overadjustment.

The results are even more striking when considering the high prevalence (46.7%) of vitamin D deficiency and insufficiency in our sample of independently living men and women, which is comparable to that reported in other studies (33, 34). This high prevalence and the results of our study could indicate that poor vitamin D status may have a large effect on nursing home admission in the general population and may lead to additional health care costs.

The higher risk of nursing home admission in those with deficient and insufficient 25(OH)D concentrations may be explained by their greater risk of sarcopenia and falls (5, 12). Vitamin D concentrations have also been associated with physical performance in cross-sectional and intervention studies (8–11,



TABLE 3

Adjusted hazard ratios (HRs) for mortality by category of serum 25-hydroxyvitamin D [25(OH)D] concentration: the Longitudinal Aging Study Amsterdam¹

	n	Event rate ²	Model 1	Model 2	Model 3	Model 4
			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
25(OH)D						
<25 nmol/L	127	66	1.61 (1.09, 2.37)	1.54 (1.04, 2.29)	1.47 (0.99, 2.19)	1.28 (0.85, 1.92)
25–49.9 nmol/L	462	42	1.17 (0.85, 1.62)	1.11 (0.80, 1.54)	1.08 (0.78, 1.51)	1.00 (0.72, 1.40)
50–74.9 nmol/L	440	30	0.93 (0.67, 1.29)	0.95 (0.68, 1.32)	0.95 (0.68, 1.32)	0.91 (0.65, 1.26)
≥ 75 nmol/L	231	29	1.0	1.0	1.0	1.0
P for trend			0.0058	0.021	0.046	0.19

¹ Model 1: adjusted for sex, age, and education; model 2: adjusted for as in model 1 and for chronic diseases, serum creatinine concentration, cognitive status, and depressive symptoms; model 3: adjusted for as in model 2 and for lifestyle variables including BMI, smoking status, alcohol consumption, and physical activity; model 4: adjusted for as in model 3 and for frailty indicators: mobility performance, low serum albumin concentration, and low serum total cholesterol concentration.

² Events/1000 person-years.

15–19). The only available prospective study reported no greater risk of new disability in disabled women with low vitamin D concentration than in those with higher vitamin D concentrations (35), although selection bias may have caused this result (36). The greater risk of nursing home admission may also be explained by the higher risk of osteoporosis, and possibly fracture, which subsequently leads to a decline in functional status, an increase in pain, and an impaired quality of life (37–39). More recently, low vitamin D concentrations have been associated with obesity, diabetes, and cardiovascular disease (40–43). These associations offer an additional explanation for the association between lower vitamin D concentrations and nursing home admission, because these diseases increase the risk of functional limitation, disability, and cognitive impairment in old age (44–47). Finally, we cannot exclude that low vitamin D concentration may act as a marker for something else related to nursing home admission. Future studies are needed to elucidate the pathways through which vitamin D deficiency may increase the risk of nursing home admission.

It is known that vitamin D supplementation in older persons increases 25(OH)D and 1,25-hydroxyvitamin D concentrations (48, 49), and supplementation could be appropriate in settings of nutritional adequacy and frailty. However, spending more time outdoors will also improve vitamin D status (50, 51). The latter option seems preferable for older persons when it is combined with physical activity, because physical activity will increase muscle strength, slow down bone loss, and lower the risks of falls, of a decline in functional performance, and of disability with aging (52–54). Regular outdoor walking has already been shown to reduce the risk of mobility decline (54, 55). Furthermore, beneficial effects of physical activity on cognitive functioning and chronic disease in older persons have been reported (56, 57).

Some of the weaknesses of the current study should be discussed. No exact date of nursing home admission was available in the study. Almost 70% of the information on nursing home admission was obtained directly from the participant at 3-y intervals. When a participant was reported to have moved to a nursing home, the date of admission was conservatively set at the midpoint of 2 follow-up examinations, in imitation of other studies (58). This nondifferential bias may have resulted in an underestimation of the reported associations and less precise estimates. Another weakness is that those excluded from the study had a poorer health status, had more frailty indicators, had lower

serum vitamin D concentrations, and were more likely to die during follow-up than were those included in the study. This selection bias may also have contributed to an underestimation of the reported associations. Finally, our results may not be generalizable to other countries because of differences in the health care systems in various countries.

In conclusion, lower serum 25(OH)D concentrations in older men and women are associated with a greater risk of future nursing home admission and may be associated with a greater mortality risk. These results could indicate that lower vitamin D concentrations may specifically affect the level of independence in old age. 

MV, DJHD, and PL contributed to the study design. MV was responsible for the statistical analysis of the data and for drafting the manuscript. All authors were responsible for critical revision of the manuscript. PL has received funds for research, fees for consulting, or both from Nycomed, Lilly, MSD, Wyeth, Servier, Aventis, and Procter & Gamble. None of the other authors had a personal or financial conflict of interest.

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Nutrition, chronic disease, and the problem of proof^{1,2}

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For the most part, the disorders that have shaped nutrition as a science have had 2 characteristics: each nutrient was the major factor in its cognate disease, and disease expression had short latency, which facilitated recognition of the connection between cause and effect. More recently, an extensive body of epidemiologic associations between nutrient intake and various outcomes has raised the possibility that insufficient nutrition may contribute to the burden of chronic disease. But true causal connections between specific nutrients and these other disorders have been hard to establish, partly because most chronic diseases are highly multifactorial and partly because they have long latency periods. Both factors make the evaluation of causality inherently difficult.

Vitamin D presents a good case in point. There has been an explosion of reports relating vitamin D status to various disorders in the past 10 y (1). Many of these disorders specifically afflict the aging population. This issue of the Journal contains another of these reports. Visser et al (2), from the Amsterdam Longitudinal Aging Study, report that the likelihood of nursing home admission was inversely related to baseline vitamin D status. The trend in risk was approximately linear up to the highest values measured (ie, >75 nmol/L). After various adjustments, persons with values <25 nmol/L had nearly 4 times the risk of being admitted to a nursing home as did persons with values >75 nmol/L. The true risk may be even higher, because some of the statistical adjustments involved factors through which vitamin D may be operating.

This finding has biological plausibility, inasmuch as low vitamin D status impairs lower-extremity function and contributes significantly to the risk of falling (3, 4). In these studies, as in the study by Visser et al, function improves in association with concentrations of 25-hydroxyvitamin D [25(OH)D] up to 80 nmol/L and perhaps even higher. More than 80% of the Amsterdam cohort had serum concentrations of 25(OH)D < 80 nmol/L; this finding is also supported by a still-growing body of studies showing that low vitamin D status is common.

In addition to the personal disaster for the persons concerned, institutionalization of the dependent elderly imposes staggering costs on society, which are destined only to increase as the population ages and family units become smaller. The high prevalence of vitamin D deficiency mandates that physicians assess and correct vitamin D status in their elderly patients (5).

However, the same high prevalence must cause us to ask why a global intervention should not be given serious consideration.

Persons are, of course, always free to act on available information, but individual initiative is rarely an efficient way of changing public health status. Food fortification is an obvious alternative (7), but any such proposal bumps up squarely against the problem of proof. Most of the studies concerned (including the study by Visser et al) are observational in character. Do such studies constitute sufficient evidence for a population-level intervention?

The randomized controlled trial (RCT), which has become the gold standard for establishing the efficacy of pharmacologic agents, is poorly suited to the evaluation of nutritional effects, a fact that I believe many have been reluctant to acknowledge. Several important differences between nutrients and drugs lead to this conclusion. In addition to long latency and multifactorial causation for the diseases concerned, nutrients and drugs differ in 3 crucial respects. First, whereas a drug-free state exists that can be contrasted with a drug-added state, with respect to nutrients, the only contrast can be between different intakes, both usually well above zero. Second, most nutrients have what is known as threshold behavior, ie, some physiologic measure improves as intake rises up to a level of sufficiency, above which higher intakes produce no additional benefit. Third, most nutrients have beneficial effects on multiple tissues and organ systems, and thus a focus on a single or "primary" outcome measure, which is favored by RCTs, is often procrustean. As a consequence of the second point, investigators using the RCT design must contrast 2 groups of subjects, at least one of which has a distinctly inadequate intake of the nutrient concerned. Failure to do that, as occurred in the calcium arm of the Women's Health Initiative (WHI) (7, 8), constitutes an invalid test of the corresponding hypothesis. However, the assignment of subjects to an intake that is inadequate by current standards, for the span of time required to produce the necessary difference in serious outcomes, raises significant and probably insurmountable ethical problems (9).

Just such a dilemma may have been part of the explanation for the high calcium intake in the placebo group in the calcium arm of WHI. The median intake from the third National Health and Nutrition Examination Survey of women in the age range concerned was ≈600 mg Ca/d, and the logical hypothesis would have been that the currently recommended calcium intake (1200 mg/d) would produce certain benefits not realizable at 600 mg/d. But both the state of the science at the time when WHI was

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designed and a multiplicity of National Institutes of Health Consensus Development Conference Reports made it effectively impossible for the WHI designers to impose a 600-mg limit on the control group's intake when National Institutes of Health policy statements had said that 600 mg/d was inadequate. Whatever the explanation, there was no low-calcium contrast group in WHI.

Unfortunately, the reports from WHI primarily stressed the outcome of the controlled intervention, as if calcium and vitamin D had been drugs, and tended to deemphasize the observational data that the study had also generated. Examples are the fact that, in addition to a baseline calcium intake in the participants nearly twice that predicted from the third National Health and Nutrition Examination Survey, the hip fracture rate was approximately half of that predicted from Medicare. No connection seems to have been made between these 2 departures from expectation. There was a similar lapse with respect to the connection between vitamin D intake and colon cancer. Whereas the designed low dose of vitamin D in WHI did not significantly alter colon cancer incidence, baseline vitamin D status was, in fact, significantly inversely related to cancer risk. The lowest 25(OH)D quartile had a risk 2.5 times that of the highest quartile. No actual contradiction exists between these findings, because the vitamin D input required to move subjects from the first quartile to the fourth quartile in WHI is now known to be ≈ 10 times the achieved dose (10).

Such circumstances raise 2 related questions: 1) to what extent should current standards of proof be relaxed for nutrient benefits? and 2) what alternative investigational design might be used to produce results that could be used as a basis for nutritional policy?

Public policy has long been comfortable in using a more relaxed standard of proof for potentially harmful effects. The studies leading to a food label for *trans* fats would not likely have been considered adequate to support the *promotion* of the use of *trans* fats (had the relation been the other way around). Nor do we require RCTs to set the cutoffs for various environmental toxins, from lead to polychlorinated biphenyl. Should the standard of proof be relaxed for benefit, as in the instance of a fortification program that elevates nutrient status (in this case vitamin D) to demonstrably safe intakes? If the balance of the potential for harm tilts in favor of fortification, then the answer should be "yes," irrespective of the level of evidence.

With respect to study design, there is one approach that offers a reasonably practicable alternative to the RCT, ie, the nonconcurrent cohort study. As are all cohort studies, it is prospective. It is "nonconcurrent" in the sense that the exposure to the various

amounts of nutrient precedes the investigation; ie, the entering of subjects into study is done after the exposure but before any analysis. As does an RCT, it equalizes the placebo effect between the contrast groups (ie, there is essentially none in either group), but, as are other observational studies, it is subject to the effects of extraneous factors that cannot be randomized. To minimize the distortions introduced by such factors, all plausible confounders must be identified in advance of the investigation and then factored into the criteria (inclusion and exclusion) for assignment of participants to the groups in which the desired outcomes may be counted or measured. If done carefully, this approach can minimize the admission rate bias inherent in most observational study designs. However, because assignment to the contrast groups is not random, it is not possible to define exact probability limits to the differences that may emerge.

The foregoing approach could be readily evaluated in existing databases, but, whatever the study design, the problem of proof remains, and, as a consequence, a substantial potential for reduction in the burden of chronic disease hangs in the balance. 

The author had no personal or financial conflict of interest with the study by Visser et al.

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