

Extraskelletal Effects of Vitamin D in Older Adults: Cardiovascular Disease, Mortality, Mood, and Cognition

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ABSTRACT

Background: Vitamin D insufficiency is prevalent among older adults and may be associated with higher risk for cardiovascular (CV) disease, mortality, depression, and cognitive deficits.

Objective: The aim of this article was to review published observational and experimental studies that explored the association between vitamin D insufficiency and CV disease, mortality, mood, and cognition with an emphasis on older adults.

Methods: PubMed and Web of Science databases were searched for English-language articles from January 1966 through June 2009 relating to vitamin D, using the following MeSH terms: *aged, vitamin D deficiency, physiopathology, drug therapy, cardiovascular diseases, blood pressure, mortality, delirium, dementia, cognitive disorders, depression, depressive disorder, seasonal affective disorder, mental disorders, and vitamin D/therapeutic use*. Publications had to include patients ≥ 65 years of age who had ≥ 1 recorded measurement of 25-hydroxyvitamin D (25[OH]D) or were receiving vitamin D supplementation. All case-control, cohort, and randomized studies were reviewed.

Results: Forty-two case-control, cohort, and randomized trials were identified and included in the review. Based on these publications, the prevalence of vitamin D insufficiency (25[OH]D concentration < 30 ng/mL) in community-dwelling older adults (≥ 65 years of age) ranged from 40% to 100%. Epidemiologic data and several small randomized trials found a potential association between vitamin D deficiency (25[OH]D concentration < 10 ng/mL) and CV disease, including hypertension and ischemic heart disease. Although subgroup analyses of data from the Women's Health Initiative Randomized Trial (the largest randomized, placebo-controlled trial of vitamin D plus calcium therapy) did not find reductions in blood pressure, myocardial infarction, or CV disease-related deaths, intervention contamination limited the findings. Observational studies and a meta-analysis of randomized controlled trials found a mortality benefit associated with higher serum 25(OH)D concentrations or vitamin D₂ or D₃ supplementation (mean dose, 528 IU/d). Observational and small randomized trials found a potential benefit of sunlight or vitamin D on symptoms of depression and cognition, but the findings were limited by methodologic problems.

Conclusions: Vitamin D insufficiency appears to be highly prevalent among older adults. Evidence from epidemiologic studies and small clinical trials suggests an association between 25(OH)D concentrations and systolic blood pressure, risk for CV disease-related deaths, symptoms of depression, cognitive deficits, and mortality. The Women's Health Initiative Randomized Trial did not find a benefit of vitamin D supplementation on blood pressure, myocardial infarction, or mortality in postmenopausal women. (*Am J Geriatr Pharmacother.* 2010;8:4-33) © 2010 Excerpta Medica Inc.

Key words: vitamin D deficiency, mortality, cardiovascular diseases, depression, cognitive disorders, aged.

INTRODUCTION

Although the fundamental role of vitamin D in calcium and phosphorus homeostasis and skeletal changes has long been recognized,¹ the extraskeletal roles of vitamin D in humans have been less fully explored. Vitamin D is now recognized to be an active hormone with endocrine and paracrine effects on many organs and tissues in the body.^{1,2} The active form, 1,25-dihydroxyvitamin D (1,25[OH]2D), acts not only in the intestines, kidneys, bones, and parathyroid glands to maintain calcium and phosphorus homeostasis,^{2,3} but also in other tissues to affect regulation of hormone secretion, regulation of immune function, and cellular proliferation and differentiation.^{4,5}

The role of vitamin D in fracture and fall prevention has been reviewed extensively by other authors.^{1,6,7} Over the past several years, research has found that many other tissues in the body contain receptors for 1,25(OH)2D (vitamin D receptors, or VDRs).^{1,4,8} Furthermore, most of these tissues also contain the enzyme 1- α -hydroxylase, which converts 25-hydroxyvitamin D (25[OH]D) to 1,25(OH)2D, suggesting a paracrine mechanism of action of vitamin D locally within tissues.² It appears that 1- α -hydroxylase requires an adequate amount of the substrate, 25(OH)D, for regulation. Therefore, the maintenance of adequate 25(OH)D concentrations is necessary for these nonskeletal functions of vitamin D.^{1,4} This article briefly reviews the basic physiology, definitions, and prevalence of vitamin D insufficiency and provides a systematic review of the evidence for the role of vitamin D in cardiovascular (CV) disease, mortality, mood, and cognition, with an emphasis on older adults. (Throughout the review, “older adults” are ≥ 65 years of age unless indicated otherwise.)

METHODS

The authors conducted a review of the literature focusing on human studies published in English in the PubMed and Web of Science databases from January 1966 through June 2009. Relevant MeSH terms were identified after a review of the literature and consultation with an academic medical librarian. A combination of searches was performed using the following MeSH terms: *aged, vitamin D deficiency, physiopathology, drug therapy, cardiovascular diseases, blood pressure, mortality, delirium, dementia, cognitive disorders, depression, depressive disorder, seasonal affective disorder, mental disorders, and vitamin D/therapeutic use*. Additional articles were found by searching the reference lists of the identified studies. Publications had to include patients ≥ 65 years of age who had ≥ 1 recorded measurement of

25(OH)D or were receiving vitamin D supplementation. All case-control, cohort, and randomized studies were included. Study data were abstracted into tables by the first author. Cochrane collaboration quality criteria⁹ were used to identify methodologic issues.

RESULTS

Forty-two case-control, cohort, and randomized trials were identified and included in the review.

Basic Physiology and Metabolism of Vitamin D

The 2 natural sources of vitamin D are sunlight and food.^{1,10} Vitamin D₃ (cholecalciferol) is the form of vitamin D that is synthesized in the skin under the influence of ultraviolet B (UVB) rays; it is also found in certain fish, fortified dairy products, and most dietary supplements. Vitamin D₂ (ergocalciferol) is produced by irradiated fungi and is the form of vitamin D found in prescription supplements (as capsules [50,000 IU]* or liquid [8000 IU/mL]†).

After vitamin D is formed in the skin, it is converted to 25(OH)D in the liver under the influence of the enzyme vitamin D 25-hydroxylase. This transport and storage form of vitamin D then circulates to the kidneys, where it is converted to the active form (1,25[OH]2D; calcitriol) by the enzyme 1- α -hydroxylase. Calcitriol is the active form of vitamin D, which binds to VDRs in the intestines, bones, and kidneys to increase calcium absorption from the intestines, promote calcium deposition in bones, and decrease parathyroid hormone concentrations (PTH).¹¹

VDR expression has also been documented in other tissues, including the brain, heart, skeletal muscle, breast, prostate, colon, activated macrophages, and skin.^{1,12} VDR expression appears to decrease with age.¹³ In vitro studies with human and animal cells have found that most tissues and cells not only express VDRs but also express the same 1- α -hydroxylase as that found in the kidneys.¹ Therefore, it appears as if these cells may produce the active form of vitamin D locally (in a paracrine fashion) to use in cellular functions. This forms the biologic basis for the association between 25(OH)D concentrations and extraskeletal conditions reviewed in this article.

Definitions

The transport and storage form of vitamin D, 25(OH)D, is measured to assess the vitamin D suffi-

*Trademark: Ergocalciferol® (Banner Pharmacaps, Inc., High Point, North Carolina).

†Trademark: Drisdol® (sanofi-aventis U.S. LLC, Bridgewater, New Jersey).

ciency status of persons with normal renal function¹⁴; when serum concentrations of 25(OH)D are low, 1,25(OH)₂D concentrations will decrease due to a lack of substrate.^{15,16} Although no scientific consensus or standardized laboratory measurement is available,¹⁷ most experts now classify 25(OH)D concentrations as follows: ≥ 30 ng/mL, optimal; 21 to 29 ng/mL, insufficient; and ≤ 20 ng/mL, deficient.^{1,10,18,19} These cutoffs are based on observations that concentrations of 20 to 30 ng/mL suppress PTH,²⁰ a concentration of 32 ng/mL is better than 20 ng/mL for calcium absorption,¹ and concentrations ≥ 40 ng/mL are associated with a decreased risk of fracture.²¹ In older adults, neuromuscular performance has been reported to peak at a concentration of 32 ng/mL.²²

Prevalence of Vitamin D Insufficiency/Deficiency

Vitamin D insufficiency/deficiency is a worldwide problem, affecting all ages and races.¹ Optimal 25(OH)D concentrations for skeletal health are >30 ng/mL.^{21,22} Serum 25(OH)D concentrations are generally lower in blacks than in whites and people who avoid the sun.^{17,23,24} The increased use of sunscreens is hypothesized to increase the prevalence of vitamin D deficiency.¹⁰ Older adults, as a result of hyperparathyroidism related to renal insufficiency, tend to require more vitamin D to achieve adequate levels of 25(OH)D.²⁵ As a result of the change in the definition of adequate concentrations, the prevalence of vitamin D deficiency is higher than previously thought. The prevalence of vitamin D deficiency among older men and women living in the United States and Europe ranges from 40% to 100%.¹

The National Health and Nutrition Examination Survey (NHANES) from 2000 to 2004¹⁷ found that ~25% of men >50 years of age and 30% to 35% of women >50 years of age had 25(OH)D concentrations <50 nmol/L and <20 nmol/L, respectively. Looker et al²⁶ compared 25(OH)D concentrations between the NHANES conducted from 1988 to 1994 and that conducted from 2000 to 2004. After adjusting for assay shifts and age, 25(OH)D concentrations decreased 5 to 9 nmol/L (2–3.6 ng/mL) from the 1988–1994 survey to the 2000–2004 survey. In the latter survey, the adjusted mean (SD) serum 25(OH)D concentrations differed significantly by age (63.86 nmol/L [25.6 ng/mL] in subjects 12–19 years of age and 57.5 nmol/L [23 ng/mL] in those ≥ 70 years of age; $P < 0.001$). Two studies performed in Colorado²⁷ and Georgia²⁸ found that despite reported consumption of more than the required daily intake of vitamin D (400–600 IU/d), the prevalence of vitamin D insufficiency (defined as

<32 ng/mL and <20 ng/mL, respectively) among community-dwelling older adults (mean age, 77.8 and 77.0 years, respectively) ranged from 36.7% to 74.0%. In a study of nonagenarian adults in Barcelona, Spain,²⁹ the prevalence of vitamin D insufficiency was 90.6%. The prevalence may be even higher in institutionalized populations. Cashman et al³⁰ conducted a randomized, placebo-controlled, double-blind trial in adults ≥ 64 years of age to determine the daily amount of vitamin D₃ required to maintain serum 25(OH)D concentrations between 25 and 80 nmol/L (10 and 32 ng/mL). They found that older adults required between 7.9 μ g (316 IU) and 42.8 μ g (1712 IU) of vitamin D₃ daily during the winter.

Role of Vitamin D in CV Disease

VDRs are found extensively within the tissues of the CV system, including vascular smooth muscle,³¹ endothelium,³² and cardiac myocytes.³² Mechanisms that may explain an association between vitamin D and CV disease include a decrease in inflammatory markers,³³ a direct effect on the blood vessel wall,³¹ and decreased renin activity.³⁴ Upregulation of the renin-angiotensin system (resulting in hypertension and left ventricular [LV] hypertrophy) has been reported in studies of VDR knockout mice.³⁵ The evidence for an association between vitamin D and blood pressure and other CV diseases is reviewed in the following sections and summarized in **Table I**^{36–46} and **Table II**.^{47–53}

Blood Pressure

Cross-Sectional Studies

Two cross-sectional studies^{36,37} have reported an association between serum 25(OH)D concentrations and systolic blood pressure (SBP). Scragg et al³⁶ examined 12,644 predominantly white patients >20 years of age from the NHANES III study⁵⁴ and excluded those with a diagnosis of hypertension. Multivariable-adjusted analyses by quintile of 25(OH)D concentration found SBP was 1.8 mm Hg lower ($P = 0.045$) and pulse pressure was 1.6 mm Hg lower ($P = 0.012$) in the highest quintile (≥ 85.7 nmol/L) than in the lowest quintile (≤ 40.4 nmol/L). Increasing 25(OH)D from 20 to 100 nmol/L predicted a decrease in SBP of 1.8 mm Hg in patients <50 years of age and 4.6 mm Hg in those ≥ 50 years of age. Ethnic differences in 25(OH)D concentrations explain 50% of the increased prevalence of hypertension in blacks compared with whites.

Judd et al³⁷ performed an analysis on 7699 patients (predominantly white women; 37% of the sample was >50 years of age) with no prior diagnosis of hyperten-

Table I. Studies evaluating the association between 25(OH)D concentrations, dietary vitamin D intake, sunlight, and blood pressure.³⁶⁻⁴⁶

| Study | Population | Design | Outcome Measures | Intervention | Results | Comments |
|----------------------------------|---|---|---------------------|--------------|--|----------------------------|
| Cross-sectional studies | | | | | | |
| Scragg et al, 2007 ³⁶ | 12,644 Patients; aged, >20 y (25% ≥60 y); 52% women; 42% white, 30% Mexican American, 28% black; normotensive | Cross-sectional, using data from NHANES III | Mean, 3 BP readings | None | Multivariable adjusted analyses, including BMI by quintile of 25(OH)D concentration, found SBP 1.8 mm Hg lower ($P = 0.045$) and pulse pressure 1.6 mm Hg lower ($P = 0.012$) in the highest quintile; increasing 25(OH)D from 20 to 100 nmol/L predicted a decrease in SBP of 1.8 mm Hg in those <50 y and 4.6 mm Hg in those ≥50 y; ethnic differences in 25(OH)D concentrations explain 50% of the increased prevalence of HTN in blacks compared with whites | Single 25(OH)D measurement |
| Judd et al, 2008 ³⁷ | 7699 Patients; 37% >50 y; 53% women; 61% white, 39% black; normotensive | Cross-sectional, using data from NHANES III | Mean, 3 BP readings | None | Yearly age-related increases in SBP lessened with increasing 25(OH)D concentrations: <20 ng/mL → 0.50 mm Hg/y, 20–30 ng/mL → 0.48 mm Hg/y, >32 ng/mL → 0.40 mm Hg/y; in white participants, 25(OH)D concentrations >80 nmol/L (32 ng/mL) reduced the predicted age-related increase in SBP by 20% compared with those with 25(OH)D concentrations <50 nmol/L (25 ng/mL; $P < 0.001$) | Single 25(OH)D measurement |

(continued)

Table I (continued).

| Study | Population | Design | Outcome Measures | Intervention | Results | Comments |
|------------------------------------|--|---|---|--------------|---|--|
| Snijder et al, 2007 ³⁸ | 1205 Subjects; aged ≥ 65 y; mostly white | Cross-sectional analysis within the LASA | SBP and DBP | None | Multivariable logistic regression analyses found no association between 25(OH)D and BP (DBP = β -coefficient, 0.00, $P = \text{NS}$; SBP = β -coefficient, 0.06, $P = \text{NS}$); intact PTH concentrations were positively associated with BP (DBP = β -coefficient, 1.93, $P = 0.03$; SBP = β -coefficient, 4.67, $P = 0.01$) after adjustment for confounding variables | Single 25(OH)D and BP measurements; low prevalence of 25(OH)D deficiency may have attenuated the association |
| Sowers et al, 1985 ³⁹ | 222 Women aged 55–80 y and 86 women aged 20–35 y; normotensive | Cross-sectional | BP measurement, dietary recall | None | Older women who reported a daily consumption of < 400 IU vitamin D had a mean SBP of 139 mm Hg, whereas those who reported a daily consumption of ≥ 400 IU had a mean SBP of 133 mm Hg ($P = 0.037$); mean DBP was similar in the 2 groups (75 and 74 mm Hg, respectively); analysis was adjusted for age, BMI, alcohol use, and calcium intake | Dietary intakes were based on patient recollection |
| Jorde and Bona, 2000 ⁴⁰ | 8053 Women and 7543 men; aged 25–69 y; community-dwelling adults in Norway | Cross-sectional analysis within Norwegian health survey | BP, BMI, smoking, calcium and vitamin D intake (questionnaire), physical activity | None | Weak positive correlation between vitamin D intake and SBP in women (β -coefficient, 0.026) and DBP in men (β -coefficient, 0.023; $P < 0.05$), but this did not remain significant after adjusting for confounding variables | Low estimated vitamin D intake (240–360 IU) may not have been sufficient to affect incident BP |

(continued)

Table I (continued).

| Study | Population | Design | Outcome Measures | Intervention | Results | Comments |
|-------------------------------------|--|---|--|---|--|---|
| Observational studies | | | | | | |
| Forman et al, 2007 ⁴¹ | 1198 Women and 613 men; mean age, >60 y; normotensive | 2 Prospective cohort studies from the HPFS and NHS followed for 4–8 y | Self-reported incident HTN | None | 4-Year follow-up: multivariable RR for HTN in patients with 25(OH)D concentrations <15 ng/mL was 6.13 (95% CI, 1.00–37.8) for men and 2.67 (95% CI, 1.05–6.79) for women; 8-year follow-up: multivariable RR for HTN in patients with 25(OH)D concentrations <15 ng/mL was 3.53 (95% CI, 1.02–12.3) for men and 1.70 (95% CI, 0.92–3.16) for women | HTN was self-reported |
| Forman et al, 2008 ⁴² | 1484 Women (742 cases with incident HTN, 742 controls); mean age, 43 y; mean BMI, <30 kg/m ² | Nested case–control study within the NHS II | Self-reported HTN | None | Median plasma 25(OH)D lower among cases (25.6 ng/mL) compared with controls (27.3 ng/mL; $P < 0.001$); adjusted OR comparing the lowest and highest quartiles of 25(OH)D was 1.66 (95% CI, 1.11–2.48) | BP was self-reported; may not be applicable to older patients |
| Forman et al, 2005 ⁴³ | NHS I: 77,436 women aged 30–55 y in 1976; NHS II: 93,803 women aged 25–42 y in 1989; HPFS: 51,529 men aged 40–75 y in 1986 | 3 Cohorts from NHS I, NHS II, and HPFS followed for 18, 8, and 16 y, respectively | Self-reported incident HTN, vitamin D intake (questionnaire) | None | NHS I: Women in the highest quartile of vitamin D intake (median, 646 IU daily) had multivariable RR 0.98; 95% CI, 0.93–1.04; $P = NS$; NHS II: multivariable RR for the highest quartile of intake was 1.13; 95% CI, 0.99–1.29; $P = NS$; HPFS: multivariable RR for men in the highest quartile of intake (mean, 748 IU daily) was 1.03; 95% CI, 0.93–1.15; $P = NS$ | |
| Randomized controlled trials | | | | | | |
| Krause et al, 1998 ⁴⁴ | 10 Men and 8 women; median age, 48 y; mild HTN | Randomized controlled trial | BP | UVB or UVA irradiation at suberythemalous doses over 6 wk | Significant rise in 25(OH)D concentrations in the UVB group (from 57.6 to 151.2 nmol/L; $P < 0.001$); significant reduction in 24-h ambulatory SBP and DBP in the UVB group (–6 and –6 mm Hg each; both, $P < 0.001$) | Small sample size, younger population |

(continued)

Table I (continued).

| Study | Population | Design | Outcome Measures | Intervention | Results | Comments |
|------------------------------------|---|--|-------------------------------|---|--|--|
| Pfeifer et al, 2001 ⁴⁵ | 148 Women; mean age, 74 y; in Germany; normotensive; vitamin D concentrations <20.8 ng/mL | Randomized, placebo-controlled, double-blind | BP | 1200 mg of calcium plus 800 IU of vitamin D ₃ /d (Ca+D) or 1200 mg calcium/d (Ca) for 8 wk | SBP decreased from 144.1 to 131.0 mm Hg in the Ca+D group and from 140.6 to 134.9 mm Hg in the Ca group ($P = 0.02$) | |
| Margolis et al, 2008 ⁴⁶ | 36,282 Postmenopausal women; aged 50–79 y; 40 clinical centers in the United States | WHIRT; double-blind, placebo-controlled | Change in BP and incident HTN | 1000 mg of elemental calcium plus 400 IU of vitamin D ₃ or placebo daily for 7 y | No significant difference in mean change in SBP (0.22 mm Hg; 95% CI, –0.05 to 0.49 mm Hg) or DBP (0.11 mm Hg; 95% CI, –0.04 to 0.27 mm Hg); HR for incident HTN, 1.01 (95% CI, 0.96 to 1.06) | Dropout and intervention contamination problematic |

25(OH)D = 25-dihydroxyvitamin D; NHANES = National Health and Nutrition Examination Survey; BP = blood pressure; BMI = body mass index; SBP = systolic BP; HTN = hypertension; LASA = Longitudinal Aging Study Amsterdam; DBP = diastolic BP; PTH = parathyroid hormone; HPFS = Health Professionals' Follow-Up Study; NHS = Nurses' Health Study; RR = relative risk; OR = odds ratio; UVB = ultraviolet B; UVA = ultraviolet A; WHIRT = Women's Health Initiative Randomized Trial; HR = hazard ratio.

Table II. Studies examining the association between 25(OH)D concentrations and cardiovascular diseases other than hypertension.^{47–53}

| Study | Population | Design | Outcome Measures | Intervention | Results | Comments |
|---------------------------------------|---|--|---|--------------|--|---|
| Cross-sectional studies | | | | | | |
| Lund et al, 1978 ⁴⁷ | 128 Patients (age not stated) admitted for chest pain compared with 409 “normal persons”; Denmark | Cross-sectional | 25(OH)D, calcium, magnesium, phosphorus, lipids | None | 25(OH)D concentrations: angina = 23.5 ng/mL; MI = 24.0 ng/mL; normal = 28.8 ng/mL; all, <i>P</i> = NS | No mention of comorbidities |
| Scragg et al, 1990 ⁴⁸ | 179 Cases and 179 controls; predominantly male; mean age, 53 y; New Zealand | Case-control | MI cases found in registry with 25(OH)D concentrations on admission | None | 25(OH)D concentrations were 13.3 ng/mL in the cases and 14.5 ng/mL in the controls (<i>P</i> = 0.017); OR of MI for 25(OH)D concentrations (nmol/L): <25 = 1.00; 25–32 = 0.56 (95% CI, 0.30–1.03); 33–42 = 0.33 (95% CI, 0.17–0.64); ≥43 = 0.30 (95% CI, 0.15–0.61) | Vitamin D concentrations measured in routine clinical care may introduce bias |
| Observational studies | | | | | | |
| Giovannucci et al, 2008 ⁴⁹ | 454 Male health care professionals and 900 controls; mean age, 63.8 y; United States | Nested case-control, HPFS 10-y follow-up | MI | None | Adjusted RR for MI (nonfatal + fatal) = 2.42 (95% CI, 1.53–3.84) in men with 25(OH)D deficiency (concentrations ≤15 ng/mL) | Outcome measures by survey and chart review |
| Wang et al, 2008 ⁵⁰ | 1739 Patients; mean age, 59 y; 55% women; all white; community dwelling; no prior CV disease | PCFO study; mean follow-up, 5.4 y | Hospital records reviewed for CV events (MI, heart failure, angina, stroke, or TIA) | None | Subjects with 25(OH)D ≤15 ng/mL, adjusted HR = 1.62 (95% CI, 1.11–2.36) for incident CV events compared with those with 25(OH)D ≥15 ng/mL | |

(continued)

Table II (continued).

| Study | Population | Design | Outcome Measures | Intervention | Results | Comments |
|--------------------------------|---|--|---|--------------|--|--|
| Pilz et al, 2008 ⁵¹ | 3299 Patients; aged 54–72.9 y; 30% female; white; Germany | Cross-sectional and prospective analyses; LURIC study (prospective cohort study of patients referred for coronary angiography) | Measurements of heart failure (serum NT-pro-BNP, LV function, NYHA class by nonvalidated questionnaire) and mortality due to heart failure and SCD (death certificates) | None | Multivariable adjusted regression β -coefficient for 25(OH)D and NT-pro-BNP = -0.082 ($P < 0.001$); 25(OH)D lower with decreased LV function ($P < 0.001$); example: 10.3% with severely impaired LV function had 25(OH)D concentrations < 10 ng/mL and 4.3% had 25(OH)D concentrations ≥ 30 ng/mL ($P < 0.001$); higher NYHA class associated with lower vitamin D concentrations ($P < 0.001$); example: NYHA class 4, 4.7% had 25(OH)D concentrations < 10 ng/mL and class 1, 1.2% had 25(OH)D concentrations ≥ 30 ng/mL ($P < 0.001$); multivariable adjusted HR for death due to heart failure = 2.63 (95% CI, 1.07–6.44) and SCD = 5.35 (95% CI, 2.09–13.67) for those with 25(OH)D concentrations < 10 ng/mL compared with concentrations ≥ 30 ng/mL; 25(OH)D concentrations not associated with prevalent CAD or fatal MI | Adjustment for multiple confounders including seasonal variation in 25(OH)D concentrations; single vitamin D measurement |

(continued)

Table II (continued).

| Study | Population | Design | Outcome Measures | Intervention | Results | Comments |
|---------------------------------------|---|--|--|---|---|--|
| Randomized controlled trials | | | | | | |
| Schleithoff et al, 2006 ⁵² | 102 Men and 21 women; mean age, 57 y; with systolic dysfunction (NYHA class ≥ 2 , ejection fraction 32%) | Randomized, placebo-controlled | Survival rates, natriuretic peptides, concentrations of inflammatory cytokines | Vitamin D ₂ (2000 IU/d) plus calcium (500 mg/d) or placebo plus calcium (500 mg/d) | 25(OH)D concentrations increased from 14.4 at baseline to 41.2 ng/mL in the treatment group vs 15.3 to 18.9 ng/mL in the placebo group ($P < 0.001$); IL-10 concentrations increased from 0.56 to 0.80 pg/mL in the treatment group but decreased from 0.91 to 0.71 pg/mL in the placebo group ($P = 0.042$); TNF- α concentrations decreased from 20.9 to 18.9 pg/mL in the treatment group but increased from 23.0 to 25.7 pg/mL in the placebo group ($P = 0.006$); no impact on CRP concentrations, CV events, hemodynamic variables, or survival at 15 mo | High dropout rate for sicker subjects |
| Hsia et al, 2007 ⁵³ | 36,282 Women; mean age, 50–79 y; 40 clinical centers (WHIRT); United States | Randomized, double-blind, placebo-controlled | All CV disease (MI, fatal or nonfatal; angina; stroke) | 1000 mg of elemental calcium plus 400 IU of vitamin D ₃ or placebo daily for 7 y | MI or CHD death HR = 1.04 (95% CI, 0.92–1.18) | Dropout and intervention contamination problematic |

25(OH)D = 25-dihydroxyvitamin D; MI = myocardial infarction; OR = odds ratio; HPFS = Health Professionals' Follow-Up Study; RR = relative risk; CV = cardiovascular; PCFO = Prospective Cohort Framingham Offspring; TIA = transient ischemic attack; HR = hazard ratio; LURIC = Ludwigshafen Risk and Cardiovascular Health; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide; LV = left ventricular; NYHA = New York Heart Association; SCD = sudden cardiac death; CAD = coronary artery disease; IL-10 = interleukin-10; TNF- α = tumor necrosis factor- α ; CRP = C-reactive protein; WHIRT = Women's Health Initiative Randomized Trial; CHD = coronary heart disease.

sion. After controlling for age, they found no significant linear relationship between 25(OH)D concentration and blood pressure. However, they found a statistically significant interaction between age and 25(OH)D, suggesting that vitamin D moderates the age-associated increase in SBP. For example, in white participants, 25(OH)D concentrations >80 nmol/L (32 ng/mL) reduced the predicted age-related increase in SBP by 20% compared with participants with 25(OH)D concentrations <50 nmol/L (25 ng/mL; $P < 0.001$).

In contrast, Snijder et al³⁸ found no association between 25(OH)D concentrations and SBP or diastolic blood pressure (DBP) in a cross-sectional analysis of older adults in the Longitudinal Aging Study Amsterdam (LASA). They examined 1205 subjects (predominantly white women ≥ 65 years of age) with single measurements of 25(OH)D, PTH, and blood pressure. Although no significant association was found between SBP or DBP and 25(OH)D concentrations (DBP: β -coefficient, 0.00; and SBP: β -coefficient, 0.06), intact PTH concentrations were positively associated with blood pressure (DBP: β -coefficient, 1.93; $P = 0.03$; and SBP: β -coefficient, 4.67; $P = 0.01$) after adjustment for confounding variables (age, sex, region, season, physical activity, alcohol intake, smoking, use of antihypertensive medication, and waist circumference). A possible explanation for the negative results is that only 10% of their subjects were 25(OH)D deficient (<12 ng/mL).

Cohort Studies

Two large cohort studies examined the relationship between 25(OH)D concentrations and incident hypertension.^{41,42} Forman et al⁴¹ performed a combined analysis using the Nurses' Health Study (NHS) and the Health Professionals' Follow-Up Study (HPFS). Blood samples and questionnaires were analyzed for 1198 women and 613 men (mean age, 66 years) without a history of hypertension. After 4 years of follow-up, the multivariable relative risk (RR) of incident hypertension for men with 25(OH)D concentrations <15 ng/mL was 6.13 (95% CI, 1.00–37.8) compared with those with concentrations >30 ng/mL; the multivariable RR for women with 25(OH)D concentrations <15 ng/mL was 2.67 (95% CI, 1.05–6.79). The risk was attenuated after 8 years of follow-up (3.53; 95% CI, 1.02–12.3 for men and 1.70; 95% CI, 0.92–3.16 for women). The investigators also performed a pooled RR assessment combining men and women with measured 25(OH)D concentrations using a random-effects model. They found an RR for incident hypertension of 3.18 (95% CI, 1.39–7.29).

In 2008, Forman et al⁴² performed a nested case-control study of incident hypertension and 25(OH)D concentrations within the NHS II. Subjects (742 women and controls; mean age, 43 years) were matched for age, race, and month of blood collection and adjusted for body mass index (BMI), physical activity, family history of hypertension, oral contraceptive use, and plasma concentrations of PTH, calcium, phosphorus, creatinine, and uric acid. The median plasma 25(OH)D concentrations were lower among those with incident hypertension (25.6 ng/mL) than among controls (27.3 ng/mL; $P < 0.001$). The adjusted odds ratio (OR) for incident hypertension comparing the lowest and highest quartiles of 25(OH)D was 1.66 (95% CI, 1.11–2.48).

Three observational studies^{39,40,43} evaluated the relationship between vitamin D intake and blood pressure or risk of incident hypertension. In a cross-sectional analysis, Sowers et al³⁹ evaluated blood pressure and calcium and vitamin D intake (assessed by 24-hour recall) in 222 normotensive women aged 55 to 80 years. No association was found between calcium intake and blood pressure. Women who reported a daily consumption of <400 IU of vitamin D had a mean SBP of 139 mm Hg, whereas those who reported a daily consumption of ≥ 400 IU had a mean SBP of 133 mm Hg ($P = 0.04$). The mean DBP was similar in the 2 groups (75 and 74 mm Hg, respectively). The analysis was adjusted for age, BMI, alcohol use, and calcium intake.

In contrast to these significant findings, Forman et al⁴³ and Jorde and Bonaa⁴⁰ found no significant association between self-reported vitamin D intake and incident hypertension in 3 large cohort studies: NHS I (77,436 women aged 30–55 years in 1976); NHS II (93,803 women aged 25–42 years in 1989); and HPFS (51,529 men aged 40–75 years in 1986); follow-up periods were 18, 8, and 16 years, respectively. For example, women in the highest quartile of vitamin D intake (median, 646 IU daily) had an RR of 0.98 (95% CI, 0.93–1.04; $P = \text{NS}$).⁴³

Jorde and Bonaa⁴⁰ performed a cross-sectional analysis within the Norwegian health survey, a population cohort study started in Tromsø, Norway, in 1994, including 8053 women and 7543 men 25 to 69 years of age. Subjects completed surveys of their dairy intake, and blood pressure and BMI were measured by study personnel. These investigators found a weak positive correlation between vitamin D intake and blood pressure (β -coefficient, 0.026 for SBP in women and 0.023 for DBP in men; $P < 0.05$), which did not remain significant after adjusting for confounding variables (age,

BMI, alcohol, coffee consumption, cigarette smoking, physical activity, and daily vitamin D intake). Estimated mean daily vitamin D intake for women and men was 240 and 360 IU, respectively. This level of supplementation may not have been sufficient to detect a correlation with incident hypertension.

Randomized Trials

Three randomized trials^{44–46} have evaluated the effects of vitamin D supplements or UVB light therapy on blood pressure. In the first 2 trials,^{44,45} blood pressure was a primary outcome; in the third trial,⁴⁶ blood pressure was an outcome in a post hoc subgroup analysis. In 1998, Krause et al⁴⁴ randomized 18 subjects (10 men, 8 women) 26 to 66 years of age with mild hypertension to full-body ultraviolet A (UVA) or UVB light therapy 3 times per week for 6 weeks. In the UVB group, significant declines were observed in 24-hour ambulatory SBP (–6 mm Hg; 95% CI, –14 to –1 mm Hg) and DBP (–6 mm Hg; 95% CI, –12 to –2 mm Hg; $P < 0.001$). In addition, 25(OH)D concentrations increased 162% (from 57.6 to 151.2 nmol/L; $P < 0.001$) and PTH concentrations decreased 15% (from 3.9 to 3.3 pmol/L; $P < 0.01$), whereas in the UVA group, no significant changes were observed in blood pressure (SBP, 0 mm Hg; 95% CI, –2 to 10 mm Hg; and DBP, 2 mm Hg; 95% CI, –1 to 3 mm Hg), biochemical indices of 25(OH)D (38.4 to 45.6 nmol/L), or PTH (4.3 to 4.5 pmol/L).

Pfeifer et al⁴⁵ performed a double-blind controlled trial in 148 community-dwelling women (mean age, 74 years). The subjects received either 1200 mg of calcium plus 800 IU of vitamin D₃ or 1200 mg of calcium alone daily. Measurements of 25(OH)D, 1,25(OH)₂D, PTH, blood pressure, and heart rate were compared at baseline and after 8 weeks of supplementation. Sixty (81%) of the 74 subjects in the calcium plus vitamin D group compared with 35 (47%) of the 74 subjects in the calcium-only group had a decrease in SBP ≥ 5 mm Hg ($P = 0.04$). No significant change in DBP was observed between the 2 groups. Increases in serum 25(OH)D concentrations from baseline were significantly higher in the calcium plus vitamin D group than in the calcium-only group ($P < 0.01$).

In contrast, a subgroup analysis of the Women's Health Initiative Randomized Trial (WHIRT)⁴⁶ found no effect of calcium and vitamin D supplementation on blood pressure in 36,282 postmenopausal women. Subjects were randomized to receive either calcium 1000 mg and 400 IU of vitamin D₃ or placebo daily for a mean of 7 years. After a mean follow-up of 7 years, no significant differences were found in blood pressure

or risk of incident hypertension between the 2 groups. However, the interpretation of these results is limited due to contamination of the intervention; 39% of control subjects took calcium and 43% took vitamin D at baseline, and 41% of the treatment subjects discontinued calcium and vitamin D therapy during the trial.

In summary, cross-sectional and cohort studies examining the relationship between vitamin D concentrations or vitamin D intake and blood pressure have reported conflicting results. Two small clinical trials^{44,45} found a significant decrease in SBP in response to light therapy or vitamin D supplementation. However, the post hoc analysis from the WHIRT⁴⁶ did not find a benefit of calcium and vitamin D supplementation on blood pressure. A large, randomized, placebo-controlled trial, in which sufficient doses of vitamin D (≥ 1000 IU/d) are given and 25(OH)D concentrations are monitored, is needed to resolve the question of whether an association exists between blood pressure and vitamin D status.

CV Diseases Other Than Hypertension

Cross-Sectional Studies

In 1978, a Danish cross-sectional study⁴⁷ reported that baseline 25(OH)D concentrations were lower in 128 patients with angina (23.5 ng/mL) than in 409 control subjects (28.8 ng/mL). However, this difference was not statistically significant. In 1990, a case-control study of 179 patients from New Zealand⁴⁸ found that the odds of having a myocardial infarction (MI) increased with decreasing quartiles of vitamin D concentrations. The ORs were as follows: 25(OH)D concentrations < 25 nmol/L (< 10 ng/mL): OR = 1.00; 25–32 nmol/L (10–13 ng/mL): OR = 0.56 (95% CI, 0.30–1.03); 33–42 nmol/L (13.1–17 ng/mL): OR = 0.33 (95% CI, 0.17–0.64); ≥ 43 nmol/L (> 17 ng/mL): OR = 0.30 (95% CI, 0.15–0.61).

Observational Studies

In 2008, 3 observational studies using existing population cohorts were published. Giovannucci et al⁴⁹ performed a nested case-control study within the HPFS, a prospective cohort study of male health care professionals in the United States. They included 454 cases with incident, nonfatal MI or fatal CV events and 900 controls (mean age, 63.8 years). After adjusting for matched variables (age, smoking, month of blood collection), men with 25(OH)D concentrations ≥ 30 ng/mL had ~50% the risk of MI compared with those with 25(OH)D concentrations ≤ 15 ng/mL, independent of other CV risk factors.

Wang et al⁵⁰ performed a prospective study on incident CV disease among 1739 offspring from participants in the Framingham study (mean age, 59 years; 55% women; all white) followed for a mean of 5.4 years. After adjustment for CV risk factors, subjects with 25(OH)D concentrations <15 ng/mL had a multivariable-adjusted hazard ratio (HR) of 1.62 (95% CI, 1.11–2.36; $P = 0.01$) for incident CV events compared with subjects with 25(OH)D concentrations ≥ 15 ng/mL. Interestingly, 37% of the study population had vitamin D concentrations <15 ng/mL, consistent with a diagnosis of vitamin D deficiency. This study used 15 ng/mL as the cutoff for vitamin D deficiency. Given that cutoffs for 25(OH)D deficiency are now <20 ng/mL and optimal concentrations are considered by many to be >30 ng/mL, this study may underestimate the HR for incident CV events.

Pilz et al⁵¹ performed an observational analysis of the association between 25(OH)D and 1,25(OH)₂D concentrations and heart failure and sudden cardiac death. The investigators used data from a prospective cohort study of 3299 patients with 25(OH)D concentrations who were referred to a tertiary center in Germany for coronary angiography. The subjects were white and 54 to 72.9 years of age; 30% were female. Measurements of heart failure included serum N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), LV function by ventriculography, and New York Heart Association (NYHA) class. Mortality rates due to heart failure and sudden cardiac death were obtained from death certificates. The results revealed a multivariable adjusted regression β -coefficient for 25(OH)D and NT-pro-BNP of -0.082 ($P < 0.001$). Concentrations of 25(OH)D decreased with decreased LV function ($P < 0.001$) (example: 10.3% of patients with severely impaired LV function had 25[OH]D concentrations <10 ng/mL and 4.3% had 25[OH]D concentrations ≥ 30 ng/mL; $P < 0.001$). Higher NYHA class was associated with lower vitamin D concentrations ($P < 0.001$) (example: for NYHA class 4, 4.7% had 25[OH]D concentrations <10 ng/mL; for class 1, 1.2% had 25[OH]D concentrations ≥ 30 ng/mL; $P < 0.001$). Multivariable adjusted HR for death due to heart failure was 2.63 (95% CI, 1.07–6.44) and sudden cardiac death was 5.35 (95% CI, 2.09–13.67) for those with 25(OH)D concentrations <10 ng/mL compared with ≥ 30 ng/mL. Interestingly, 25(OH)D concentrations were not associated with prevalent coronary artery disease or fatal MI. The investigators adjusted for many potential confounding variables and adjusted 25(OH)D concentrations according to seasonal variation.

Randomized Trials

A prespecified subgroup analysis of the WHIRT,⁵³ the largest randomized controlled trial of vitamin D plus calcium therapy, did not find a reduction in MI- or coronary heart disease (CHD)-related deaths. Among 36,282 postmenopausal women randomized to receive 1000 mg of elemental calcium plus 400 IU of vitamin D₃ or placebo daily for 7 years, the HR for death due to MI or CHD was 1.04 (95% CI, 0.92–1.18). As discussed, methodologic problems with contamination limited the findings. None of the identified studies found a trend to harm with vitamin D supplementation.

One hypothesized explanation for the relationship between CV disease, low vitamin D, and elevated PTH concentrations may be the development of an inflammatory state.⁵⁵ Schleithoff et al⁵² randomized 123 subjects (mean age, 57 years) with systolic dysfunction (NYHA class, ≥ 2 ; ejection fraction, 32%) to receive either vitamin D₂ (2000 IU) plus calcium (500 mg) or placebo plus calcium (500 mg) daily. The primary end points were survival rates and concentrations of natriuretic peptides and inflammatory cytokines. At baseline, the vitamin D₂-supplemented group had significantly higher concentrations of interleukin-10 (IL-10; 0.91 vs 0.56 pg/mL; $P = 0.04$) and were less likely to be receiving anticoagulant therapy. Baseline vitamin D concentrations were below the normal range in both groups (14.4 and 15.3 ng/mL in the treatment and placebo groups, respectively). Ninety-three subjects completed the study over 9 months. After 9 months, the vitamin D plus calcium group had significantly greater increases in 25(OH)D concentrations (from 14.4 to 41.2 ng/mL) than did the placebo group (from 15.3 to 18.9 ng/mL; $P = 0.001$). IL-10 concentrations increased in the vitamin D plus calcium group (from 0.56 to 0.80 pg/mL) but decreased in the placebo group (from 0.91 to 0.71 pg/mL; $P = 0.042$). A significantly greater decrease in PTH concentration was found in the vitamin D-supplemented group (from 34.6 to 29.7 pg/mL) than in the placebo group (from 39.2 to 34.8 pg/mL; $P = 0.007$), whereas tumor necrosis factor- α concentrations decreased in the vitamin D-supplemented group (from 20.9 to 18.9 pg/mL) and increased in the placebo group (from 23.0 to 25.7 pg/mL; $P = 0.006$). No impact was found on C-reactive protein (CRP) concentrations, CV events, hemodynamic variables, or survival at 15-month follow-up. An important limitation of this study was the high dropout rate, which limited its power to detect a significant difference in CV events.

In summary, data on the association between vitamin D and CV disease are conflicting. Substantial epidemio-

logic data^{47–51} and 1 small randomized trial⁵² indicate a potential association. Although a prespecified subgroup analysis of data from the WHIRT,⁵³ the largest randomized controlled trial on vitamin D₃ plus calcium supplementation, failed to find a reduction in MI- or CHD-related deaths, methodologic problems limited the findings. Well-designed, randomized, double-blind, placebo-controlled trials are needed to evaluate the effect of vitamin D supplementation on CV outcomes, but such trials may be difficult to complete given the ethical and practical issues in randomizing high-risk patients to placebo in light of the known beneficial effects of vitamin D on fracture and fall prevention. To date, we have not found a published study suggesting that vitamin D supplementation is detrimental to CV outcomes.

Role of Vitamin D in Mortality

The studies that have evaluated the association between 25(OH)D concentrations (or vitamin D supplementation) and mortality (all cause or CV disease-related) are reviewed here and shown in tabular form in **Table III**.^{56–63}

Observational Studies

Two observational studies^{56,57} did not find an association between 25(OH)D concentrations and mortality. Visser et al⁵⁶ performed a nested prospective study within the LASA to evaluate the associations between serum 25(OH)D concentrations, the risk of nursing home admission, and mortality among community-dwelling adults >65 years of age in the Netherlands over 6 years of follow-up. Although they found a statistically significant association between 25(OH)D concentrations and nursing home admission (multivariable-adjusted HR = 2.88; 95% CI, 1.15–7.23) for 25(OH)D concentrations <25 nmol/L compared with 25(OH)D ≥75 nmol/L ($P = 0.011$), they did not find a statistically significant association between 25(OH)D concentrations and mortality after adjusting for sex, age, education, chronic disease, serum creatinine, cognitive status, symptoms of depression, smoking, physical activity, mobility, low serum albumin, or total cholesterol concentration (HR = 1.28; 95% CI, 0.85–1.92) for 25(OH)D concentrations <25 nmol/L compared with 25(OH)D ≥75 nmol/L.

Zittermann et al⁵⁷ prospectively followed 510 German patients, 80% of whom had end-stage heart failure, for 1 year. After adjusting for age, BMI, smoking, diagnosis, use of aspirin, renal function, and inflammatory markers, they reported an HR of 1.46 (95% CI, 0.57–

3.78) for 25(OH)D concentrations <7.09 ng/mL and 0.90 (95% CI, 0.34–2.38) for 25(OH)D concentrations 16.39 to 26.95 ng/mL ($P = \text{NS}$).

In contrast, 4 observational studies^{58–61} reported a significant association between 25(OH)D concentration and mortality. Dobnig et al⁵⁸ evaluated mostly white subjects (mean age, 62 years) referred for angiography in Germany and followed them for a median of 7.7 years. Melamed et al⁵⁹ used the NHANES III cohort of 13,331 adults ≥20 years of age living in the United States and followed them for a mean of 8.7 years. Ginde et al⁶⁰ also used the NHANES III cohort but limited their analysis to those ≥65 years of age and followed them for a median of 7.3 years. All 3 studies examined the HR for death by vitamin D level divided into quartiles or quintiles and found an increased risk of all-cause mortality (after adjusting for the appropriate confounding variables) among subjects with vitamin D insufficiency.

In the study by Dobnig et al,⁵⁸ after adjusting for traditional CV risk factors, serum phosphate, calcium, PTH, and 1,25(OH)₂D levels, the HR for all-cause mortality was 1.53 (95% CI, 1.17–2.01) for 25(OH)D concentrations <13 ng/mL and 2.08 (95% CI, 1.6–2.70) for concentrations <7.6 ng/mL. The multivariable-adjusted HR for CV disease-related mortality was 2.22 (95% CI, 1.57–3.13) for 25(OH)D concentrations <7.6 ng/mL and 1.82 (95% CI, 1.29–2.58) for 25(OH)D concentrations <13 ng/mL. In the study by Melamed et al,⁵⁹ after adjusting for age, sex, race, season, hypertension, history of CV disease, diabetes, smoking, BMI, HDL-C, total cholesterol, use of cholesterol-lowering medication, estimated glomerular filtration rate categories, serum albumin level, log CRP, physical activity, vitamin D supplementation, and socioeconomic status, the multivariable-adjusted all-cause mortality rate ratio (MRR) for 25(OH)D concentrations <17.8 ng/mL was 1.26 (95% CI, 1.08–1.46). No statistically significant association with CV disease-related mortality was found after adjustment for confounding variables. In addition, no significant interaction was observed between mortality risk, 25(OH)D quartile, and age. However, in women, the adjusted MRR was increased for 25(OH)D concentrations <20 ng/mL (MRR = 1.5; 95% CI, 1.1–1.9) and >50 ng/mL (MRR = 1.6; 95% CI, 1.0–2.0). This finding has not been reproduced in other studies.

In a study in older adults conducted by Ginde et al,⁶⁰ after adjusting for demographic variables, CV risk factors, and season, the HR for all-cause mortality for 25(OH)D concentrations <25 nmol/L was 1.83 (95%

Table III. Studies evaluating the effect of vitamin D concentrations or vitamin D supplementation on total mortality.^{56–63}

| Study | Population | Design | Variables/ Intervention | Outcomes | Results | Comments |
|--------------------------------------|---|---|--|---|---|---|
| Observational studies | | | | | | |
| Visser et al, 2006 ⁵⁶ | 1260 Community-dwelling older adults; aged 65–85 y; 50% women; the Netherlands | Nested prospective cohort within the LASA | 25(OH)D measurement; mortality data from local registries; 6-y follow-up | Time to nursing home admission, mortality | Multivariable adjusted HR for nursing home admission for 25(OH)D <25 nmol/L = 2.88; 95% CI, 1.15–7.23; for 50–74.9 nmol/L = 1.78; 95% CI, 0.73–4.33; <i>P</i> = 0.011; adjusted HR for mortality = NS; HR for 25(OH)D <25 nmol = 1.28; 95% CI, 0.85–1.92; <i>P</i> = NS | Selection bias (excluded sicker patients) may underestimate the association |
| Zittermann et al, 2009 ⁵⁷ | 510 Patients; mean age, 53 y; >50% men; 80% with end-stage heart failure; mean age, 53 y; >50% male; white; Germany | Prospective cohort to establish association between 1,25(OH)2D concentrations and mortality | 1,25(OH)2D and 25(OH)D concentrations; mortality data from electronic records, follow-up visits, and family; 1-y follow-up | Total and CV disease-related mortality | 16% Mortality at 1 y (majority from cardiac failure); multivariable adjusted HR for 25(OH)D concentrations <7.09 ng/mL, 1.46; 95% CI, 0.57–3.78 and for 25(OH)D 16.39–26.95 ng/mL, 0.90; 95% CI, 0.34–2.38; <i>P</i> = 0.069 | Follow-up rate, 100%; only 10 patients were aged >70 y |
| Dobnig et al, 2008 ⁵⁸ | 3258 White subjects; mean age, 62 y; 70% men; referred for angiography; Germany | Prospective cohort | 25(OH)D and 1,25(OH)2D measurements; mortality data from local registries; 7.7-y follow-up | All-cause and other mortality | Multivariable adjusted HR for all-cause mortality: 25(OH)D <13 ng/mL, 1.53; 95% CI, 1.17–2.01; <7.6 ng/mL, 2.08; 95% CI, 1.6–2.70; HR for death from CV disease: <7.6 ng/mL, 2.22; 95% CI, 1.57–3.13; <13 ng/mL, 1.82; 95% CI, 1.29–2.58 | |

(continued)

Table III (continued).

| Study | Population | Design | Variables/ Intervention | Outcomes | Results | Comments |
|-----------------------------------|--|--|--|---|--|----------|
| Melamed et al, 2008 ⁵⁹ | 13,331 Subjects; mean age, 43 y; 54% women | Nested prospective cohort within NHANES III | 25(OH)D measurement; mortality from National Death Index; 8.7-y follow-up | All-cause, cancer, and CV disease mortality | Multivariable adjusted MRR for 25(OH)D concentrations <17.8 ng/mL, 1.26; 95% CI, 1.08–1.46 compared with highest quartile; in women, 25(OH)D concentrations >50 ng/mL and <20 ng/mL were associated with a higher mortality risk (MRR = ~1.6; 95% CI, ~1.0–2.0 and ~1.5; 95% CI, ~1.1–1.9, respectively); no interaction between mortality risk, 25(OH)D quartile, and age; no significant association with CV disease mortality (MRR = 1.20; 95% CI, 0.87–1.64) | |
| Ginde et al, 2009 ⁶⁰ | 3408 Subjects; aged ≥65 y; 56% women | Nested prospective cohort within NHANES III | 25(OH)D measurement; mortality data from National Death Index; 7.3-y follow-up | All-cause, cancer, and CV disease mortality | Multivariable adjusted HR for all-cause mortality for 25(OH)D concentration <25 nmol/L, 1.83; 95% CI, 1.14–2.94; <i>P</i> < 0.05; for 25(OH)D 25.0–49.9 nmol/L, 1.47; 95% CI, 1.09–1.97; <i>P</i> < 0.05 compared with 25(OH)D ≥75 nmol/L; multivariable adjusted HR for CV disease mortality for 25(OH)D concentrations <25 nmol/L, 2.36; 95% CI, 1.17–4.75; <i>P</i> < 0.05 | |
| Kuroda et al, 2009 ⁶¹ | 1232 Post-menopausal volunteers; mean age, 63.9 y; Japan | Prospective observational study to determine association between bone mineral density, 25(OH)D concentrations, and mortality | 25(OH)D measurement; mortality data from hospital records, certificates, and family; 6.9-y follow-up | All-cause, cancer, and CV disease mortality | Causes of death were: vascular events (28.0%), cancer (21.5%), senile decay (21.5%), other (10.3%), and unknown (18.7%); multivariable HR for death for 25(OH)D concentrations <50 nmol/L vs ≥50 nmol/L, 2.17; 95% CI, 1.27–3.72; <i>P</i> = 0.01 | |

(continued)

Table III (continued).

| Study | Population | Design | Variables/ Intervention | Outcomes | Results | Comments |
|--|--|-----------------------|---|--|--|---|
| Randomized controlled trials | | | | | | |
| LaCroix et al, 2009 ⁶² | 36,282 Women, aged 50–79 y, 40 US centers, WHIRT | Double-blind RCT | 1000 mg of elemental calcium carbonate and 400 IU of vitamin D ₃ daily vs placebo; 7-y follow-up | Total and cause-specific mortality, by age and adherence | HR for total mortality, 0.91; 95% CI, 0.83–1.01; HR for total mortality in women <70 y, 0.89; 95% CI, 0.79–1.01; and in those ≥70 y, 0.95; 95% CI, 0.80–1.12 | Dropout and intervention contamination problematic |
| Autier and Gandini, 2007 ⁶³ | 57,311 Subjects, aged 33–106 y; 17 RCTs and 1 quasi-RCT from Europe, United States, and United Kingdom | Meta-analysis of RCTs | Mean daily dose of vitamin D ₂ or D ₃ , 528 IU; 5.7-y follow-up | All-cause mortality | SRR, 0.93; 95% CI, 0.87–0.99; absolute risk vitamin D vs placebo, 8.2% vs 8.5%; RRR = 7%, 95% CI, 1–13; NNT = 169; 95% CI, 91–178 | Only 1 study had mortality as a primary end point; results similar across all studies |

LASA = Longitudinal Aging Study Amsterdam; 25(OH)D = 25-dihydroxyvitamin D; HR = hazard ratio; 1,25(OH)₂D = 1,25-dihydroxyvitamin D; CV = cardiovascular; NHANES = National Health and Nutrition Examination Survey; MRR = mortality rate ratio; WHIRT = Women's Health Initiative Randomized Trial; RCT = randomized controlled trial; SRR = summary relative risk; RRR = relative risk ratio; NNT = number needed to treat.

CI, 1.14–2.94; $P < 0.05$) and 1.47 (95% CI, 1.09–1.97; $P < 0.05$) for 25(OH)D concentrations 25.0 to 49.9 nmol/L compared with concentrations ≥ 75 nmol/L. In addition, the multivariable-adjusted HR for CV disease-related mortality was significantly inversely correlated with 25(OH)D concentrations (< 25 nmol/L = 2.36; 95% CI, 1.17–4.75; $P < 0.05$).

Kuroda et al⁶¹ performed a prospective study among 1232 postmenopausal Japanese volunteers (mean age, 63.9 years) to determine the associations between bone mineral density, 25(OH)D concentrations, and mortality. Causes of death were vascular events (28.0%), cancer (21.5%), senile decay (21.5%), other (10.3%), and unknown (18.7%). After adjusting for age, presence of malignancy, and bone mineral density, the HR for death for 25(OH)D concentrations < 50 nmol/L (< 20 ng/mL) versus ≥ 50 nmol/L was 2.17 (95% CI, 1.27–3.72; $P = 0.01$).

Several studies have evaluated the association between supplementation of active vitamin D (1,25[OH]2D) and mortality in patients with chronic renal disease and have reported mixed results. Because of the complex interaction between renal disease and vitamin D metabolism, these studies are not reviewed in this article.^{64–68}

Randomized Controlled Trials and Meta-Analyses

LaCroix et al⁶² reported the results of a secondary analysis of the effect of calcium and vitamin D supplementation on mortality using data from the WHIRT. The trial methods and primary outcomes were described in the section on CV disease. The HR for total mortality was 0.91 (95% CI, 0.83–1.01) and 0.89 (95% CI, 0.79–1.01) in women < 70 years of age and 0.95 (95% CI, 0.80–1.12) in women ≥ 70 years. The HRs for CV, coronary artery, cerebrovascular, and cancer deaths in women ≥ 70 years were 1.01 (95% CI, 0.78–1.32), 1.02 (95% CI, 0.71–1.47), 1.20 (95% CI, 0.72–2.01), and 0.86 (95% CI, 0.65–1.12), respectively. No statistically significant mortality benefit was found. The interpretation is limited by the fact that although the WHIRT was a large controlled trial with 7 years of follow-up, it was not powered to detect a mortality benefit, and the doses of vitamin D used may not have been adequate.

Autier and Gandini⁶³ performed a meta-analysis of 18 randomized controlled trials that evaluated the effect of vitamin D supplementation (vitamin D₂ or D₃) on a health outcome such as fractures, bone mineral density, falls, and colorectal cancer incidence. All of the trials also reported mortality. Only one of these trials was powered to detect a mortality difference. Seven of these studies did not contain a placebo group. These

studies took place in the United States, Europe, and the United Kingdom, and included the WHIRT. The mean vitamin D supplement was 528 IU daily, and the mean follow-up was 5.7 years. The results show a summary RR of all-cause mortality for all the trials of 0.93 (95% CI, 0.87–0.99). Subjects who received vitamin D supplementation had a 7% RR reduction (ie, 1 death was prevented for every 169 subjects receiving supplementation).⁶⁹ No reported analysis was conducted to assess a dose-response relationship. Insufficient data were available on serum vitamin D concentrations to draw conclusions regarding an association between vitamin D concentration and mortality.

Effect of Vitamin D on Mood and Cognition

VDRs and the enzyme 1- α -hydroxylase have been isolated in the cerebral cortex and cerebellum, suggesting that the brain may be able to convert 25(OH)D to 1,25(OH)2D for local cellular function.⁷⁰ This section reviews the studies that examined the effectiveness of vitamin D or sunlight therapy in the treatment of depression in older adults (Table IV),^{71–76} as well as the associations between 25(OH)D concentrations and mood alone or mood and cognition in adults of all ages, including older adults (Table V).^{72,74,77–79}

Depression

Cross-Sectional and Observational Studies

In cross-sectional and observational studies of the association between 25(OH)D concentrations and depression,^{71–74} subjects with lower 25(OH)D concentrations were more likely to have diagnoses of depression. Schneider et al⁷¹ reported that among 29 hospitalized subjects with depression, 25(OH)D concentrations were 29.7 ng/mL compared with 43.6 ng/mL in controls ($P < 0.02$). Methodologic concerns included a single measurement of 25(OH)D, no reported CIs, no adjustment for confounding variables, and unclear method of selection of the control group.

Wilkins et al⁷² performed a cross-sectional analysis of 40 community-dwelling patients with dementia and 40 controls (mean age, 75 years) in the United States to determine the relationships between 25(OH)D concentrations, cognitive performance, mood, and physical performance. The results related to mood disorders are discussed here; the cognitive results are discussed in the next section. In the total sample, the investigators found 25(OH)D deficiency (7.87 ng/mL) was significantly ($P = 0.022$) associated with the presence of a mood disorder (as measured by the Depression Symptoms Inventory). The adjusted OR for mood disorder

Table IV. Studies examining the effectiveness of vitamin D or sunlight therapy in the treatment of depression in older adults.⁷¹⁻⁷⁶

| Study | Population | Design | Variables/ Outcomes | Intervention | Results | Comments |
|--|--|---|---|--------------|--|---|
| Cross-sectional and observational studies | | | | | | |
| Schneider et al, 2000 ⁷¹ | 89 Inpatients (34 with schizophrenia, 30 with alcoholism, 25 with major depression) and 31 controls; mean age, 47 y; Germany | Cross-sectional study to compare concentrations of 25(OH)D, 1,25(OH)2D, calcium, phosphorus, and PTH in patients vs controls | Concentrations of 25(OH)D, 1,25(OH)2D, calcium, phosphorus, PTH | None | 25(OH)D concentrations were significantly lower in patients with psychiatric diagnoses compared with controls (depression, 29.7 vs 43.6 ng/mL; schizophrenia, 30.4 vs 43.6 ng/mL; alcoholism, 33.3 vs 43.6 ng/mL; all, $P < 0.02$) | CI's not reported; reliability of measurements unknown; no assessment of confounding variables; control group selection unclear |
| Wilkins et al, 2006 ⁷² | 40 Subjects with mild dementia and 40 controls; mean age, 75 y; community dwelling; United States | Cross-sectional study to determine relationship between 25(OH)D concentrations, cognitive performance, mood, and physical performance | CDR sums of boxes score (0 = no dementia; 1 = mild; 2 = moderate; 3 = severe); SBT; MMSE; CDR (0 = no dementia); psychometric battery | None | 25(OH)D concentration was not associated with a diagnosis of dementia using the MMSE ($P = \text{NS}$); the adjusted linear regression model for the CDR composite (sum of boxes) score was higher for those in the 25(OH)D-deficient group (7.87 ng/mL; Wald $F = 3.20$; $P = 0.047$); 25(OH)D deficiency was associated with a worse performance on the SBT (Wald $F = 5.22$; $P = 0.044$) | Well-validated measurement tools were used; single 25(OH)D measurement; seasonality was factored into the regression model |

(continued)

Table IV (continued).

| Study | Population | Design | Variables/ Outcomes | Intervention | Results | Comments |
|--|---|--|---|---|---|--|
| Hoogendijk et al, 2008 ⁷³ | 95 Subjects with depression and 1087 controls; mean age, 76 y; 99% white; Amsterdam | Nested case-control within the LASA to determine association between depression, 25(OH)D, and PTH concentrations | CES-D depression scale confirmed with psychiatric interview | None | Mean 25(OH)D concentrations were 19 ng/mL in all depressed subjects vs 22 ng/mL in controls ($P < 0.001$); after adjustment for confounders, depression severity (CES-D score) was associated with decreased 25(OH)D concentrations; β -coefficient 8; 95% CI, 0.8–15.2; $P = 0.03$ | Clinical significance of difference in 25(OH)D concentrations questionable; unclear whether controls were obtained from the cohort |
| Jorde et al, 2006 ⁷⁴ | 21 Subjects and 63 age- and sex-matched controls; mean age, 62.5 y; SHPT and normal kidney function; Norway | Nested case-control study to examine neuropsychologic function among subjects with 25(OH)D deficiency | Multiple tests of cognitive function (working memory capacity, speed of information processing, memory, language, cognitive flexibility/executive function, intelligence) | None | Serum PTH concentration negatively associated with tests of working memory capacity ($P < 0.01$) and speed of information processing ($P < 0.05$); in the multiple linear regression model, 25(OH)D was not correlated with cognitive performance | No adjustment for multiple testing was done (sample size too small) |
| Randomized, placebo-controlled trials | | | | | | |
| Sumaya et al, 2001 ⁷⁵ | 10 Subjects; mean age, 83 y; with depression; in long-term care facility; United States | Crossover trial to determine the efficacy of morning bright light on depression | GDS scores | 1 Wk of 10,000 lux vs 1 wk of 300 lux (placebo) or 1 wk of no treatment (control) | Mean GDS score decreased significantly, from 14.9 to 11.3 ($P < 0.01$) in the 10,000-lux group; GDS pretest scores were significantly correlated to differences in GDS scores before and after 10,000 lux ($r = 0.62$; $P < 0.05$) | Single facility; small sample size; results may not be applicable to older adults with mild depression who are not institutionalized |

(continued)

Table IV (continued).

| Study | Population | Design | Variables/ Outcomes | Intervention | Results | Comments |
|---------------------------------|--|---|------------------------|--|--|---|
| Jorde et al, 2008 ⁷⁶ | 441 Overweight or obese outpatients with depressive traits; mean age, 47 y; Norway | Cross-sectional analysis; double-blind trial to determine relationship between 25(OH)D concentrations and depression and the effect of vitamin D supplementation on depressive symptoms | BDI | 40,000 or 20,000 IU vitamin D ₂ or placebo weekly for 1 y | Subjects with higher BDI scores (6.0 vs 4.5) had lower 25(OH)D concentrations (<16.7 vs ≥16.7 ng/mL; <i>P</i> < 0.05); significant improvement in BDI score (from 4.5 to 3.0; <i>P</i> < 0.01) in the 40,000-IU group at 1 y compared with the placebo group | Difference in BDI score of questionable clinical importance; 25% dropout rate in all groups |

25(OH)D = 25-dihydroxyvitamin D; 1,25(OH)₂D = 1,25-dihydroxyvitamin D; PTH = parathyroid hormone; CDR = Clinical Dementia Rating; SBT = Short Blessed Test; MMSE = Mini-Mental State Examination; LASA = Longitudinal Aging Study Amsterdam; CES-D = Center for Epidemiological Studies-Depression; SHPT = secondary hyperparathyroidism; GDS = Geriatric Depression Scale; BDI = Beck Depression Inventory.

Table V. Cross-sectional and observational studies exploring the association between 25(OH)D concentrations and mood alone or mood and cognition.^{72,74,77–79}

| Study | Population | Design | Outcome Measures | Intervention | Results | Comments |
|-----------------------------------|---|---|---|--------------|--|---|
| Wilkins et al, 2006 ⁷² | 40 Patients with mild dementia and 40 controls; mean age, 75 y; community dwelling; United States | Cross-sectional study to determine relationship between 25(OH)D concentrations, cognitive performance, mood, and physical performance | DSI; for cognition: sums of boxes (greater score indicates greater dementia severity), SBT, MMSE, CDR, psychometric battery | None | 25(OH)D deficiency (7.87 ng/mL) was significantly associated with the presence of a mood disorder ($P = 0.022$); adjusted OR for mood disorder = 11.69 in 25(OH)D-deficient group (95% CI, 2.04–66.86), 2.54 (95% CI, 0.63–10.51) in the 25(OH)D-insufficient group (15.38 ng/mL); all compared with 25(OH)D-sufficient group (26.07 ng/mL) | Well-validated measurement tools were used; single 25(OH)D measurement; seasonality was factored into the regression model |
| Jorde et al, 2006 ⁷⁴ | 21 Subjects with SHPT (normal kidney function) and 63 age- and sex-matched controls; mean age, 62 y; Norway | Nested case–control within the Tromsø cohort to examine neuropsychologic function among subjects with SHPT and 25(OH)D deficiency | Multiple tests of cognitive function; BDI; GHQ | None | The SHPT group (PTH concentration, 9.2 pmol/L) performed worse on the BDI vs the control group (PTH concentration, 3.1 pmol/L) (2.67 vs 2.03, respectively; $P < 0.05$); BDI scores in the lowest quartile of 25(OH)D (<20 ng/mL) and the highest quartile (>30 ng/mL) were 3.7 and 1.3, respectively; $P = 0.04$; 25(OH)D significantly correlated with the BDI 1–13, which assesses both cognitive and affective symptoms of depression ($P = 0.01$) | Difference in scores was of questionable clinical importance; no adjustment for multiple testing was done (sample size was too small) |

(continued)

Table V (continued).

| Study | Population | Design | Outcome Measures | Intervention | Results | Comments |
|--|--|---|--|--------------|---|--|
| Przybelski and Binkley, 2007 ⁷⁷ | 80 Patients; mean age, 79.5 y; in memory clinic (mean MMSE score, 19.2); United States | Retrospective cohort study to examine association between 25(OH)D concentrations and cognition | MMSE scores | None | Significant positive correlation between 25(OH)D and MMSE ($R^2 = 0.225$; $P < 0.001$); vitamin B ₁₂ was unrelated to MMSE score ($R^2 < 0.001$) | No adjustment for confounders |
| McGrath et al, 2007 ⁷⁸ | 11,232 Subjects (1676 aged 12–17 y; 4747 aged 20–60 y; and 4809 aged 60–90 y;) community dwelling; United States | Cross-sectional analysis within the NHANES III cohort to examine the relationship between 25(OH)D concentrations and performance of cognitive tasks | 1 Measure of learning and memory for the elderly (higher scores indicate superior performance) | None | Score in the elderly was 6.5 for the lowest 25(OH)D quintile (<17 ng/mL) and 6.4 for the highest quintile (>34 ng/mL) (Wald F = 3.38; $P = 0.02$); those with the highest score (superior performance) were within the lowest 25(OH)D quintile | Difference in scores of questionable clinical importance; large cohort with adjustment for confounders |

(continued)

Table V (continued).

| Study | Population | Design | Outcome Measures | Intervention | Results | Comments |
|---------------------------------|--|---|---|--------------|--|---|
| Buell et al, 2009 ⁷⁹ | 703 Mainly white and 377 black subjects; age, 65–99 y; 75% women; mean BMI, 31 kg/m ² ; recruited through Boston home care agencies | Cross-sectional analysis within the NAME study to determine the association between 25(OH)D concentrations and cognitive function | MMSE, NAART, supraspan learning (WMS-III word list learning), auditory and visual retention (WMS-III logical memory), executive function/mental processing speed (digit symbol coding, trail-making test, mental alternations, WAIS-III block design), visual construction/ fluid reasoning (matrix reasoning), verbal fluency (controlled oral word association), and anxiety (self-rated anxiety scale) | None | 25(OH)D concentrations <20 ng/mL in >65%; adjusted Pearson correlation significant for 25(OH)D and MMSE, $r = 0.06$; $P = 0.05$; tests of executive function: block design, $r = 0.07$; $P = 0.04$; digit symbol, $r = 0.12$; $P < 0.01$; digit span, $r = 0.08$; $P < 0.01$; matrix reasoning, $r = 0.08$; $P < 0.02$; trails A, $r = -0.08$; $P < 0.03$; and trails B, $r = -0.10$; $P < 0.02$; adjusted regression analysis showed 25(OH)D associated with better performance on tests of executive reasoning (each, $P < 0.05$); no observed associations between 25(OH)D and memory tests (β -coefficient = -0.004 ; $P < 0.54$) | Large cohort; large battery of neuropsychologic tests were performed; statistical data reduction techniques addressed issues associated with multiple testing |

25(OH)D = 25-dihydroxyvitamin D; DSI = Depression Symptoms Inventory; SBT = Short Blessed Test; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating; OR = odds ratio; SHPT = secondary hyperparathyroidism; BDI = Beck Depression Inventory; GHQ = General Health Questionnaire; PTH = parathyroid hormone; NHANES = National Health and Nutrition Examination Survey; BMI = body mass index; NAME = Nutrition and Memory in Elders; NAART = North American Adult Reading Test; WMS = Wechsler Memory Scale; WAIS = Wechsler Adult Intelligence Scale.

was 11.69 (95% CI, 2.04–66.86) in the group with 25(OH)D deficiency (7.87 ng/mL) and 2.54 (95% CI, 0.63–10.51) in the group with 25(OH)D insufficiency (15.38 ng/mL) compared with the group with sufficient 25(OH)D concentration (26.07 ng/mL).

Hoogendijk et al⁷³ performed a nested case–control study within the LASA. Ninety-five subjects with depression (defined as Center for Epidemiological Studies–Depression [CES–D] score of ≥ 16 and confirmed with psychiatric interview) who were >65 years of age had serum concentrations of 25(OH)D and PTH measured. Mean 25(OH)D concentrations were 19 ng/mL in all depressed subjects and 22 ng/mL in controls ($P < 0.001$). After adjusting for age, sex, BMI, smoking, and number of chronic conditions, depression severity (CES–D score) was associated with decreased 25(OH)D concentrations (β -coefficient, 8; 95% CI, 0.8–15.2; $P = 0.03$).

Jorde et al⁷⁴ performed a nested case–control study within the Tromsø prospective population cohort in Norway to examine neuropsychologic function among subjects with secondary hyperparathyroidism (SHPT) and 25(OH)D deficiency. Their sample consisted of 84 subjects (mean age, 62 years): 21 with SHPT (PTH concentration, 9.2 pmol/L) and 63 controls (PTH concentration, 3.1 pmol/L). They evaluated mood disorders using the validated Beck Depression Inventory (BDI). The SHPT group performed worse on the BDI (score 2.67 vs 2.03 in the control group; $P < 0.05$). Those in the lowest quartile of 25(OH)D concentrations (<20 ng/mL) had mean BDI scores of 3.7 versus 1.3 in the highest quartile (>30 ng/mL; $P = 0.04$).

Randomized, Placebo-Controlled Trials

Two trials evaluated the effectiveness of vitamin D therapy using bright light therapy⁷⁵ or vitamin D₂ supplementation⁷⁶ in subjects with depression. In the first trial, Sumaya et al⁷⁵ performed a crossover study in 10 elderly institutionalized subjects (mean age, 83 years) with depression who were randomized to receive bright light therapy (10,000 lux), placebo light therapy (300 lux), or no treatment for 30 minutes daily for 5 days. This was followed by a 1-week washout period. Each participant cycled through all 3 arms of the study. A statistically significant improvement in depression scores (as measured by the Geriatric Depression Scale [GDS]) was observed after only 1 week of 10,000-lux therapy (GDS scores decreased from 14.9 to 11.3; $P < 0.01$). This was a small, nonblinded, single-site study that required confirmation in a larger randomized trial.

In the second trial, Jorde et al⁷⁶ randomized overweight or obese outpatients (mean age, 47 years) with depressive traits in Norway to receive either 40,000 or 20,000 IU of vitamin D₂ or placebo weekly for 1 year. At baseline, subjects with higher BDI scores (6.0 vs 4.5) had lower 25(OH)D concentrations (<16.7 ng/mL vs ≥ 16.7 ng/mL; $P < 0.05$). By intention-to-treat analysis, a significant decrease in symptoms of depression (using the BDI) was reported in the group that received the higher dose of vitamin D compared with the placebo group (4.5 to 3.0; $P < 0.01$). This was a well-designed trial; however, there was a high dropout rate ($\sim 25\%$ of participants in all groups), and the change in BDI score, although statistically significant, was of questionable clinical importance. None of the identified studies found a trend to harm with vitamin D supplementation.

Cognition

Cross-Sectional and Observational Studies

The studies evaluating the association between cognition and vitamin D in older adults^{72,74,77–79} reported conflicting results. Studies conducted by Wilkins et al⁷² and Jorde et al⁷⁴ have already been described in detail. In the study by Wilkins et al, cognitive performance was measured by several tests (Table V). The 25(OH)D concentration was not associated with a diagnosis of dementia using the Mini-Mental State Examination (MMSE). However, the adjusted linear regression models for 2 other tests of cognition, the Clinical Dementia Rating (CDR)⁸⁰ and the Short Blessed Test (SBT),⁸¹ were significantly correlated with 25(OH)D concentrations. In the group with 25(OH)D deficiency (<7.87 ng/mL), the CDR composite (sum of boxes) score was higher (Wald $F = 3.20$; $P = 0.047$) and associated with worse performance on the SBT (Wald $F = 5.22$; $P = 0.044$).

Jorde et al⁷⁴ did not find a correlation between serum 25(OH)D and any of the multiple tests of cognition they performed. However, serum PTH concentration was negatively associated with tests of working memory capacity ($P < 0.01$) and speed of information processing ($P < 0.05$). In this study, the sample size was too small to perform multiple comparison testing; therefore, the results should be interpreted with caution.

Przybelski and Binkley⁷⁷ performed a retrospective chart review of 80 patients presenting to a community behavior clinic in the United States. They included patients who had MMSE scores and 25(OH)D and vitamin B₁₂ concentrations determined. The mean age was 79.5 years, and the mean MMSE score was 19.2. An unadjusted linear regression analysis found a posi-

tive correlation between 25(OH)D concentrations and MMSE score ($R^2 = 0.225$; $P < 0.001$). Vitamin B₁₂ was unrelated to MMSE score ($R^2 = 0.001$). The lack of adjustment for confounding variables in this study is a methodologic problem; hence, the results should be interpreted with caution.

McGrath et al⁷⁸ performed a cross-sectional analysis within the NHANES III cohort to examine the relationship between 25(OH)D concentrations and performance on cognitive tasks. They examined 3 age groups: adolescents (12–17 years of age; $n = 1676$), young adults (20–60 years; $n = 4747$), and older adults (60–90 years; $n = 4809$) living in the community. The results in the older adults are discussed here. Contrary to the hypothesis, those with the highest score (indicating superior performance) were within the lowest 25(OH)D quintile, and no significant overall difference in mean score was observed between those in the lowest 25(OH)D quintile (<17 ng/mL; score, 6.5) and those in the highest quintile (>34 ng/mL; score, 6.4) (Wald $F = 3.38$; $P = 0.02$).

Buell et al⁷⁹ performed a cross-sectional analysis within the Nutrition and Memory in Elders (NAME) study to determine the association between 25(OH)D concentrations and cognitive function; 703 mainly white subjects and 377 black subjects (aged 65–99 years; mean BMI, 31 kg/m²; 75% women) were included in the study. Subjects were recruited through Boston home care agencies. A comprehensive battery of neuropsychologic tests was administered: MMSE, North American Adult Reading Test, supraspan learning (Wechsler Memory Scale–III [WMS–III] word list learning), auditory and visual retention (WMS–III logical memory), executive function/mental processing speed (digit symbol coding, trail-making test, mental alternations, Wechsler Adult Intelligence Scale–III block design), visual construction/fluid reasoning (matrix reasoning), verbal fluency (controlled oral word association), and anxiety (self-rated anxiety scale). The 25(OH)D concentrations were <20 ng/mL in $>65\%$ of subjects. Statistical data reduction techniques addressed issues associated with multiple testing. The adjusted Pearson correlation was not significant for 25(OH)D and MMSE, but was significant for tests of executive function (block design $r = 0.07$; $P = 0.04$; digit symbol $r = 0.12$; $P < 0.01$; digit span $r = 0.08$; $P < 0.01$; matrix reasoning $r = 0.08$; $P < 0.02$; trails A $r = -0.08$; $P < 0.03$; and trails B $r = -0.10$; $P < 0.02$). Adjusted regression analysis showed 25(OH)D concentrations were associated with better performance on tests of executive reasoning (each $P < 0.05$). No significant associa-

tions were observed between 25(OH)D and memory tests. None of the identified studies reported a trend to harm with vitamin D supplementation.

In summary, the studies evaluating the effect of 25(OH)D concentrations on cognition reported mixed results, in part depending on which tests were used to assess cognitive function and differences in sample sizes. Overall, it appears that cognitive function, as assessed by the MMSE, is not associated with 25(OH)D concentrations. However, other instruments that assess executive functioning have been associated with better performance with higher 25(OH)D concentrations. Most of the studies are also limited by cross-sectional methodology and a single measurement of 25(OH)D, which does not allow for seasonal fluctuation, but provide data to justify a randomized, placebo-controlled trial to evaluate the effect of vitamin D therapy on cognition in the elderly.

DISCUSSION

A growing awareness of the prevalence of vitamin D insufficiency, along with recognition of its role in fall and fracture prevention, is resulting in an increasing number of high-dose vitamin D prescriptions for older adults. Because VDRs are found in a variety of extraskelatal tissues, it is important for clinicians to understand the potential extraskelatal clinical impact of vitamin D supplementation. This review evaluated the literature on the association between vitamin D and mortality, hypertension, CV disease, mood, and cognition in older adults.

Although intriguing observational data support a link between 25(OH)D concentrations and reductions in SBP, CV disease, mortality, and symptoms of depression, and improved cognition, no clear benefit was observed in the largest randomized controlled trial of calcium and vitamin D supplementation (the WHIRT).^{46,53,62} Intervention contamination limited the power of this study to find a true difference; therefore, whether vitamin D supplementation is beneficial to CV, mortality, mood, and cognitive outcomes remains uncertain. An increased mortality risk in women with 25(OH)D concentrations >50 ng/mL in the prospective cohort by Melamed et al⁵⁹ has not been reproduced.

Guidelines currently recommend daily intake of 400 IU of vitamin D for adults 51 to 70 years of age and 600 IU for adults ≥ 71 years, with at least 800 IU of vitamin D₂ daily for adults >65 years of age. However, uncertainty remains about the optimal dose, dosing interval (low-dose daily vs high-dose weekly or monthly supplements), and formulation (D₃ vs D₂ vs “activated”

1,25[OH]₂D vitamin D products). Further studies are needed to clarify these important issues.

This review has several limitations. Publication bias may have resulted in a failure to identify pertinent studies that reported a negative association between vitamin D and these syndromes. The changing definition of vitamin D deficiency resulted in a wide variety of cutoff concentrations in the primary studies that may be less clinically relevant today. Many studies used self-reported vitamin D intake, which may not correlate with serum concentrations. Changes in vitamin D assays have occurred, which make older studies difficult to interpret.

Vitamin D is an intriguing substance with paracrine effects on a wide range of tissues. The current data suggest that, in addition to its established role in fracture and fall prevention in older adults, vitamin D may have beneficial effects on mortality and some common illnesses in older adults. Future studies are needed to evaluate high-dose supplements using current recommendations and to prospectively monitor changes in serum 25(OH)D concentrations.

CONCLUSIONS

Vitamin D insufficiency appears to be highly prevalent among older adults. Evidence from epidemiologic studies and small clinical trials suggests an association between 25(OH)D concentrations and SBP, risk for CV disease–related deaths, symptoms of depression, cognitive deficits, and mortality. The WHIRT did not find a benefit of vitamin D supplementation on blood pressure, MI, or mortality in postmenopausal women.

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