Some New Food for Thought: The Role of Vitamin D in the Mental Health of Older Adults

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Vitamin D, a multipurpose steroid hormone vital to health, has been increasingly implicated in the pathology of cognition and mental illness. Hypovitaminosis D is prevalent among older adults, and several studies suggest an association between hypovitaminosis D and basic and executive cognitive functions, depression, bipolar disorder, and schizophrenia. Vitamin D activates receptors on neurons in regions implicated in the regulation of behavior, stimulates neurotrophin release, and protects the brain by buffering antioxidant and anti-in ammatory defenses against vascular injury and improving metabolic and cardiovascular function. Although additional studies are needed to examine the impact of supplementation on cognition and mood disorders, given the known health bene ts of vitamin D, we recommend greater supplementation in older adults.

Introduction

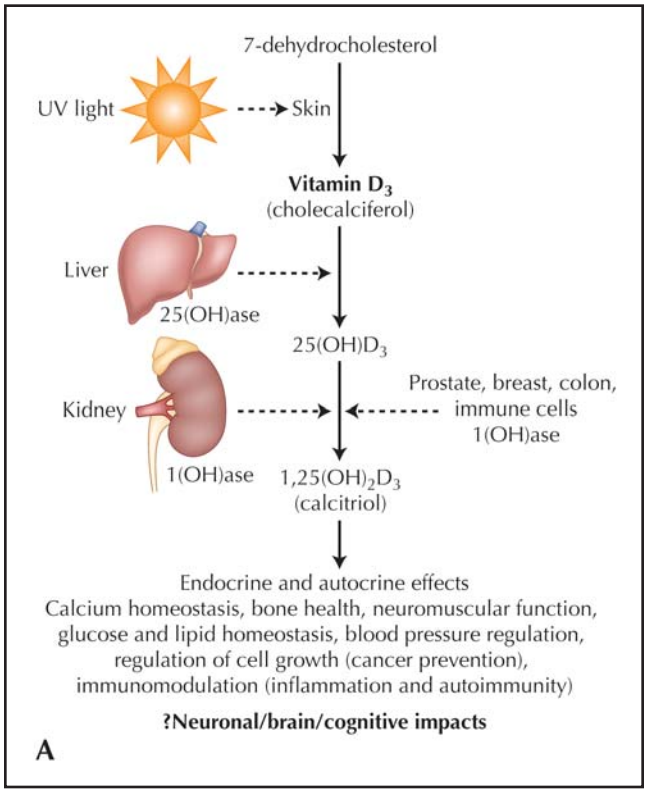
The multipurpose steroid hormone vitamin D, long known to be vital to health, is increasingly implicated in the pathology of mental and cognitive illness. Vitamin D has been found to be involved in many physiologic processes, including muscle function, cancer prevention, cardiovascular and bone health, immunity, and metabolic signaling (Fig. 1A). Low serum vitamin D concentrations in older adults have been associated with higher mortality [1•] and increased risk of future nursing home admission [2]. Thus far, the bulk of the evidence for the involvement of vitamin D in the function of multiple organ systems has been gleaned from cross-sectional studies in people with a range of vitamin D levels or from larger epidemiologic observations in populations with differing sun exposures.

The presence of cognitive and mental pathology may be associated with an age-associated increase in the prevalence of hypovitaminosis D (HVD), de ned as a serum 25-OH vitamin D level less than 75 nM (30 ng/L) [3]. Between 40% and 90% of older adults suffer from HVD [4,5], including a population we surveyed in amply sunlit south Florida [5]. An accumulating number of reports support an effect of HVD on cognition and/or mental health [6•]. Age-related changes in cognition or sleep also may be related to vitamin D de ciency. This review summarizes our understanding of how vitamin D insuf ciency affects the well-being of older adults and outlines the evidence for vitamin D's role in cognition and behavior. By searching the PubMed database using the search terms "vitamin D," "cognitive impairment," and "mental illness," we obtained an initial list of publications to consider for this review. We also used references found in the bibliographies of the articles obtained in the initial search.

Effects on Cognition

Basic cognitive functions

Several studies suggest an association between HVD and basic cognitive functions, including attention, memory, and perception [7]. A limited number have used global tests of mental status to assess domains of basic cognitive functions and ascertain a relationship between HVD and mental status. In a retrospective chart review, a direct linear correlation was found between serum vitamin D level and total Folstein Mini-Mental Status (MMSE)



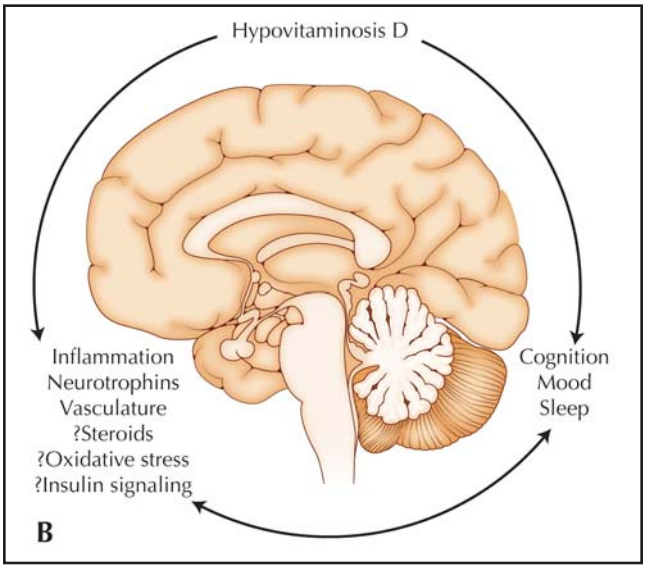


Figure 1. A, The physiology of vitamin D. **B,** The relationship between vitamin D and the central nervous system.

score in 32 older individuals (age range, 61–92 years) who attended a memory disorders clinic for evaluation [8•]. In a second study, 225 patients with a clinical diagnosis of Alzheimer's disease (AD) among those seen in an ambulatory geriatrics clinic in The Netherlands exhibited a direct correlation between lower levels of vitamin D and poorer performance on the MMSE [9].

In 69 healthy, randomly selected older outpatients in Italy, greater dietary vitamin D intake was associated with a higher MMSE score [10]. An inverse relationship also existed between vitamin D level intake and the oxidative stress marker malondialdehyde, suggesting that vitamin D may exert an antioxidant effect.

MMSE and vitamin D levels were measured in a group of 80 older volunteers: 40 normal and 40 "mildly demented" participants [11]. The mean MMSE score for the group was 25.87, and the 25-OH vitamin D level was 46.45 nM. Participants were then classi ed into three groups: vitamin D suf cient (≥ 50 nM), insuf cient (< 50 nM but ≥ 25 nM), or de cient (< 25 nM). Forty-two percent of the study population met the criteria for vitamin D suf ciency. There was no association between MMSE and vitamin D levels among the three groups, but less replete vitamin D status was associated with worse performance on a nine-item cognitive screen, the Short Blessed Test, and a more comprehensive assessment, the Clinical Dementia Rating. It is possible that the study would have found a stronger association between vitamin D and the results of neuropsychological testing if a higher upper limit of HVD had been used (eg, 75 nM).

Thus, the evidence for the association between vitamin D and basic cognitive functions is incomplete. Further evaluation of populations using more comprehensive cognitive testing and an appropriate de nition of HVD may demonstrate stronger associations.

Executive cognitive functions

Although the possibility of an association between basic cognitive functions and HVD is intriguing, a potentially more important association might exist if there was a relationship between HVD and executive functions. Executive functions integrate and control basic cognitive functions, including tasks such as planning, problem solving, organizing, starting activities, maintaining a working memory, regulating emotional response, shifting tasks, and stopping processes [12]. Tests of executive function include the Stroop test, Wisconsin Card Sorting tests, verbal uency tests, and Tower and Trail Making tests [12]. A few efforts have been made to correlate results on these tests with 25-OH vitamin D levels in population studies.

The relationships between HVD and executive functions have not been well studied. In the Nutrition, Aging, and Memory in Elders (NAME) study, 318 older adults had serum micronutrient levels drawn and underwent neurocognitive testing [13]. The serum vitamin D levels of demented participants were signi cantly lower than those of nondemented individuals (41.25 nM vs 48.75 nM; $P = 0.03$), and those with serum vitamin D levels less than 50 nM were more likely to have AD compared with those with higher levels (17.1% vs 6.9%; $P < 0.01$) [6•]. There was a relationship

between vitamin D and some neuropsychological tests and an association between vitamin D and parameters of executive function [6•]. An additional correlation was observed between low vitamin D concentrations and evidence on brain imaging of infarcts and white matter structural integrity [6•]. The mean vitamin D level in those without AD was actually quite low: 48.75 nM. Consequently, comparisons between groups may have understated the contribution of vitamin D status to performance on neuropsychological tests.

Other studies, however, implied that vitamin D insufficiency was not related to cognitive impairment. Among more than 10,000 participants in the Third National Health and Nutrition Examination Survey epidemiologic study, including adolescents (ages 12–16 years) and adults (ages 20–90), no relationship was found between vitamin D level and test scores in younger participants [14]. The older participants (ages 60–90) actually took part in only two tests of cognition (repeating details of a story they had read, both immediately and later), whose relevance to overall cognitive functioning is uncertain. Older adults who scored highest on the test were actually in the lowest quintiles of vitamin D levels. However, there was only a small difference in the mean test scores of participants in all the different quintiles. In another investigation, 21 individuals with secondary hyperparathyroidism (parathyroid hormone [PTH] levels > 6.4 pM/L and calcium < 2.4 mM/L without renal failure) performed significantly more poorly on neurocognitive tests (digit span forward, Stroop test parts one and two, and a word association test) than those with normal PTH [15]. Interestingly, low 25-OH vitamin D levels were not similarly associated with impaired cognition but were correlated with depression. This finding is somewhat surprising because low vitamin D levels generally result in higher PTH levels. However, not enough information was provided to determine the explicit relationships between vitamin D and PTH in this study. The few studies conducted with a very small number of tests provided an inconclusive answer as to the relationship between vitamin D and executive cognitive functions.

Effects on mood

Several investigations have also suggested a relationship between vitamin D levels and depression, bipolar disease, and schizophrenia [16–23]. The few treatment trials of vitamin D supplementation's effect on mood and psychiatric disorders have yielded mixed results, perhaps in part because most have used low doses of vitamin D. Several studies have attempted to define a relationship between vitamin D and depression. In a cohort of 1087 community-dwelling adults 65 to 95 years old, depressed individuals had significantly lower vitamin D levels and higher PTH levels than those without depression [16]. Seventy-five patients with fibromyalgia who had low vitamin D levels had more strongly positive scores on depression- and anxiety-screening questionnaires than those who had higher levels [21]. In the study of hyperparathyroid individuals described previously, low vitamin D levels were also associated with higher scores on a depression screening test, the Beck Depression Inventory [15]. However, an intervention trial of 250 women ages 43 to 72 did not demonstrate benefit in the setting of depression [24]. In this study, half were supplemented with 400 IU/d of both vitamin D and calcium or calcium alone for 1 year. Baseline and postintervention vitamin D levels were not provided. Participants who took vitamin D together with calcium or calcium alone had comparably improved Profile of Mood States scores during months of increased sunlight, but the dose of vitamin D supplementation (400 IU) was very low; thus, the failure to find a greater benefit from vitamin D was not unexpected. Therefore, the relationship between vitamin D and depression is unclear.

Vitamin D also has been used to treat seasonal affective disorder (SAD). Fifteen individuals with SAD were randomized to receive a single 100,000-IU dose of vitamin D or phototherapy [22]. The mean vitamin D level in patients given vitamin D increased from 27.75 nM to 47.5 nM, and all participants who received vitamin D had improved scores on questionnaire assessments of depression. The degree of improvement was directly and linearly correlated with an increase in the vitamin D level. Individuals who received phototherapy also had an increase in vitamin D level to 46.5 nM and improved scores on the questionnaire. In another investigation, 912 women older than 70 years of age with SAD were supplemented with vitamin D, 800 IU/d [25]. However, no improvement was seen in the treatment group of participants over a control group that received only education about the disorder [26]. Vitamin D levels were not measured as part of the trial. Forty-four healthy younger participants (age range, 18–43 years) were given a 400-IU dose of vitamin D orally for 5 days, an 800-IU dose, or a placebo [23]. Those receiving either dose of vitamin D improved on subjective symptom scores of positive and negative affect. Given the variation in the response of SAD to different doses of vitamin D in different populations, its potential efficacy in people with SAD must be elucidated. The possibility of varying responses to vitamin D supplementation by different individuals, particularly frail older adults, may apply to other conditions and is discussed subsequently.

One study hints at a relationship between vitamin D and bipolar disorder. Fourteen of 17 inpatients with bipolar disorder had a vitamin D level below 60 nM [17]. Although the study included no serum vitamin D level from a control population, the authors noted that the mean serum vitamin D level was 32 ng/mL in a population study from the same region in Australia in which the bipolar patients lived [27]. More research will be needed to establish the relationship between vitamin D status and bipolar disorder.

Lack of prenatal vitamin D may be a risk factor for schizophrenia [18]. Children born in the winter and early spring at northern latitudes in the United States are more

Table 1. Vitamin D in cognition and mood

Disorder	Studies showing positive association	Studies showing no association
Dementia	Buell and Dawson-Hughes [6•], Przybelski and Binkley [8•], Oudshoorn et al. [9], Wilkins et al. [11], Scott et al. [13]	McGrath et al. [14]
Depression	Hoogendijk et al. [16]	Harris and Dawson-Hughes [24]
Seasonal affective disorder	Gloth et al. [22]	
Bipolar disorder	Berk et al. [17], Pasco et al. [27]	
Schizophrenia	McGrath [18], McGrath et al. [19], Torrey et al. [28], Jarvis [29]	

likely to become schizophrenic [28]. The incidence of schizophrenia is higher in children of immigrants from the Caribbean who move to cities in countries farther north [29]. Male infants in Finland who received vitamin D supplementation were less likely to develop schizophrenia than unsupplemented children [19]. HVD in these children may be the result of preexisting HVD that often occurs among breastfeeding mothers [30]. As described subsequently, animal studies suggest that HVD affects the brains of infants born to HVD-de cient mothers [25]. Vitamin D's effect on schizophrenic adults has not been determined.

The evidence for the role of vitamin D in cognition and mental illness is intriguing but quite incomplete (Table 1). Investigations should examine potential links between impacts of HVD on mood and cognition and mechanisms of vitamin D action.

Possible Mechanisms of Vitamin D Effects on the Central Nervous System

Mechanisms of vitamin D action in the brain

Vitamin D may have multiple actions on the central nervous system (Table 2) [31]. It may activate receptors on neurons in regions implicated in the regulation of behavior, such as the limbic system, cortex, and cerebellum, and may also stimulate the release of neurotrophins, factors that regulate neuronal development [31]. Cerebral and cerebellar neurons in regions important for cognition can produce 1-α-hydroxylase, an enzyme that converts 25-OH vitamin D to the active form of 1,25-dihydroxy-vitamin D (also known as calcitriol) [31]. In vitro treatment of neurons with calcitriol results in the release of neurotrophins, including neurotrophin-3, which augments synaptic transmission in the hippocampus, and glial cell line–derived neurotrophic factor (GDNF), which promotes the development of dopaminergic neurons. Vitamin D receptor (VDR) knockout mice have decreased levels of neural growth factors and abnormal brain shape and also exhibit behavioral disturbances such as alterations in grooming, parenting, and social interaction [31]. One study reported that VDR knockout mice had motor dysfunction but no cognitive dysfunction, as measured by a marble burying test, acoustic startle responses, and time needed to negotiate a maze [32]. Pups born to vitamin D–de cient rats also have a thinner cortex, enlarged ventricles, lower levels of neural growth factor and GDNF, and fewer neurotrophin receptors [25]. Motor or cognitive function was not measured in these pups.

The interaction between vitamin D and its receptor may play a role in the pathogenesis of dementing disorders. VDR gene polymorphisms in humans have been associated with cognitive impairment in two studies. In a sample of a population of 563 individuals 85 years of age and older, those who carried one of three polymorphisms, BsmI, TaqI, or haplotype 2(BAt), performed more poorly on neuropsychological tests [33]. In another study of 109 individuals with AD and an identical number of age-matched controls, those whose VDR genes carried one copy of the ApaI polymorphism were 2.3 times more likely to have AD, and those who had a VDR gene allele with both the Apa and TaqI polymorphism were 2.3 times less likely to have AD [34]. No vitamin D levels or any other associated clinical phenotypes were reported [33,34].

Mechanisms of vitamin D action outside the brain

Vitamin D may protect the brain by buffering antioxidant and anti-in ammatory defenses against vascular injury [6•]. Vitamin D upregulates production of the antioxidants GDNF and glutathione [35,36]. Normal older rats given vitamin D had reduced losses of hippocampal neurons—cells that commonly atrophy in AD—compared with untreated rats [37]. Rat hippocampal neurons cultured with calcitriol have been found to be more resistant to excitotoxic injury caused by stimulation with electrical current [38].

Vitamin D also exerts multiple anti-in ammatory effects that may affect the brain. Vitamin D suppresses the release of cytokines and metalloproteinases that promote vascular in ammation and may protect against vascular injury and calci cation in human tissues [39,40]. In human participants, vitamin D level was inversely associated with metalloproteinase MMP9 and C-reactive protein, which induce vascular in ammation. Supplementation of vitamin D–de cient participants lowered serum levels of MMP9 and C-reactive protein [41].

Table 2. Potential mechanisms of vitamin D action on the central nervous system

Mechanism	Studies
Neurotrophin stimulation via vitamin D receptor activation	Kalueff and Tuohimaa [31], Kuningas et al. [33], Gezen-Ak et al. [34]
Antioxidant	Buell and Dawson-Hughes [6•], Wion et al. [35], Naveilhan et al. [36]
Anti-inflammatory via cytokines, metalloproteinases	Zittermann et al. [39], Zittermann et al. [40], Timms et al. [41]
Insulin- and lipid-mediated effects	Cherniack and Troen [42]
Cardiovascular protective effects	Buell and Dawson-Hughes [6•], Judd et al. [43], Zittermann et al. [44], Li et al. [45]

Reduced vitamin D levels correlate with metabolic changes that may adversely affect the brain, including reduced insulin sensitivity, impaired insulin signaling, higher glucose levels, diabetes, lower high-density lipoprotein cholesterol, hypertriglyceridemia, obesity, and metabolic syndrome [42]. Because vitamin D is lipid soluble, obese individuals—who have a larger distribution space—may need more vitamin D [42]. An inverse association exists between vitamin D level and body fat percentage [42], and obese individuals have a lower bioavailability of vitamin D.

Vitamin D levels also have been correlated with hypertension and congestive heart failure [43,44], which in turn further impair cerebral blood flow. Murine studies suggest that vitamin D inhibits renin and angiotensin [45]. In a human study, 800-IU vitamin D supplementation led to a decrease in systolic blood pressure of 9.3% after 2 months [46]. In vascular disease, the anti-inflammatory, metabolic, and vasculoprotective effects of vitamin D may preserve cognition by maintaining the cerebral vasculature [6•]. Therefore, it seems increasingly likely that vitamin D exerts its effects on cognition, mood, and behavior by acting directly on the brain and indirectly via multiple physiologic pathways (Fig. 1B).

Vitamin D supplementation

Although we may not be certain of the mechanism of vitamin D action on mood and cognition, given the multiple other health benefits of vitamin D, it seems prudent to ensure that all older adults receive an adequate intake of vitamin D. Vitamin D levels of at least 75 nM are now commonly believed to be necessary to avoid the adverse effects of HVD [47]. Doses that approach 2600 IU/d may be required to enable 97% of the population to remain vitamin D sufficient [48]. We conducted a trial in which we provided 17 older adults with a 2000-IU/d supplement for 6 months [49]. This dose reduced the incidence of HVD (< 75 nM) from 47% to 18% ($P < 0.01$). Individuals with baseline HVD had a larger mean increase in serum vitamin D levels, especially those older than 80 years of age. The safety of vitamin D supplementation is excellent; doses as high as 10,000 U/d can be given without adverse effects, excluding patients with primary hyperparathyroidism [50]. Adverse effects have not been observed in individuals with vitamin D levels up to 140 nM [50]. In two studies of frail older adults, 1500 to 5000 IU/d of cholecalciferol was given without hypercalcemia [51,52]. A dose of 1500 IU/d still left 35% of patients with a 25-OH vitamin D level of less than 75 nM after 8 weeks, and a dose of 5000 IU/d still left 10% of patients with a 25-OH vitamin D level of less than 75 nM after 12 months. Individuals who received an intramuscular dose of 600,000 IU cholecalciferol (equivalent to 1600 IU/d over 1 year) exhibited an increase in serum vitamin D concentration after 4 months to 114 ± 35 nM from a baseline of 32 ± 8.4 nM. Two thirds of recipients with an initially elevated PTH level exhibited a reduction to normal levels. The mean 25-OH vitamin D serum concentration after 1 year was 72.5 nM [53]. Although the single large dose was clearly effective in raising vitamin D levels, the mean level at 1 year implied that many individuals were once again hypovitaminotic D. Mild hypercalcemia was noted in only 4%.

Recommendation

In the United States, ergocalciferol is available in 50,000-IU capsules by prescription only, but smaller doses are available over the counter; cholecalciferol is available over the counter in doses up to 50,000 IU. Cholecalciferol or ergocalciferol will restore 25-OH vitamin D levels to sufficiency, although some studies suggest that cholecalciferol increases serum 25-OH vitamin D more efficiently than ergocalciferol [54–56]. We strongly believe that the current dietary recommendations of 400 to 800 IU of cholecalciferol daily will not replete a significant percentage of the older adult population [4].

Ideally, we advise that all older adults have their serum 25-OH vitamin D concentrations measured [4]. Those with baseline levels of less than 50 nM should be prescribed 50,000 IU of ergocalciferol weekly for 3 months. If levels are still less than 80 nM, treatment should continue with this dose until 25-OH vitamin D concentrations reach 80 nM or higher with an assessment of compliance. Once levels of 80 nM are reached, cholecalciferol, 2000 IU/d, or a monthly 50,000-IU dose of ergocalciferol should be given. If baseline levels before treatment are between 50 and 80 nM, one should

initiate treatment with 2000 IU/d of cholecalciferol for 3 months. If levels are still less than 80 nM after reassessment of levels and compliance, one should increase the dose by 1000 to 2000 IU/d, continue treatment, and reassess in another 3 months. When vitamin D measurements cannot be obtained easily, individuals may be initiated on 2000 IU/d and have their serum vitamin D concentrations measured after 3 months of supplementation, with an increase in dose if their levels are found to be inadequate as outlined previously.

Conclusions

Although overt vitamin D de ciency is now rare, HVD is extremely common, particularly in older adults [4]. Epidemiologic, cross-sectional, and intervention studies indicate that long-term HVD contributes to the development of many diseases prevalent in older adults and also may have a role in changes in mood and cognition. However, such epidemiologic and cross-sectional studies may miss the entire scope of the association because cognitive and mental illness may take many years to develop. If lack of vitamin D affects cognition and mental health, it is uncertain whether the mechanism shares a common pathophysiologic process with other systems or acts by a unique pathway. As noted previously, several studies support the in uence of HVD on the development of hypertension and diabetes, which could subsequently in uence cognition. Current estimates of normal vitamin D concentrations are based on optimal levels for calcium absorption, normalization of PTH, and reduction of fracture risk [47]. Some meta-analyses and epidemiologic studies suggest that even higher levels are needed to reduce the risk of breast, colon, and prostate cancer [57,58]. However, optimal levels for preventing other conditions have not yet been established and may differ from those de ned for calcium and skeletal health. Finally, it is not yet clear how dependent the action of vitamin D is on calcium, as most investigations have relied on a combination of vitamin D and calcium.

Older individuals need to be protected from the various consequences of HVD by maintaining vitamin D levels above 75 nM, preferably between 80 and 100 nM. Given the dif culty of obtaining enough vitamin D from sunlight and diet with their current lifestyle, most older individuals require supplementation of at least 2000 IU/d.

Additional understanding of these mechanisms through studying supplementation at doses beyond those established as bene ting the skeleton, establishing biomarkers for suf - ciency other than 25-OH vitamin D serum concentrations, and differentiating between the contributions of vitamin D and calcium to different aspects of health will help to determine how much vitamin D is necessary for general optimal health, including alleviating the burden of cognitive and psychiatric disorders.

Disclosures

No potential con icts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.• Autier P, Gandini S: Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007, 167:1730–1737.

This was an important meta-analysis of 18 independent randomized trials including 57,311 participants. The authors found an association of 0.93 (95% CI, 0.87–0.99) between vitamin D level and all-cause mortality.

2. Visser M, Deeg DJ, Puts MT, et al.: Low serum concentrations of 25-hydroxyvitamin D in older persons and the risk of nursing home admission. *Am J Clin Nutr* 2006, 84:616–622; quiz 671–672.

3. Melamed ML, Michos ED, Post W, Astor B: 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med* 2008, 168:1629–1637.

4. Cherniack EP, Florez H, Roos BA, et al.: Hypovitaminosis D in the elderly: from bone to brain. *J Nutr Health Aging* 2008, 12:366–373.

5. Levis S, Gomez A, Jimenez C, et al.: Vitamin D de ciency and seasonal variation in an adult south Florida population. *J Clin Endocrinol Metab* 2005, 90:1557–1562.

6.• Buell JS, Dawson-Hughes B: Vitamin D and neurocognitive dysfunction: preventing "D"ecline? *Mol Aspects Med* 2008, 29:415–422.

This is the best published review of vitamin D and cognition. The authors review the human evidence for the relationship between vitamin D and cognition and mechanistic evidence from animal studies of the effect of vitamin D on the brain, theorizing that vitamin D in uences cognition in the context of vascular pathology.

7. Riddle DR: *Brain Aging: Models, Methods, and Mechanisms.* Boca Raton, FL: CRC Press; 2007.

8.• Przybelski RJ, Binkley NC: Is vitamin D important for preserving cognition? A positive correlation of serum 25-hydroxyvitamin D concentration with cognitive function. *Arch Biochem Biophys* 2007, 460:202–205.

This review explores the relationship between vitamin D and scores on a frequently used cognitive screening test, the MMSE. In a retrospective chart review, the authors found a direct linear correlation between serum vitamin D level and total MMSE score in 32 older individuals attending a memory disorders clinic for evaluation.

9. Oudshoorn C, Mattace-Raso FU, van der Velde N, et al.: Higher serum vitamin D3 levels are associated with better cognitive test performance in patients with Alzheimer's disease. *Dement Geriatr Cogn Disord* 2008, 25:539–543.

10. Rondanelli M, Trotti R, Opizzi A, Solerte SB: Relationship among nutritional status, pro/antioxidant balance and cognitive performance in a group of free-living healthy elderly. *Minerva Med* 2007, 98:639–645.

11. Wilkins CH, Sheline YI, Roe CM, et al.: Vitamin D de ciency is associated with low mood and worse cognitive performance in older adults. *Am J Geriatr Psychiatry* 2006, 14:1032–1040.

12. Roth RM, Isquith PK, Gioia GA: Assessment of and intervention for executive dysfunction. In *Psychologist's Desk Reference,* edn 2. Edited by Koocher GP, Norcross JC, Hill SS. New York: Oxford University Press; 2005:38–41.

13. Scott TM, Peter I, Tucker KL, et al.: The Nutrition, Aging, and Memory in Elders (NAME) study: design and methods for a study of micronutrients and cognitive function in a homebound elderly population. *Int J Geriatr Psychiatry* 2006, 21:519–528.
14. McGrath J, Scragg R, Chant D, et al.: No association between serum 25-hydroxyvitamin D3 level and performance on psychometric tests in NHANES III. *Neuroepidemiology* 2007, 29:49–54.
15. Jorde R, Waterloo K, Saleh F, et al.: Neuropsychological function in relation to serum parathyroid hormone and serum 25-hydroxyvitamin D levels. The Tromso study. *J Neurol* 2006, 253:464–470.
16. Hoogendijk WJ, Lips P, Dik MG, et al.: Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. *Arch Gen Psychiatry* 2008, 65:508–512.
17. Berk M, Sanders KM, Pasco JA, et al.: Vitamin D de ciency may play a role in depression. *Med Hypotheses* 2007, 69:1316–1319.
18. McGrath J: Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? *Schizophr Res* 1999, 40:173–177.
19. McGrath J, Saari K, Hakko H, et al.: Vitamin D supplementation during the rst year of life and risk of schizophrenia: a Finnish birth cohort study. *Schizophr Res* 2004, 67:237–245.
20. Schaffer A, Levitt AJ, Boyle M: In uence of season and latitude in a community sample of subjects with bipolar disorder. *Can J Psychiatry* 2003, 48:277–280.
21. Armstrong DJ, Meenagh GK, Bickle I, et al.: Vitamin D de ciency is associated with anxiety and depression in bromyalgia. *Clin Rheumatol* 2007, 26:551–554.
22. Gloth FM 3rd, Alam W, Hollis B: Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. *J Nutr Health Aging* 1999, 3:5–7.
23. Lansdowne AT, Provost SC: Vitamin D3 enhances mood in healthy subjects during winter. *Psychopharmacology (Berl)* 1998, 135:319–323.
24. Harris S, Dawson-Hughes B: Seasonal mood changes in 250 normal women. *Psychiatry Res* 1993, 49:77–87.
25. Eyles D, Brown J, Mackay-Sim A, et al.: Vitamin D3 and brain development. *Neuroscience* 2003, 118:641–653.
26. Dumville JC, Miles JN, Porthouse J, et al.: Can vitamin D supplementation prevent winter-time blues? A randomised trial among older women. *J Nutr Health Aging* 2006, 10:151–153.
27. Pasco JA, Henry MJ, Nicholson GC, et al.: Vitamin D status of women in the Geelong Osteoporosis Study: association with diet and casual exposure to sunlight. *Med J Aust* 2001, 175:401–405.
28. Torrey EF, Torrey BB, Peterson MR: Seasonality of schizophrenic births in the United States. *Arch Gen Psychiatry* 1977, 34:1065–1070.
29. Jarvis E: Schizophrenia in British immigrants: recent nd-ings, issues and implications. *Transcult Psychiatry* 1998, 35:39–74.
30. Ziegler EE, Hollis BW, Nelson SE, Jeter JM: Vitamin D de ciency in breastfed infants in Iowa. *Pediatrics* 2006, 118:603–610.
31. Kalueff AV, Tuohimaa P: Neurosteroid hormone vitamin D and its utility in clinical nutrition. *Curr Opin Clin Nutr Metab Care* 2007, 10:12–19.
32. Burne TH, McGrath JJ, Eyles DW, Mackay-Sim A: Behavioural characterization of vitamin D receptor knockout mice. *Behav Brain Res* 2005, 157:299–308.
33. Kuningas M, Mooijaart SP, Jolles J, et al.: VDR gene variants associate with cognitive function and depressive symptoms in old age. *Neurobiol Aging* 2007 Aug 20 (Epub ahead of print).
34. Gezen-Ak D, Dursun E, Ertan T, et al.: Association between vitamin D receptor gene polymorphism and Alzheimer's disease. *Tohoku J Exp Med* 2007, 212:275–282.
35. Wion D, MacGrogan D, Neveu I, et al.: 1,25-Dihydroxyvitamin D3 is a potent inducer of nerve growth factor synthesis. *J Neurosci Res* 1991, 28:110–114.
36. Naveilhan P, Neveu I, Wion D, Brachet P: 1,25-Dihydroxyvitamin D3, an inducer of glial cell line-derived neurotrophic factor. *Neuroreport* 1996, 7:2171–2175.
37. Land eld PW, Cadwallader-Neal L: Long-term treatment with calcitriol (1,25(OH)2 vit D3) retards a biomarker of hippocampal aging in rats. *Neurobiol Aging* 1998, 19:469–477.
38. Brewer LD, Thibault V, Chen KC, et al.: Vitamin D hormone confers neuroprotection in parallel with downregulation of L-type calcium channel expression in hippocampal neurons. *J Neurosci* 2001, 21:98–108.
39. Zittermann A, Schleithoff SS, Koerfer R: Vitamin D and vascular calci cation. *Curr Opin Lipidol* 2007, 18:41–46.
40. Zittermann A, Schleithoff SS, Koerfer R: Putting cardiovascular disease and vitamin D insuf ciency into perspective. *Br J Nutr* 2005, 94:483–492.
41. Timms PM, Mannan N, Hitman GA, et al.: Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for in ammatory damage in chronic disorders? *QJM* 2002, 95:787–796.
42. Cherniack EP, Troen BR: Calciotropic hormones. In *Senile Osteoporosis: Advances in Pathophysiology and Therapeutic Approach.* Edited by Duque G, Kiel DP. London: Springer-Verlag; 2008:34–46.
43. Judd SE, Nanes MS, Ziegler TR, et al.: Optimal vitamin D status attenuates the age-associated increase in systolic blood pressure in white Americans: results from the third National Health and Nutrition Examination Survey. *Am J Clin Nutr* 2008, 87:136–141.
44. Zittermann A, Schleithoff SS, Tenderich G, et al.: Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? *J Am Coll Cardiol* 2003, 41:105–112.
45. Li YC, Kong J, Wei M, et al.: 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest* 2002, 110:229–238.
46. Pfeifer M, Begerow B, Minne HW, et al.: Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab* 2001, 86:1633–1637.
47. Heaney RP: Functional indices of vitamin D status and rami cations of vitamin D de ciency. *Am J Clin Nutr* 2004, 80(6 Suppl):1706S–1709S.
48. Heaney RP: The vitamin D requirement in health and disease. *J Steroid Biochem Mol Biol* 2005, 97:13–19.
49. Cherniack EP, Florez H, Hollis B, et al.: High dose of vitamin D3 reduces the prevalence of hypovitaminosis D in elderly veterans. *Gerontologist* 2007, 47:13–14.
50. Vieth R: Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr* 1999, 69:842–856.
51. Ish-Shalom S, Salganik T, Segal E, et al.: Daily, weekly or monthly protocols to reach the desired serum 25-hydroxyvitamin D concentration for the elderly. *J Bone Miner Res* 2005, 20(Suppl 1):S288.
52. Mocanu V, Stitt PA, Costan A, et al.: Safety and bone mineral density effects of bread forti ed with 125 mcg vitamin D3/day in Romanian nursing-home residents [abstract]. *J Bone Miner Res* 2005, 20(Suppl 1):S288.
53. Diamond TH, Ho KW, Rohl PG, Meerkin M: Annual intramuscular injection of a megadose of cholecalciferol for treatment of vitamin D de ciency: ef cacy and safety data. *Med J Aust* 2005, 183:10–12.

54. Trang HM, Cole DE, Rubin LA, et al.: Evidence that vitamin D3 increases serum 25-hydroxyvitamin D more ef ciently than does vitamin D2. *Am J Clin Nutr* 1998, 68:854–858.
55. Armas LA, Hollis BW, Heaney RP: Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab* 2004, 89:5387–5391.
56. Holick MF, Biancuzzo RM, Chen TC, et al.: Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. *J Clin Endocrinol Metab* 2008, 93:677–681.
57. Giovannucci E: The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). *Cancer Causes Control* 2005, 16:83–95.
58. Bischoff-Ferrari HA, Giovannucci E, Willett WC, et al.: Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 2006, 84:18–28.