Molecular Aspects of Medicine 29 (2008) 415–422

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Review

Vitamin D and neurocognitive dysfunction: Preventing "D"ecline?

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ARTICLE INFO

Article history:
Received 15 March 2008
Received in revised form 7 May 2008
Accepted 7 May 2008

Keywords:
Vitamin D
Cognitive function
Cognition
25-hydroxyvitamin D
Alzheimer's disease
Dementia
Neurodegenerative diseases
Nutrition
Aging

ABSTRACT

A preponderance of evidence supports a role for vitamin D beyond the classical function in mineral homeostasis. Epidemiologic investigations have revealed a beneficial role of vitamin D in muscle function, cardiovascular health, diabetes, and cancer prevention. More recently, studies have suggested a potential beneficial role of vitamin D in cognitive function.

Vitamin D exhibits functional attributes that may prove neuroprotective through antioxidative mechanisms, neuronal calcium regulation, immunomodulation, enhanced nerve conduction and detoxification mechanisms. Compelling evidence supports a beneficial role for the active form of vitamin D in the developing brain as well as in adult brain function. The vitamin D receptor and biosynthetic and degradative pathways for the hydroxylation of vitamin D have been found in the rodent brain; more recently these findings have been confirmed in humans. The vitamin D receptor and catalytic enzymes are colocalized in the areas of the brain involved in complex planning, processing, and the formation of new memories. These findings potentially implicate vitamin D in neurocognitive function.

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doi:10.1016/j.mam.2008.05.001

1. Introduction

Nutritional factors play an important role in promoting health and a preponderance of evidence has linked nutritional deficiencies to exacerbating cognitive deterioration. Elderly individuals with inadequate dietary intake of certain nutrients score lower than average on tests of cognitive function (Riggs et al., 1996; Masaki et al., 2000; Cherubini et al., 2005; Tucker et al., 2005). Historically, antioxidative nutrients and B vitamins have been evaluated for neuroprotective effects. Recently other nutrients, such as vitamin D have come under investigation for a role in cognitive preservation.

Vitamin D is a steroid hormone that has long been known for its important role in regulating body levels of calcium, phosphorus, and bone mineralization. Vitamin D can be obtained from the diet or synthesized in the skin from 7-dehydrocholesterol during sunlight exposure. Upon intake, the hormone is biologically inert and requires activation through a two-step enzymatic pathway involving 25-hydroxylase (25OHase) and 1α-hydroxylase (1,α-OHase) for the conversion to the active form of vitamin D ($1,25(OH)_2D_3$). Once activated, vitamin D influences a wide range of metabolic systems through both genomic and nongenomic pathways. In addition to regulating intestinal calcium absorption and mineral homeostasis, $1,25(OH)_2D_3$ binds to the vitamin D receptor (VDR) which interacts with the nuclear receptor retinoic acid X receptor (RXR). In the presence of $1,25(OH)_2D_3$ the VDR/RXR complex binds small sequences of DNA known as vitamin D response elements (VDREs) and initiates a cascade of molecular interactions that modulate the transcription of a myriad of genes in tissues throughout the body.

While a role for vitamin D in tissue growth and bone metabolism is well established, the presence of the vitamin D receptor and enzymes involved in the hydroxylation of vitamin D (25OHase and 1,α-OHase) in the brain implicates a role for this hormone in cognitive function and dementia (Garcion et al., 2002; Guyton et al., 2003; DeLuca, 2004).

Dementia is the progressive decline in cognitive function due to the presence of disease or damage in the brain. The pathology of dementia is complex and may involve a number of mechanisms including oxidation, inflammation, disease induced neurotoxicity, and genetic vulnerability. Alzheimer's type dementia (AD) is the most common form of age-associated dementia (NIA, 2006) affecting approximately half of adults aged over 85 years (NCCDP, 1999). Vascular dementia (VaD) is the second most common form of age-associated dementia and comprises over 20% of dementia cases in the United States (Geldmacher and Whitehouse, 1996; Roman, 2003; Vermeer et al., 2003).

Alzheimer's disease and vascular dementia, though etiologically distinct frequently coexist. The presence of dementia with concomitant Alzheimer's and vascular features is termed "mixed dementia" and may encompass over 45% of the cases of dementia (Langa et al., 2004). Other forms of dementia, such as, Lewy body dementia, frontotemporal dementia, and Parkinson's disease, are less common and share unique etiologic and pathologic features.

Vitamin D may help to protect against cognitive deterioration and dementia, specifically, vascular dementia and Alzheimer's disease, through vasculoprotection (Lind et al., 1987; Burgess et al., 1990; O'Connell et al., 1997; Pfeifer et al., 2001; Wang et al., 2001; Zittermann et al., 2003; Wang et al., 2008a,b), preservation of neurons (Sutherland et al., 1992; Landfield and Cadwallader-Neal, 1998; Brewer et al., 2001), and protection against risk factors for cognitive dysfunction (Lind et al., 1987; Burgess et al., 1990; Hypponen et al., 2001; Pfeifer et al., 2001; Li et al., 2002, 2004; Zittermann et al., 2003; Bischoff-Ferrari et al., 2004; Wang et al., 2008a,b).

In this review, we will discuss the current evidence for the presence of metabolic pathways for vitamin D in the brain, review the biological plausibility of a role of vitamin D in neuronal health, and discuss new evidence of a link between vitamin D, cognitive function, Alzheimer's disease, and vascular dementia in elders.

2. Alzheimer's disease and vascular dementia

Neurodegenerative diseases involve the loss of neurons involved in cognitive, emotional, motor and sensory functions. Dementia of the Alzheimer's type is characterized by progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perceptions (agnosia) (McKhann et al., 1984; American Psychiatric Association, 1994). The diagnosis is supported by impaired activities of daily living, altered behavioral patterns, memory loss, and evidence of cerebral atrophy on radiographic or magnetic resonance imaging scans (Geldmacher and Whitehouse, 1997; NIA, 2006). Histopathologically, AD brains show synaptic loss and neuronal loss concentrated in the cerebral cortex, hippocampus, and amygdala as well as hallmark amyloid B plaques and neurofibrillary tangles (NIA, 2006).

Vascular dementia, conversely, is characterized by cognitive dysfunction secondary to ischemic or hemorrhagic brain lesions due to cerebrovascular disease or cardiovascular disease. The blood vessels may become compromised secondary to concomitant illnesses such as hypertension or diabetes, or injury from a blood clot. Ischemic brain injury is the third leading cause of death in the United States; over 50% of survivors have resultant neurologic disorders and require chronic care (Roman, 2003). In addition to this, cerebrovascular disease may lead to cognitive dysfunction even in the absence of stroke (Geldmacher and Whitehouse, 1997; Skoog, 2000; Kuller et al., 2003; Zittermann et al., 2005).

Cognitive dysfunction in vascular dementia differs from Alzheimer's Disease in that executive dysfunction is impaired and memory impairment is less profound (Roman et al., 1993). Executive functions are those involved in complex cognitive tasks, such as planning, problem solving or sequencing. Patients with Alzheimer's disease and those with subcortical ischemic vascular disease show selective deficits in these areas (Roman et al., 1993).

2.1. Relevant risk factors for neurodegeneration

Aging is the most common risk factor for the development of neurodegenerative disease. Age-associated neuropathological changes include reductions in total brain volume and atrophy. Microscopically, age-associated neurodegeneration leads to deleterious changes in essential central nervous system structures. These changes include loss of density in nerve synapses, reduction in number and length of dendrites, neuronal atrophy, loss of cortical and hippocampal neurons, and loss of cerebellar perkinje cells and cells within the substantia nigra (Zehnder et al., 2001).

Oxidative stress may also contribute to the pathophysiology of neurodegenerative disorders (Markesbery, 1997). Increases in reactive oxygen species results in cellular damage through the generation of free radicals (hydroxyl radical, superoxide, nitrogen oxide, etc.). These stressors may also impair innate antioxidative mechanisms (Halliwell, 1992; Coyle and Puttfarcken, 1993). Consistent with these degenerative changes, behavioral changes and impairments in cognitive function exist.

3. Vitamin D and the brain: mechanisms of action

Interest in the relationship between vitamin D and central nervous system function was inspired by the evaluation of the neuroactivity of central nervous system steroids rather than the presence of clinical deficiency syndromes (Luine et al., 1987). Evidence for a role of vitamin D in brain function began to accumulate over two decades ago with autoradiographic findings of vitamin D receptors in the brains of experimental animals (Stumpf et al., 1982) and the demonstration that $1,25(OH)_2D_3$ was present in cerebrospinal fluid (Balabanova et al., 1984). Animal studies revealed the presence of VDR in the neuroepithelium during early neurogenesis, and in later stages, in an area involved in the maintenance of neural stem cells, the subventricular zone (Veenstra, 1998). More recent animal data confirm the expression of VDR in specific brain regions, including but not limited to, the temporal lobe, cingulate cortices, thalamus, cerebellum, amygdala and hippocampal regions (Clemens et al., 1988; Stumpf et al., 1988; Prufer et al., 1999; Langub et al., 2001; Garcion et al., 2002; Eyles et al., 2003; McGrath et al., 2004).

3.1. Co-localization of VDR and 1, $25(OH)_2D_3$ in the brain

While in vitro and animal data confirm the presence of vitamin D in the brain, until recently, little evidence existed to support a ligand mediated VDR pathway in the human brain. An early study of patients with Alzheimer's disease revealed the presence of VDR mRNA in humans (Sutherland et al., 1992), yet the presence and accessibility of $1,25(OH)_2D_3$, necessary for activation of the nuclear pathway, remained unclear. Previously, brain concentrations of $1,25(OH)_2D_3$ were thought to be dependent on plasma concentrations (Taylor, 1977; Gascon-Barre and Huet, 1983), until biosynthetic and degradative pathways for the hormone were found in neuronal and glial cells (Clemens et al., 1988; Neveu et al., 1994a,b), cerebral perkinje cells, and cells in the cerebral cortex (Zehnder et al., 2001). These areas are particularly vulnerable to age and disease related degeneration.

It is of particular importance that a novel study in human brains confirmed the presence of the vitamin D receptor as well as genes encoding catalytic enzymes in $1,25(OH)_2D_3$ metabolism in both neuronal and glial cells within brain structures critical for cognition (Zehnder et al., 2001; Burne et al., 2005; Eyles et al., 2005). Furthermore, the VDR and catalytic enzymes were colocalized in the brain; these findings support a functional role for vitamin D in the human brain.

3.2. $1,25(OH)_2D_3$ and neuronal protection

The physical and mechanistic evidence of vitamin D in the brain underscores the potential for biologic function. Studies have shown that vitamin D may protect the structure and integrity of neurons through detoxification pathways and neurotrophin synthesis (Neveu et al., 1994a,b; Kang and Schuman, 1995a,b; Kang and Schuman, 2000). Similar to the benefits of traditional antioxidant nutrients, $1,25(OH)_2D_3$ inhibits inducible nitric oxide synthase (iNOS) (Garcion et al., 1997), an enzyme that is upregulated during ischemic events, and in patients with Alzheimer's and Parkinson's disease. $1,25(OH)_2D_3$ also enhances innate antioxidant pathways. The hormone upregulates gamma glutamyl transpeptidase (Baas et al., 2000) and subsequently increases glutathione. Glutathione is an innate antioxidant which protects oligodendrocytes and the integrity of the nerve conduction pathway critical to mental processing.

Neurotrophins (NT) are proteins necessary for neuronal survival in aging and neuropathological conditions (Siegel and Chauhan, 2000). When neurotrophin synthesis is decreased, spatial navigation is compromised (Siegel and Chauhan, 2000). The hippocampus is involved in spatial navigation, processing, and learning, and is especially sensitive to age or pathology related degeneration. $1,25(OH)_2D_3$ upregulates neurotrophin factors, such as neurotrophin-3 (NT-3) and glial cell line derived neurotrophic factor (GDNF) (Neveu et al., 1994a,b).

NT-3, a protein found in the hippocampus and neocortex, protects nerve transmission and synapticity (Kang and Schuman, 1995a,b, 2000; Siegel and Chauhan, 2000). The protein also increases signal transmission in hippocampal cells which are known to have high levels of VDR mRNA (Kang and Schuman, 1995a,b; Eyles et al., 2005). Another protective neurotrophin, GDNF, affects the survival and differentiation of dopaminergic cells. In animal models, treatment with $1,25(OH)_2D_3$

increased GDNF concentrations and reduced oxidative stress in Parkinson's disease (Wang et al., 2001). In support of these findings, vitamin D depletion in utero resulted in reduced levels of NGF and GDNF in addition to morphological brain changes in newborn rodents (Becker et al., 2005). These deleterious characteristics remained through adulthood (Becker et al., 2005).

4. Vitamin D and neuronal calcium regulation

Age-related changes and, to a greater extent, in neurodegenerative diseases, hippocampal cell loss and neuronal aging have been attributed to elevated L-type voltage calcium channel density and glucocorticoid (GC) neurotoxicity (Kimura et al., 1998). Vitamin D is a major calcium regulatory steroid hormone in peripheral tissues and modulates L-type sensitive calcium channels in the periphery. Studies have shown that vitamin D confers regulatory benefits in neuronal calcium homeostasis and protects neurons from excess calcium entry in the brain (Brewer et al., 2001). These beneficial changes protect brain neurons during ischemic events or excitotoxic insults.

While excessive calcium levels are deleterious for memory formation and cognitive function (Thibault, 2001; Veng et al., 2003), Kuningas et al. showed that certain variations in VDR polymorphisms contribute to differences in cognitive function that were postulated to be independent of calcium levels (Kuningas et al., 2007). *BsmI* and *TaqI* carriers experienced impairments in memory and attention – domains most vulnerable to age related deterioration. Interestingly, the haplotype associated with better cognitive performance, *ApaI* in haplotype 1 (baT), is the same haplotype associated with increased risk of fractures (Uitterlinden et al., 1996, 2004; Turner et al., 2004; Becker et al., 2005). Calcium concentrations did not vary across the phenotypes and suggest that vitamin D may be neuroprotective beyond its role in calcium regulation.

5. Vitamin D, cerebrovascular disease, and vascular dementia

Vascular-related brain damage may result from an influx of excitatory amino acids, inflammatory responses, and changes in cellular polarity, which result in excessive calcium entry. In concert with these changes is an increase in intracellular nitric oxide production and increased oxidative stress.

Vitamin D may help ameliorate vascular-related brain disease by mediating deleterious effects of inflammation, calcium dysregulation, and increased oxidative stress. During transient ischemic events, transforming growth factor and GDNF are upregulated in hippocampal cells to promote survival (Garcion et al., 1999). As discussed earlier, vitamin D augments innate antioxidative defenses by increasing glutathione and GDNF concentrations (Wion et al., 1991; Naveilhan et al., 1996). These particular changes were shown to attenuate ischemic brain disease in rodents (Wang et al., 2001). In in vitro and animal models of cerebral ischemia, vitamin D inhibits antigen presenting cell maturation (Carthy et al., 1989), down regulates NF-κB activity (Kong et al., 1999), and stimulates anti-inflammatory cytokine production (Timms et al., 2002). Epidemiological studies show an inverse association between vitamin D and C-reactive protein levels, a marker of inflammation (Timms et al., 2002).

In addition to these vasculoprotective benefits, vitamin D may play a role in protection against cardiovascular and cerebrovascular disease secondary to benefits that extend beyond those mentioned above (Zittermann et al., 2005; Zittermann, 2006; Wang et al., 2008a,b). Therapeutic intervention with vitamin D regulates blood pressure (Lind et al., 1989; Pfeifer et al., 2001), cardiac hypertrophy (O'Connell et al., 1997), and plasma rennin activity (Burgess et al., 1990; Li et al., 2002). There is an inverse relationship between vitamin D levels and congestive heart failure (CHF) (Zittermann et al., 2003) and C-reactive protein levels (CRP). A recent study from the Framingham Heart Study revealed that vitamin D insufficiency is associated with incident cardiovascular disease (Wang et al., 2008a,b). It is plausible that vitamin D may influence vascular-related dementia via these indirect mechanisms.

6. Vitamin D and Alzheimer's disease

Hippocampal neuronal loss is a characteristic finding in Alzheimer 's disease. Information flow through the hippocampus originates in the dentate gyrus to common amuns 3 (CA3) to CA1 to the subiculum. Treatment with $1,25(OH)_2D_3$ attenuated hippocampal atrophy and protected neuron density (a marker for neuronal health) in aging rats (Landfield and Cadwallader-Neal, 1998). Data in human subjects with Alzheimer's disease revealed a reduction in VDR mRNA in specific regions of the hippocampus (CA1 and CA2) compared to controls (Sutherland et al., 1992) and a higher frequency of VDR polymorphisms were found in Alzheimer's brains than in age-matched controls (Gezen-Ak et al., 2007).

There is a higher prevalence of falls and fractures in patients with Alzheimer's Disease (Buchner and Larson, 1987) and community studies have shown that residents with Alzheimer's Disease and dementia had lower serum concentrations of 25(OH)D (Kipen et al., 1995; Sato et al., 1998). While the temporal association of these findings remains unclear, in a study in patients with Alzheimer's disease, 25(OH)D concentrations were significantly elevated after year-round sun exposure. Additionally, the sun-exposed cohort had a reduced risk of falls and fractures compared to the unexposed (Sato et al., 2005).

Data from the Nutrition and Memory in Elderly study (NAME) (Scott et al., 2004) supported these findings. In subjects who completed a full neurological and psychiatric examination, in addition to magnetic resonance imaging ($n = 318$), we observed that vitamin D concentrations were lower in patients with dementia than those without (19.5 vs. 16.5; $P = 0.03$). In

addition vitamin D concentrations lesser than 50 nmol/L were associated with a higher prevalence of a diagnosis of possible or probable Alzheimer's Disease (17.1% vs 6.9%; $p < 0.01$).

7. Vitamin D and neurocognitive function: deciphering the evidence

Deficiency studies in animal models and epidemiologic investigations have supported a role of vitamin D in neuropsychiatric and neurodegenerative disorders. The behavioral characterization of the VDR knock-out (VDR-KO) mouse revealed changes consistent with diminished musculoskeletal development and motor impairment (reduced stride length, hyperlocomotion, and reduced habituation in the open field test) (Burne et al., 2005). While some studies reported no observed impairments in working memory or anxiety in the VDR-KO model (Burne et al., 2005), others showed anxiety-like behavior and behavioral impairment (Kalueff et al., 2004, 2006). In embryonic animal models, vitamin D deficiency during fetal development resulted in morphological brain changes (Eyles et al., 2003), motor impairments (Burne et al., 2004) and memory and learning impairments (McGrath et al., 2003; Becker et al., 2005).

While in vitro and animal models suggest neuroprotective benefits from vitamin D upon exposure, there are inconsistencies in the clinical literature related to vitamin D and cognitive function in the elderly. In a small case control study ($n = 84$) in subjects in the Tromso study, participants with secondary hyperparathyroidism (SHPT) ($n = 21$) performed worse on cognitive tests associated with working memory (digit span) (Wechsler, 1987), processing speed (Stroop test) (Golden, 1978), language (controlled oral word association) (Spreen and Strauss, 1998) and mood (Becks Depression Inventory) compared to subjects without SHPT ($n = 63$). While the authors also revealed that low serum 25(OH)D concentrations were significantly associated with mood, they were unable to detect an association with 25(OH)D and cognitive function; this may in large part be due to the limited cognitive battery implemented as well as the small sample size under study.

In a much larger cross-sectional investigation of NHANES III data, McGrath et al. found no association between 25(OH)D and cognitive function in adolescence (16–19 years) and adults (20–59 years), but revealed an inverse association between 25(OH)D and a test of learning and memory in older adults (60–90 years) (McGrath et al., 2007). This finding was somewhat surprising, but should be carefully evaluated in the context of the detected difference. Subjects in the highest quintile of vitamin D had the lowest score on this test (6.4 (0.1), compared to scores in the lowest quintile (6.5 (0.1) ($n = 4809$). This detected difference is very small and the clinical relevance is questionable. Additionally, the evaluation of an association between 25(OH)D and one test of cognition is not representative of cognitive function.

More recent positive associations between vitamin D and cognitive function in older adults have been revealed. In a cross-sectional study of eighty ambulatory elders (40 with mild dementia and 40 non-demented elders >60 years), Wilkins et al. reported that vitamin D deficiency (<50 nmol/L) was associated with poorer performance on global tests of cognitive function such as the Short Blessed Test (Katzman et al., 1983) and a higher score (indicative of poorer cognition) on the Clinical Dementia Rating Sum of Box Scores (CDR) (Morris, 1993) (Wilkins et al., 2006). The authors were not able to detect an association with vitamin D and the cognitive factor score, which is likely due to the small sample size under study (Wilkins et al., 2006). Another positive association between vitamin D and a measure of global cognition was reported by Pryzbesky et al. In a retrospective chart review of 32 subjects over 60 years of age that were being evaluated in a memory clinic, the authors reported positive correlations between 25(OH)D concentrations and performance on the Mini-Mental State Examination (MMSE) ($r = 0.23$; $P = 0.01$) (Przybelski and Binkley, 2007).

In the cases above, the studies were limited in the sample size as well as the outcome evaluation tools used to explore 25(OH)D and cognitive function in older adults. For example, McGrath et al. evaluated cognition in the elderly group using only one cognitive tool, a learning and memory tool. Given the preponderance of evidence of vitamin D in hippocampal health, a more sophisticated cognitive evaluation battery designed to evaluate multiple facets of cognitive performance is necessary. While the study by Jorde et al. had a more detailed cognitive battery, the study was limited by its size ($n = 84$). Additionally, the authors did not adjust for multiple testing in their analyses and are thereby limited in the interpretation of their findings.

Contrary to the findings in the NHANES III and Tromso study, and consistent with the findings from Wilkins et al. and Przybelski et al., we recently found a positive association between 25(OH)D and cognitive function. Using data from the NAME study, (Scott et al., 2006), a large cross-sectional study ($n = 1200$) with a comprehensive neuropsychological battery, 25(OH)D was associated with both global and specific aspects of cognitive function (Buell et al., in preparation). These associations were not consistent across all cognitive domains. Our results showed positive associations between 25(OH)D and primarily measures of executive functioning. These findings suggest that 25(OH)D may play a role in subcortical health and are consistent with vasculoprotective mechanisms of vitamin D. Further, these results may help to explain the null association with 25(OH)D and cognition in the earlier studies (Jorde et al., 2006; McGrath et al., 2007) and help elucidate a potential mechanism through with vitamin D may exert neuroprotective effects.

8. Vitamin D and brain morphology

To date, we are not aware of any published findings of 25(OH)D and morphological measures in humans without schizophrenia. In our analyses of the NAME study, after adjusting for intracranial volume, there were no observed associations between vitamin D concentrations and hippocampal or amygdala volume (Buell et al., in preparation). However, we did

observe an inverse association between 25(OH) D concentration and presence of white matter hyperintensities and large vessel infarcts; indicators of cerebrovascular disease (Buell et al, in preparation). Consistent with this finding, we observed a positive association between vitamin D concentrations and the integrity and structural arrangement of white matter fibers using diffuser tensor imaging. Further studies designed to provide information on the temporal relationship of 25(OH)D and brain morphology are warranted.

9. Conclusions

While the extent to which vitamin D deficiency and cognitive function are related remains unclear, the biological plausibility of this relationship is well supported. The quality of life of aging individuals depends profoundly on functional capacity and dementia is one of the most common causes of institutionalization, morbidity, and mortality among the elderly.

The benefits of vitamin D on physical function in elders are well established. Vitamin D enhances skeletal integrity, muscle strength, as is associated with a reduction in falls and fractures. In addition to the physical benefits; the neurocognitive benefits of vitamin D are becoming clearer. The presence of VDR protein and catabolic enzymes in the parts of the brain most vulnerable to aging is compelling. The growing evidence of clinical associations between vitamin D status and both global and specific areas of cognitive function is of great importance. The potential modulation of risk factors and pathologic processes in vascular dementia and Alzheimer's disease underscore the importance of vitamin D status in the elderly.

Nutritional deficiencies in the elderly are common. Despite fortification, nutritional inadequacies in elders continue to be a problem (Posner et al., 1987; Buell et al., 2007). The elderly population is particularly at risk for vitamin D insufficiency because of sunlight deprivation, in addition to other age-associated risk factors for vitamin D insufficiency, such as, inadequate nutriture, age-related dermatological changes, and impairments in renal function.

Worldwide studies of vitamin D status in healthy community dwellers have shown that 40–100% of elders have vitamin D inadequacy (Chapuy et al., 1997; Holick, 2006) and these elders usually have year-round insufficient concentrations (Bhattoa et al., 2004).

While there are currently no standards for optimal vitamin D concentrations, concentrations $\geqslant$75 nmol/L are recommended to optimize skeletal health. Without adequate sun exposure, dietary intakes of at least 800–1000 IU are necessary to achieve this concentration (Dawson-Hughes et al., 2005; Bischoff-Ferrari et al., 2006), and intakes this high are rarely seen in elders. In a cross-sectional investigation of over 1000 community dwelling elders in Boston, MA, fewer than 10% of non-supplement users, had vitamin D intakes greater than 400 IU and fewer than 5% had intakes over 600 IU/day (Buell et al., in preparation).

The health care costs and public health burden of institutionalization of the elderly are significant. Current estimates are that those $\geqslant$85 years have the highest risk for dementia and represent the fastest growing segment of the population. U.S. Census Bureau estimates that nearly 19 million Americans will be age 85 by 2050 and over half of those will have some form of dementia (Evans, 1990). The prevalence of Alzheimer's disease is even higher in offspring of parents with the disease. A recent report in Archives of Neurology revealed a prevalence of AD in children when both parents have had AD of 31% in those over 60 and 42% in those over 70 years (Jayadev et al., 2008). The costs associated with care of dementia are staggering with annual national direct and indirect costs estimated to be as high as $100 billion (Ernst and Hay, 1997).

The need for well designed longitudinal investigations of vitamin D and cognitive function are critical. The aging global population and escalating healthcare costs impose a sense of urgency for cost-effective interventions. If these current positive associations are validated, maintenance of adequate vitamin D concentrations would prove a cost-effective means to mediate cognitive dysfunction and delay institutionalization; significantly off-setting healthcare costs.

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