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Vitamin D and Age-Related Health Outcomes: Movement, Mood, and Memory

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Abstract

It has long been recognized that vitamin D plays an important role in calcium homeostasis and musculoskeletal health. More recent evidence supports a role of vitamin D in physical and cognitive function and depressive symptoms through direct effects on skeletal muscle and the brain as well as indirectly through its reported roles in chronic conditions such as cardiovascular disease and diabetes, conditions that frequently lead to declines in physical and cognitive function and depressed mood. The purpose of this review is to summarize the prospective cohort and randomized controlled trial evidence for vitamin D on physical and cognitive function and depressed mood in older adults. Results from both prospective cohort studies and randomized controlled trials of vitamin D supplementation are mixed. Thus, controversy remains over the optimal vitamin D concentration for physical and cognitive function and depressed mood and whether vitamin D supplementation is beneficial for these outcomes.

Keywords

Vitamin D; 25-hydroxyvitamin D; Physical function; Physical performance; Muscle strength; Mobility; Depressive symptoms; Depressed mood; Cognitive function; Dementia; Alzheimer's disease; Older adults

Introduction

It has long been recognized that vitamin D plays an important role in calcium homeostasis and musculoskeletal health. In the past two decades, it has become evident that the role of vitamin D extends beyond calcium homeostasis and musculoskeletal health with low 25-hydroxyvitamin D [25(OH)D], the accepted measure of vitamin D status, being associated with an increased risk of co-morbid conditions including cardiovascular disease, diabetes, hypertension, osteoarthritis, and inflammatory conditions [1], conditions that are also related to the development of physical and cognitive limitations. A large number of tissues have

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Compliance with Ethics Guidelines

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vitamin D receptors (VDRs) and are able to convert 25(OH)D to the active metabolite, 1,25-dihydroxyvitamin D [1,25(OH)₂D], indicating an autocrine or paracrine role [2].

The major source of vitamin D is exposure to sunlight with efficiency of the conversion of 7-dehydrocholesterol to vitamin D₃ dependent on season, latitude, time of day, skin pigmentation, sunscreen use, cloud cover, pollution, and age [1]. There are few naturally occurring foods that are good sources of vitamin D – fatty fish such as salmon, tuna, and mackerel, beef liver, and egg yolks. In the U.S., fortified foods such as vitamin D fortified milk are the major dietary source of vitamin D [3]. The current recommended dietary allowance (RDA) for adults aged >70 years is 800 IU/day [4•]. However, data from the 2005–2006 National Health and Nutrition Examination Surveys (NHANES) show that adults aged >70 years consume an average of 200 IU/day from food alone and only 400 IU/day from food and supplements combined [5].

The Institute of Medicine (IOM) recently concluded that 25(OH)D concentrations 20 ng/mL was adequate for bone (to convert to nmol/L, multiply by 2.496), but that there was insufficient scientific evidence to support recommendations for non-bone health outcomes [4•]. However, others have suggested that 25(OH)D concentrations of 30 ng/mL or greater be maintained for health outcomes other than bone [6, 7, 8•]. Low 25(OH)D is common in older adults with approximately one-third of community-dwelling adults aged >70 years having 25(OH)D concentrations <20 ng/mL in the most recent NHANES data (2001–2006) [9]. Both behavioral and physiological changes associated with aging put older adults at risk of low 25(OH)D including low dietary intake, reduced exposure to sunlight, and reduced efficiency of cutaneous vitamin D synthesis [10].

With a growing older population, there is an increasing need to identify potentially modifiable risk factors for the onset of limitations in physical and cognitive function and depressed mood. Many cross-sectional studies have examined the role of vitamin D on physical function, depressed mood, and cognitive function in older adults and found that low 25(OH)D concentrations are associated with lower physical performance and muscle strength, impaired mobility and disability, depressed mood, and impaired cognitive function [11–16]. However, it is difficult to rule out the potential for reverse causality in cross-sectional studies as impaired physical and cognitive function and depressed mood may lead to behaviors predisposing individuals to low 25(OH)D concentrations, such as limited outdoor activity and poor dietary intake. Thus, the purpose of this review is to summarize the evidence from prospective (i.e., longitudinal) cohort studies (Table 1) and randomized, controlled trials (RCTs; Table 2) regarding the potential role of vitamin D on physical function and mobility, depressed mood, and cognitive function in community-dwelling older adults (mean age at baseline, 60 years).

Physical Function and Mobility

The prevalence of physical limitations increases with age. Recent evidence supports a role of vitamin D in physical performance and strength through both direct effects on muscle function [17, 18], as well as indirectly through its reported roles in diabetes, hypertension, cardiovascular disease, chronic obstructive pulmonary disease, and osteoarthritis [1],

conditions that frequently lead to declines in physical performance and strength. Vitamin D receptors (VDRs) have been identified in skeletal muscle [19], and VDR gene polymorphisms have been associated with muscle strength [20–22]. Vitamin D metabolites have been shown to affect muscle metabolism by influencing calcium uptake, phosphate transport across the cell membrane, phospholipid metabolism, initiation of myogenesis, and muscle cell proliferation, differentiation and apoptosis [18, 19, 23•].

Various physical function measures have been used to assess physical performance in prospective cohort studies of vitamin D. Two of the more common global physical performance measures are the Timed Up and Go (TUG; time to rise from a chair, walk 3 m, and return to a sitting position [24]) and the Short Physical Performance Battery (SPPB; ability to stand in progressively more challenging positions: side-by-side, semi-tandem, and full-tandem, timed 4-m walk, and time to complete 5 chair stands [25]) or variations of these measures. Several studies have included measures of upper (grip) and lower (knee extensor/quadriceps) body strength. Measures of body sway to assess balance have also been assessed in some studies.

Prospective cohort studies examining 25(OH)D concentrations and change in physical performance and strength have been inconsistent. Several studies have shown greater declines in or worse physical performance and strength over time with lower 25(OH)D concentrations [26–29]. In the Longitudinal Aging Study Amsterdam (LASA-I), older adults with 25(OH)D concentrations <20 ng/mL had a two-fold or greater decline in physical performance at 3-year follow-up compared with those with 25(OH)D ≥30 ng/mL [26]. Older women, but not men, in the Rancho Bernardo Study with 25(OH)D concentrations <30 ng/mL had three-fold greater declines in physical performance than those with 25(OH)D ≥30 ng/mL over 2.5 years of follow-up [27]. Among older black and white men and women in the Health, Aging, and Body Composition (Health ABC) cohort and older women in the Women's Health Initiative Calcium and Vitamin D (WHI CaD) trial, those with lower 25(OH)D concentrations had worse physical performance at every time point measured over 4 and 6 years of follow-up, respectively; however, lower 25(OH)D concentrations were not associated with an increased rate of decline in physical performance [28, 29].

Other studies, however, have not found an association between vitamin D and physical performance and strength over time [30–34]. In the Women's Health and Aging Study (WHAS) cohort of frail older women there was no association between 25(OH)D concentrations and physical performance or strength over 3 years of follow-up [30]. In the Invecchiare in Chianti (InCHIANTI) study, 25(OH)D was not associated with change in physical performance (–1 point decline on SPPB) in older adults at 3-year follow-up [32]. Among older women in the Study of Osteoporotic Fractures (SOF), 25(OH)D concentrations were not associated with change in physical performance or strength [31]. There was also no association between 25(OH)D concentrations and physical performance among older Chinese men at 4-year follow-up [33]. Although lower 25(OH)D concentrations were associated with greater decline in physical performance in the older (mean age, 75.3 years) LASA-I cohort [26], 25(OH)D concentrations were not associated

with decline in physical performance among the younger (mean age, 60 years) LASA-II cohort over 6 years of follow-up [34].

Low 25(OH)D concentrations have also been associated with incident mobility limitation and disability (e.g., self-reported difficulty walking various distances and up steps). In the Cardiovascular Health Study (CHS) All Stars cohort (mean age, 85.2 years), 25(OH)D concentrations <20 ng/mL were associated with increased risk of mobility limitation over 3 years of follow-up compared to 25(OH)D concentrations ≥30 ng/mL [35]. In the Health ABC cohort (mean age, 74.6 years), 25(OH)D concentrations of <20 and 20 to <30 ng/mL were associated with increased risk of mobility limitation and 25(OH)D concentrations <20 ng/mL were associated with increased risk of mobility disability over 6 years of follow-up compared to 25(OH)D concentrations ≥30 ng/mL [36]. In the LASA-I and LASA-II cohorts, 25(OH)D concentrations <20 ng/mL were associated with greater risk of decline in physical function among the younger cohort (mean age, 60 years) over 6 years of follow-up and the older cohort (mean age, 75.3 years) over 3 years of follow-up compared to 25(OH)D concentrations of ≥30 ng/mL [37]. However, there was no association between 25(OH)D concentrations and risk of physical disability in the WHAS cohort of frail older women [30].

The inconsistencies among these prospective cohort studies may stem from differences in baseline 25(OH)D concentrations and physical function, cut-offs used to define 25(OH)D, tests used to assess physical function, duration of follow-up, adjustment for potential confounders, and the heterogeneity of the study populations (men vs. women, age, US vs. European vs. Asian). Methods used to assess change in physical function also differed with some studies using a clinically relevant cutoff [26, 32, 34] and others examining continuous change over time [27–31, 33].

RCTs of vitamin D supplementation and physical performance and muscle strength in older adults have also been inconsistent [11, 38]. While some RCTs of vitamin D supplementation found improved physical performance with vitamin D supplementation [39, 40], others did not [41–45]. Vitamin D supplementation was also found to improve balance in some RCTs [39, 40, 46], but not in others [43]. Vitamin D supplementation has not been found to increase muscle strength in older adults [39–42, 44, 45]. In two RCTs, vitamin D supplementation was found to improve body sway and physical performance among those with the worst function at baseline [43, 44]. One RCT included both vitamin D₃ and calcium supplementation with or without resistance training and found an additive effect of vitamin D supplementation on physical performance among those in the resistance training group [47]. In a small pilot RCT of mobility limited older women with 25(OH)D concentrations of 9–24 ng/mL, vitamin D₃ supplementation increased intramyonuclear VDR concentration and total (type I and type II) muscle fiber size over 4 months [48].

The discrepancies among these RCTs may be the result of differences in the study population characteristics and baseline 25(OH)D concentrations, inadequate vitamin D dose (<800 IU/day), and inadequate trial duration (<6 months). The vitamin D supplementation regimen varied by type of vitamin D (cholecalciferol, D₃, vs. ergocalciferol, D₂), frequency of dosing (daily, weekly, every 3 months, once), and whether vitamin D was combined with calcium and compared to calcium alone or to a placebo. Furthermore, in several RCTs

physical function measures were secondary outcomes in trials primarily designed to examine the effect of vitamin D supplementation on falls and fractures [40, 42, 44, 45].

Depressive Symptoms and Depressed Mood

Depression is associated with increased risk of chronic conditions and decreased physical and cognitive function in older adults, with more than half experiencing their first episode of depression in late life [49]. Among community-dwelling older adults, the prevalence of major depression has been estimated to range from 1–5 % while the prevalence of clinically significant depressive symptoms is approximately 15 % [49]. Both increasing age and female gender increase the risk of major depression and depressive symptoms.

A growing body of literature suggests that low 25(OH)D concentrations may be associated with depression in later life. Vitamin D receptors (VDR) and the enzyme involved in converting 25(OH)D to the active metabolite, 1,25(OH)₂D, have been found in areas of the brain known to be associated with mood regulation [50]. VDR gene polymorphisms have been associated with depressive symptoms [51, 52]. Vitamin D has been shown to play a role in neuroimmunomodulation, neurotrophic signaling, and neuroprotection [53, 54].

Prospective cohort studies have examined the association between 25(OH)D concentrations and depressed mood using both the Center for Epidemiological Studies Depression scale (CES-D [55]) and the Geriatric Depression Scale (GDS [56]) to assess depressive symptoms and ICD-9 codes to assess clinical diagnoses of depression. Three of the five prospective studies demonstrated greater increases in depressive symptoms or onset of depression in participants with low 25(OH)D concentrations [57–59]. In the InCHIANTI study, women, but not men, with 25(OH)D concentrations <20 ng/mL had greater increases in CES-D scores and were at greater risk of developing depressed mood (CES-D 20 score 16) compared to those with 25(OH)D concentrations ≥20 ng/mL [57]. In the Health ABC cohort, older black men and women with 25(OH)D concentrations <20 ng/mL had the greatest increases in CES-D scores and were also at greater risk of developing depressed mood (CES-D 10 score 10 or antidepressant medication use) over 4 years of follow-up compared to those with 25(OH)D concentrations ≥30 ng/mL [58]. Among older cardiovascular disease patients, those with 25(OH)D concentrations <30 ng/mL were at greater risk of having a clinical diagnosis of depression compared to those with 25(OH)D concentrations ≥50 ng/mL over a maximum of 6.6 years of follow-up [59]. However, among older Chinese men, there was no association between 25(OH)D concentrations and depression (GDS score 8) at 4-year follow-up [60]. Similarly, there was no association between 25(OH)D concentrations and depression (GDS score 8) over 4.4 years of follow-up in older adults in the *Progetto Veneto Anziani* (Pro.V.A.) cohort [61].

Only one prospective study examined the association between dietary intake of vitamin D and depressive symptoms. In the Women's Health Initiative (WHI) Observational Study, older women who consumed ≥400 IU/day of vitamin D from food sources had a 20 % lower risk of depressive symptoms (Burnam score 0.6 [62]) at 3-year follow-up compared to those who consumed <100 IU of vitamin D [63]. However, there was no association

between vitamin D from supplements or total vitamin D intake from food and supplements combined and depressive symptoms.

Few RCTs have investigated the effects of vitamin D supplementation on risk of onset of depressive symptoms in older adults [64]. In a small subset of the Vital D study of older women randomized to a large annual dose of vitamin D₃ or placebo, there were no differences in WHO Well-Being Index scores or onset of depression (WHO Well-Being Score Index score <13 [65]) over 3 to 5 years of follow-up by treatment group [66]. Among older women in the WHI CaD trial, randomization to calcium and vitamin D₃ was not associated with depressive symptoms (Burnam score = 0.6) or change in depressive symptom scores over 2 years of follow-up compared to placebo [67]. However, personal supplementation of calcium (1000 mg/day) and vitamin D (600 IU/day) was allowed which may have blunted differences between the treatment groups and the vitamin D₃ dose used in the intervention (400 IU/day) was low.

The inconsistencies among these prospective studies could be due to differences in baseline 25(OH)D concentrations and depressive symptoms, cut-offs used to define 25(OH)D as well as depressive symptoms, tests used to assess depressive symptoms, duration of follow-up, and adjustment for potential confounders, and the heterogeneity of the study populations (men vs. women, age, US vs. European vs. Asian). RCTs are also difficult to compare due to differences in doses of vitamin D₃ being tested and frequency of dosing (annual vs. daily), baseline 25(OH)D status, and duration of the intervention. Furthermore, depressive symptoms were secondary outcomes in trials primarily designed to examine the effect of vitamin D supplementation on falls [66] and fractures [66, 67].

Cognitive Function and Dementia

With the aging of the population, the prevalence of cognitive impairment and dementia, the decline in at least two cognitive domains (e.g., memory, language, attention, or learning) that affects a person's ability to perform everyday activities, have increased. The estimated prevalence of Alzheimer's disease (AD), the most common form of dementia, is currently 5 million older Americans and is projected to affect nearly 14 million older Americans by 2050 [68]. Advancing age is the strongest risk factor for cognitive decline and dementia.

Recent evidence suggests a potential beneficial role of vitamin D in maintaining cognitive function. Vitamin D receptors (VDR) and the enzyme involved in converting 25(OH)D to the active metabolite 1,25(OH)₂D, have been found in the brain, including the hippocampus [50]. VDR gene polymorphisms have been associated with cognitive function and AD [51, 69–71]. Vitamin D has also been shown to have a neuronal protective effect by inhibiting inducible nitric oxide synthase, enhancing antioxidant pathways, upregulating neurotrophin factors, and promoting calcium homeostasis [72]. Vitamin D may also indirectly affect cognitive function, and, in particular, vascular-related dementia, as vitamin D has been shown to be associated with cardiovascular and cerebrovascular disease [73].

Prospective cohort studies examining the association between 25(OH)D concentrations and decline in cognitive function have used a variety of cognitive tests to assess global cognitive function (Mini-Mental State Examination (MMSE) [74]) and Modified Mini-Mental State

Examination (3MS [75])) as well as specific cognitive domains including executive function and processing speed (Trails Making Test Part B (Trails B) and Digit Symbol Substitution Test (DSST)), executive function and language (Word Fluency Test (WFT)), and verbal learning and memory (Delayed Word Recall Test (DWRT)). Four of the six prospective studies have demonstrated greater cognitive decline over time in participants with low 25(OH)D concentrations [76–79]. In the InCHIANTI cohort of older adults followed over 6 years, 25(OH)D concentrations <10 ng/mL were associated with greater odds of decline in the MMSE (3 points) and Trails B (lowest 10 % of decline or discontinued testing) compared to those with 25(OH)D concentrations 30 ng/mL [76]. Among older women in the SOF cohort, those with 25(OH)D concentrations <20 ng/mL had greater odds of decline in the MMSE (2.9 points) at 4-year follow-up, but not with Trails B (>1 SD of the sample mean change), compared to those with 25(OH)D concentrations 30 ng/mL [77]. In the Pro.V.A. cohort, those with 25(OH)D concentrations <30 ng/mL had greater odds of decline in the MMSE (3 points) over 4.4 years of follow-up compared to those with 25(OH)D concentrations 30 ng/mL [78]. Among older black and white adults in the Health ABC cohort, those with 25(OH)D concentrations <30 ng/mL had greater declines in the 3MS score, but not the DSST score, over 4 years of follow-up compared to those with 25(OH)D concentrations 30 ng/mL [79].

However, other prospective studies have not found an association between 25(OH)D concentrations and cognitive function [80, 81]. In the Osteoporotic Fractures in Men (MrOS) Study, there was no association between 25(OH)D concentrations and decline in 3MS (score <80 or a decline of 5 points) or Trails B (>1 SD of the sample mean change) in older men over 4.6 years of follow-up [80]. Among middle aged and older black and white adults, 25(OH)D concentrations were not associated with declines in DSST, WFT, or DWRT over 3 and 10 years of follow-up in the Atherosclerosis Risk in Communities (ARIC) Brain MRI Study [81].

Several prospective cohort studies have also examined the association between vitamin D and clinical diagnoses of dementia and AD [81–84]. Among older women who were not taking vitamin D supplements at baseline in the Epidemiologie de l'Osteoporose (EPIDOS) Toulouse cohort, those with higher vitamin D intake had a lower odds of developing AD, but not other dementias, at 7-year follow-up [82]. However, the mean reported vitamin D intake was higher than that typically reported in older adults (333.8 ± 171.9 IU/day). In a small subset of the EPIDOS Toulouse cohort with measured serum 25(OH)D, older women with 25(OH)D concentrations <10 ng/mL were at greater odds of developing other dementia, but not AD, at 7-year follow-up compared to those with 25(OH)D concentrations 10 ng/mL [83]. Using data from CHS, older adults free of cardiovascular disease at baseline with 25(OH)D concentrations <20 ng/mL had an increased risk of both dementia and AD over 5.6 years of follow-up [84]. However, in the ARIC Brain MRI Study, 25(OH)D concentrations were not associated with hospitalization for dementia among middle aged and older black and white adults over a median 16.6 years of follow-up [81].

The discrepancies among these prospective cohort studies could be due to differences in baseline 25(OH)D concentrations and cognitive function, cut-offs used to define 25(OH)D as well as declines in cognitive function, tests used to measure cognitive function (global

cognitive functions and/or tests to assess specific cognitive domains), duration of follow-up, and adjustment for potential confounders, and the heterogeneity of the study populations (men vs. women, age, US vs. European). Determination of cases of dementia and AD also varied with some studies adjudicating cases based on clinical criteria [82, 84] and others using medical records [81]. There may also be differences in the cognitive domains affected by vitamin D [72].

To date, only one randomized clinical trial has examined the effect of vitamin D supplementation on cognitive function in community-dwelling older adults. Among older women in the WHI CaD trial who also participated in WHI Memory Study (WHIMS), randomization to calcium and vitamin D₃ was not associated with decreased risk of cognitive impairment (defined as probable dementia or mild cognitive impairment based on clinical criteria) or with 3MS or domain-specific cognitive function over 8 years of follow-up compared to placebo [85]. However, this population was not vitamin D deficient at baseline, personal supplementation of calcium (1000 mg/day) and vitamin D (600 IU/day) was allowed which may have blunted differences between the treatment groups, there were few cases of cognitive impairment, and the vitamin D₃ dose (400 IU/day) used in the intervention was low. Furthermore, the WHI CaD trial was primarily designed to examine the effect of vitamin D supplementation on fractures.

Conclusions

In summary, prospective cohort studies examining the role of vitamin D on physical function, depressive symptoms/depressed mood, and cognitive function have found both no association as well as greater declines or onset of impaired physical and cognitive function and depressed mood with lower 25(OH)D concentrations. The inconsistencies across studies likely stem from differences in baseline 25(OH)D concentrations and physical and cognitive function and depressive symptoms, cut-offs used to define vitamin D status as well as declines in physical and cognitive function and depressed mood, tests used to measure physical and cognitive function and depressive symptoms, duration of follow-up, adjustment for potential confounders, and the heterogeneity of the study populations (men vs. women, young old vs. older old, US vs. European vs. Asian). Attrition in these studies may have also resulted in generally healthier analytical samples which could potentially bias the results towards the null. Another limitation of these studies is that, with the exception of the Health ABC and ARIC Brain MRI cohorts [29, 36, 81], participants were primarily Caucasian.

Although the IOM concluded that 25(OH)D concentrations 20 ng/mL is adequate for bone health [4•], others have suggested that the optimal 25(OH)D concentration for health conditions other than bone may indeed be higher [6, 7, 8•]. Among older women in the Rancho Bernardo Study, physical performance increased up to 25(OH)D concentrations of 32 ng/mL [27]. In the Health ABC cohort, physical performance and strength were higher in older adults with 25(OH)D concentrations up to approximately 28–32 ng/mL depending on the measure assessed and then leveled off [29]. The 25(OH)D concentration observed to be associated with increased risk of impaired physical [26, 35–37] and cognitive [76–78, 84] function and depressed mood [57–59] has varied across studies from 20 ng/mL to 30 ng/mL.

Thus, the controversy over the “optimal” 25(OH)D concentration for physical and cognitive function and depressed mood continues.

While some, but not all, RCTs found positive effects of vitamin D supplementation on physical function, the few RCTs of vitamin D supplementation and depressive symptoms/depressed mood and cognitive function did not find a treatment effect. The discrepancies among these RCTs may be the result of differences in the study population characteristics and baseline 25(OH)D concentrations and inadequate vitamin D dose and trial duration. The vitamin D supplementation regimen also varied across trials by type of vitamin D (vitamin D₃ vs. vitamin D₂), frequency of dosing (e.g., daily, weekly, annually), and whether vitamin D was combined with calcium and compared to calcium alone or to a placebo. Many of the RCTs examining physical function, and all of those examining depressive symptoms/depressed mood and cognitive function, were trials primarily designed to examine the effect of vitamin D supplementation on falls and fractures.

Thus, clinical trials designed to determine whether vitamin D supplementation can slow or prevent declines in physical and cognitive function and depressive symptoms/depressed mood are needed to make evidence-based recommendations on vitamin D supplementation for these important health outcomes in older adults. There are several ongoing trials such as the Vitamin D and Omega-3 Trial (VITAL, *n*= 25,875; [86]) and DO-HEALTH (vitamin D, omega-3 fatty acids, and a home-based exercise program; <http://do-health.eu/wordpress/>; *n*=2158) that include either primary or secondary outcomes related to physical and cognitive function and depression that will help guide future vitamin D recommendations.

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Table 1

Description of published prospective cohort studies of vitamin D and physical function, depressed mood, and cognitive function in older adults

First author, year (ref)	Country	No. of participants (% female)	Age range (mean age)	Population; baseline year	Follow-up duration	Vitamin D exposure	Outcome measures: overall prevalence	Main findings
Physical function and mobility								
Verreault, 2002 (30)	USA	628 (100 %)	65 years	WHAS; the one-third most disabled older women living in the community; 1992–95	3 years of follow-up	Serum 25(OH)D: <10 ng/mL 10–<21 ng/mL 21 ng/mL	Change in physical performance: lower extremity muscle strength, grip strength, walking speed over 4 m, time to complete 5 chair stands Disability: reported difficulty: walking one-fourth mile, across a small room, up 10 steps without resting; getting in/out of bed/chair; raising arms over head; using fingers to grasp/handle; lifting/carrying 10 lbs	Adjusted rates of decline in physical performance were similar by 25(OH)D group (all $p>0.10$). No significant increase in risk of new disability over 3 years of follow-up by 25(OH)D group (all $p>0.05$).
Faulkner, 2006 (31)	USA	389 (100%)	65 years	SOF subset: community-dwelling older women; 1986–88	Average of 2.2- and 3.7-year follow-up	Serum 25(OH)D quartiles: <20 ng/mL 20–25 ng/mL 26–31 ng/mL 32 ng/mL	Change in neuromuscular function: grip strength, time to complete 5 chair stands, 6-m gait speed, and balance-walk time ($n=264–303$)	Serum 25(OH)D was not associated with change in neuromuscular function (all p -values >0.05).
Wicherts, 2007 (26)	Netherlands	1234 (51.4%)	65 years 75.3 years	LASA-I: random age- and sex-stratified sample; 1995–96	3-year follow-up	Serum 25(OH)D: <10 ng/mL 10–20 ng/mL 20–30 ng/mL 30 ng/mL	Clinically significant decline in physical performance	Adjusted OR (95% CI) vs. 25(OH)D 30 ng/mL ($n=979$):

First author, year (ref)	Country	No. of participants (% female)	Age range (mean age)	Population; baseline year	Follow-up duration	Vitamin D exposure	Outcome measures: overall prevalence	Main findings
Bartali, 2008 (32)	Italy	698 (54.4%)	65 years (73.7 years)	InCHIANTI: population-based study of community-dwelling older adults; 1998–2000	3-year follow-up	Serum 25(OH)D (lowest quartile vs. all others)	Decline of 1 point on the SPPB (standing balance in progressively more challenging positions - side-by-side, semi-tandem, and full-tandem, 4-m walk, time to complete 5 chair stands): 50.4%	Adjusted OR (95% CI) for lowest 25(OH)D quartile vs. upper three quartiles: 0.92 (0.63–1.36)
Dam, 2009 (27)	USA	1065 (61.6%)	(74.6 years)	Rancho Bernardo Study: surviving community-dwelling participants originally enrolled in 1972–74; 1997–99	~2.5-year follow-up (range 0.4 to 5 years)	Serum 25(OH)D sex-specific quartiles and clinical cutoffs: <30 vs 30 ng/mL <20 vs 20 ng/mL	Change in TUG (time to rise from a chair, walk 3 m, and return to a sitting position), time to complete 5 chair stands (TCS), and	In women, those with 25(OH)D <30 ng/mL had ~3-fold greater percent change in TUG and TCS compared to 30 ng/mL (25% vs. 8%,

First author, year (ref)	Country	No. of participants (% female)	Age range (mean age)	Population; baseline year	Follow-up duration	Vitamin D exposure	Outcome measures: overall prevalence	Main findings
Houston, 2011 (35)	USA	988 (64.5%)	77–100 years (85.2 years)	CHS All Stars (survivors of the CHS study); community-dwelling men and women; 2005–06	3 years	Serum 25(OH)D: <20 ng/mL 20–<30 ng/mL 30 ng/mL	grip strength () walking speed ()	$p<0.0001$). There was a 4-fold greater percent change in TUG and TCS in those with 25(OH)D <20 ng/mL compared to 20 ng/mL (39% vs. 10%). No significant associations were observed in men. Adjusted HR (95% CI) vs. 25(OH)D 30 ng/mL: <20 ng/mL: 1.56 (1.06–2.30) 20–<30 ng/mL: 0.83 (0.56–1.21)

First author, year (ref)	Country	No. of participants (% female)	Age range (mean age)	Population; baseline year	Follow-up duration	Vitamin D exposure	Outcome measures: overall prevalence	Main findings
Michael, 2011 (28)	USA	534 (100%)	50–79 years (70.3 years)	WHI CaD Trial: postmenopausal women with baseline measures of serum 25(OH)D and physical performance; 1993–98	1-, 3-, and 6-year follow-up	Serum 25(OH)D: <10 ng/mL 10–<20 ng/mL 20–<30 ng/mL 30 ng/mL	Change in physical function summary score (sum of the decile ranking for timed 6-m walk, number of chair stands in 15 s, and grip strength; $n=498-534$)	Over 6 years, participants with 25(OH)D 30 ng/mL had higher physical function scores ($p=0.01$). However, 25(OH)D was not associated with rate of change in physical function scores over follow-up (time*serum 25 (OH)D, $p=0.85$).
Houston, 2012 (29)	USA	2641 (51.1%)	70–79 years (74.7 years)	Health ABC: population-based study of well-functioning community-dwelling older adults; 1997–98	2- and 4-year follow-up	Serum 25(OH)D: <20 ng/mL 20–<30 ng/mL 30 ng/mL	Change in SPPB, Health ABC PPB (SPPB with addition of one leg stand and 6-m narrow walk), usual walking speed over 20 m, walking endurance over 400 m, knee extensor strength, and grip strength ($n=2307$)	Participants with 25(OH)D <20 ng/mL had worse SPPB, Health ABC PPB, 20-m and 400-m gait speed, but not knee extensor or grip strength, at baseline, 2- and 4-year follow-up compared to 25(OH)D 30 ng/mL ($p<0.05$). Except for SPPB, 25(OH)D was not associated with the rate of change in physical performance or gait speed (time*serum 25(OH)D, $p=0.20$).

First author, year (ref)	Country	No. of participants (% female)	Age range (mean age)	Population; baseline year	Follow-up duration	Vitamin D exposure	Outcome measures: overall prevalence	Main findings
Chan, 2012 (33)	Hong Kong	939 (0%)	65 years (72.8 years)	Community-dwelling older men; 2001–03	4-year follow-up	Serum 25(OH)D (continuous)	Change in grip strength, time to complete 5 chair stands, and 6-m walk (n=714)	Serum 25(OH)D was not associated with change in physical performance (all $p>0.10$).
Houston, 2013 (36)	USA	2099 (47.9%)	70–79 years (74.6 years)	Health ABC: population-based study of well-functioning community-dwelling older adults; 1997–98	6 years of follow-up	Serum 25(OH)D: <20 ng/mL, 20–30 ng/mL, >30 ng/mL	Incident mobility limitation and disability (two consecutive reports of having any/severe difficulty walking up 10 steps or walking half a mile assessed every 6 months): mobility limitation = 36.3%, mobility disability = 22.0%	Adjusted HR (95% CI) vs. 25(OH)D 30 ng/mL: Mobility limitation: <20 ng/mL: 1.29 (1.04–1.61) 20–<30 ng/mL: 1.27 (1.05–1.53) Mobility disability: <20 ng/mL: 1.93 (1.32–2.81) 20–<30 ng/mL: 1.30 (0.92–1.83)
Sohl, 2013 (34)	Netherlands	707 (53.6%)	55–65 years (60.0 years)	LASA-I & II: random age- and sex-stratified sample; 2002–03 (younger cohort)	3- and 6-year follow-up	Serum 25(OH)D: <20 ng/mL, 20–30 ng/mL, >30 ng/mL	Clinically significant decline in physical performance (time to walk 3 m, turn 180°, and walk back; time to complete 5 chair stands; and tandem stand) based on Edwards-Nunnally Index	Adjusted OR (95% CI) vs. 25 (OH)D >30 ng/mL: At 3 years (n=639): <20 ng/mL: 3.4 (0.7–16.0) 20–30 ng/mL: 2.1 (0.4–10.2) At 6 years (n=561): <20 ng/mL: 1.4 (0.5–3.7) 20–30 ng/mL: 1.3 (0.5–3.6)
Sohl, 2013 (37)	Netherlands	1237 (51.4%) 725 (53.9%)	65–88 years (75.3 years) 55–65 years (60.0 years)	LASA-I & II: random age- and sex-stratified sample; 1995–96 (older cohort) and 2002–03 (younger cohort)	3- and 6-year follow-up	Serum 25(OH)D: <20 ng/mL, 20–30 ng/mL, >30 ng/mL	Decline in function (having at least 2 more limitations than at	Adjusted OR (95% CI) in older cohort vs. 25(OH)D >30 ng/mL;

First author, year (ref)	Country	No. of participants (% female)	Age range (mean age)	Population; baseline year	Follow-up duration	Vitamin D exposure	Outcome measures: overall prevalence	Main findings
Depressive symptoms and depressed mood May, 2010 (59)	USA	7358 (58.8%)	50 years (73.1 years)	Cardiovascular patients with no history of depression, 2000–09	0–2500 days	Serum 25(OH)D: 15 ng/mL 16–30 ng/mL 31–50 ng/mL >50 ng/mL	Clinical diagnosis of depression (ICD-9 codes 296.2–296.36 and 311): 4.6%	Adjusted HR (95% CI) vs. 25(OH)D >50 ng/mL: 1.5 ng/mL: 2.70 (1.35–5.40) 16–30 ng/mL: 2.15 (1.10–4.21) 31–50 ng/mL: 1.95 (0.99–3.87)
								At 3 years (n=677) <20 ng/mL: 0.8 (0.3–1.8) 20–30 ng/mL: 0.7 (0.3–1.5) At 6 years (n=597) <20 ng/mL: 3.3 (1.1–10.1) 20–30 ng/mL: 2.9 (1.0–8.9)
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Milaneschi, 2010 (57)	Italy	954 (55.7%)	65 years (75.0 years)	InCHIANTI: population-based study of community-dwelling older adults; 1998–99	3- and 6-year follow-up	Serum 25(OH)D: Tertiles and clinical cut-offs: <20 ng/mL 20 ng/mL	Change in 20-item CES-D scale score (range 0–60) Depressed mood (CES-D	Among women, 3- and 6-year follow-up CES-D scores were 2.05 (p=0.02)

First author, year (ref)	Country	No. of participants (% female)	Age range (mean age)	Population; baseline year	Follow-up duration	Vitamin D exposure	Outcome measures: overall prevalence	Main findings
Bertone-Johnson, 2011 (63)	USA	56,366 (100%)	50–79 years	WHI OS: community-dwelling post-menopausal women; 1993–98	3-year follow-up	Dietary vitamin D intake (122-item food frequency questionnaire): <100 IU/day 100–<200 IU/day 200–<400 IU/day 400 IU/day Supplemental vitamin D: None <400 IU/day 400–<800 IU/day 800 IU/day	Depressive symptoms (Burnam 8-item scale for depressive disorders score 0.06; range 0–0.99); 6.2%	Adjusted OR (95% CI): Food sources (vs. <100 IU/day): 100–<200 IU/day: 0.86 (0.79–0.94) 200–<400 IU/day: 0.79 (0.71–0.88) 400 IU/day: 0.80 (0.67–0.95) Supplemental vitamin D (vs. none): <400 IU/day: 0.95 (0.84–1.06) 400–<800 IU/day: 1.02 (0.95–1.10)
							score 16); 43.6% in women (20.5% in men) 16); 43.6% in women (20.5% in men) 16); 43.6% in women (20.5% in men)	Houston, 2011 Among men, 3 and 6-year follow-up CES-D scores were 1.91 ($p=0.01$) and 1.07 ($p=0.20$) points higher in 25(OH)D <20 vs. 20 ng/mL. Adjusted HR (95% CI) of 25(OH)D <20 vs. 20 ng/mL ($n=639$): Women, 1.97 (1.22–3.17) Men, 1.61 (0.92–2.82)

First author, year (ref)	Country	No. of participants (% female)	Age range (mean age)	Population; baseline year	Follow-up duration	Vitamin D exposure	Outcome measures: overall prevalence	Main findings
Chan, 2011 (60)	Hong Kong	629 (0%)	65 years	Community-dwelling older men; 2001–03	4-year follow-up	Serum 25(OH)D: Quantiles and clinical cut-offs: <20 ng/mL 20–<30 ng/mL 30–<40 ng/mL 40 ng/mL	Depression (15-item GDS score 8): 4.1%	800 IU/day: 1.02 (0.83–1.25) 800 IU/day: 1.02 (0.83–1.25) 800 IU/day: 1.02 (0.83–1.25) Adjusted OR (95% CI) vs. 25(OH)D <20 ng/mL (n=604): 20–<30 ng/mL: 1.50 (0.16–14.56) 30–<40 ng/mL: 1.27 (0.13–12.89) 40 ng/mL: 2.27 (0.18–28.10) Depression (15-item GDS score 8): 4.1%
Toffanello, 2014 (61)	Italy	1675 (62.0%)	65 years (73.1 years)	Pro.V.A: population-based study of community-dwelling older adults; 1995–97	4.4-year follow-up	Serum 25(OH)D: <20 ng/mL 20–<30 ng/mL 30 ng/mL	Change in 30-item GDS score Depressive symptoms (30-item GDS score 11): 14.0% in women and 11.6% in men	Change in GDS scores were not significantly different by baseline 25 (OH)D status in women (p=0.15) or men (p=0.80). Adjusted HR (95% CI) vs. 25(OH)D 30 ng/mL: Women (n=661): <20 ng/mL: 0.74 (0.47–1.16) 20–<30 ng/mL: 0.54 (0.54–1.35) Men (n=521): <20 ng/mL: 0.96 (0.45–2.06) 20–<30 ng/mL: 1.08 (0.56–2.07)
Williams, 2014 (58)	USA	2598 (51.5%)	70–79 years (74.7 years)	Health ABC: population-based study of well-functioning community-	4-year follow-up	Serum 25(OH)D: <20 ng/mL 20–<30 ng/mL 30 ng/mL	Change in 10-item CES-D score	Mean increases in CES-D scores were 2.40,

First author, year (ref)	Country	No. of participants (% female)	Age range (mean age)	Population; baseline year	Follow-up duration	Vitamin D exposure	Outcome measures: overall prevalence	Main findings
Cognitive function and dementia	USA	1604 (0%)	65 years	MrOS: community-dwelling older men; 2000–02	4.6 years	Serum 25(OH)D quartiles (19.9, 20–25.09, 25.1–29.79, 29.8 ng/mL)	Depressive symptoms (CES-D score 10 or anti-depressant medication use); 26.9%	2.04, and 1.49 in 25(OH)D <20, 20–<30, and 30 ng/mL, respectively (p<0.001). Adjusted HR (95% CI) vs. 25(OH)D 30 ng/mL (n=2156): <20 ng/mL: 1.65 (1.23–2.22) 20–<30 ng/mL: 1.31 (0.99–1.74)
Slinin, 2010 (80)	USA	1604 (0%)	65 years	MrOS: community-dwelling older men; 2000–02	4.6 years	Serum 25(OH)D quartiles (19.9, 20–25.09, 25.1–29.79, 29.8 ng/mL)	Incident cognitive decline: 3MS score <80 or decline of 5 points (primary): 22.8% 1 SD (50.7 s) increase in time to complete Trails B (secondary): 8.0%	Adjusted OR (95% CI) vs. 25(OH)D =29.8 ng/mL): 3MS (n=1138): 19.9; 1.41 (0.89–2.23) 20–25.09; 1.28 (0.84–1.95) 25.1–29.79; complete Trails B 1.06 (0.70–6.62) Trails B (n=1053): 19.9; 1.08 (0.53–2.19) 20–25.09; 1.08 (0.57–2.04) 25.1–29.79; 0.96 (0.50–1.82)
Llewellyn, 2010 (76)	Italy	858 (56.8%)	65 years	InCHIANTI: population-based study of community-dwelling older adults; 1998	3- and 6-year follow-up	Serum 25(OH)D: <10 ng/mL 10–<20 ng/mL 20–<30 ng/mL 30 ng/mL	Cognitive decline: Decline in MMSE score of 3 points; 33.8%	Adjusted OR (95% CI) vs. 25(OH)D 30 ng/mL (n=829): MMSE: 33.8%

First author, year (ref)	Country	No. of participants (% female)	Age range (mean age)	Population; baseline year	Follow-up duration	Vitamin D exposure	Outcome measures: overall prevalence	Main findings
Annweiler, 2011 (83)	France	40 (100%)	75 years (median, 78.4 years)	EPIDOS Toulouse subset: high-functioning older women; 1992–94	7 years	Serum 25(OH)D: <10 ng/mL 10 ng/mL	Scoring in worst 10% of decline or discontinuation of	Adjusted OR (p-value) of other dementia for 25(OH)D <10 ng/mL vs. 10 ng/mL: 19.57 (p=0.04). No association between baseline 25(OH)D and AD (p=0.22).
							Scoring in worst 10% of decline or discontinuation of	Adjusted OR (95% CI) vs. 25(OH)D ≥ 30 ng/mL: 3.03 (1.06–8.61)
							Scoring in worst 10% of decline or discontinuation of	Adjusted OR (95% CI) vs. 25(OH)D ≥ 30 ng/mL: 3.03 (1.06–8.61)
							Scoring in worst 10% of decline or discontinuation of	Adjusted OR (95% CI) vs. 25(OH)D ≥ 30 ng/mL: 3.03 (1.06–8.61)
							Scoring in worst 10% of decline or discontinuation of	Adjusted OR (95% CI) vs. 25(OH)D ≥ 30 ng/mL: 3.03 (1.06–8.61)
							Scoring in worst 10% of decline or discontinuation of	Adjusted OR (95% CI) vs. 25(OH)D ≥ 30 ng/mL: 3.03 (1.06–8.61)
							Scoring in worst 10% of decline or discontinuation of	Adjusted OR (95% CI) vs. 25(OH)D ≥ 30 ng/mL: 3.03 (1.06–8.61)
							Scoring in worst 10% of decline or discontinuation of	Adjusted OR (95% CI) vs. 25(OH)D ≥ 30 ng/mL: 3.03 (1.06–8.61)
							Scoring in worst 10% of decline or discontinuation of	Adjusted OR (95% CI) vs. 25(OH)D ≥ 30 ng/mL: 3.03 (1.06–8.61)
							Scoring in worst 10% of decline or discontinuation of	Adjusted OR (95% CI) vs. 25(OH)D ≥ 30 ng/mL: 3.03 (1.06–8.61)
Slinin, 2012 (77)	USA	6257 (100%)	65 years (76.6 years)	SOF: community-dwelling older women; 1986–88	4 year follow-up	Serum 25(OH)D: <10 ng/mL 10–<20 ng/mL 20–<30 ng/mL 30 ng/mL	Cognitive decline: mMMSE decline of 2.9 points; 15.7% Change in time to complete Trails B > 1 SD	Adjusted OR (95% CI) vs. 25(OH)D ≥ 30 ng/mL: 1.58 (1.12–2.22)
							Cognitive decline: mMMSE decline of 2.9 points; 15.7% Change in time to complete Trails B > 1 SD	Adjusted OR (95% CI) vs. 25(OH)D ≥ 30 ng/mL: 1.58 (1.12–2.22)

First author, year (ref)	Country	No. of participants (% female)	Age range (mean age)	Population; baseline year	Follow-up duration	Vitamin D exposure	Outcome measures: overall prevalence	Main findings
Annweiler, 2012 (82)	France	498 (100%)	75 years (79.8 years)	EPIDOS Toulouse cohort: subset of community-dwelling women free of vitamin D supplements; 1992–94	7 years	Dietary vitamin D intake (modified Fardellone self-administered 21-item food frequency questionnaire); continuous and quintiles	Clinical diagnosis of other dementia using the DSM-IV criteria: 13.4% Clinical diagnosis of AD using the NINCDS-ADRDA working group criteria: 14.1%	Adjusted OR (95% CI) per 40 IU/week increment in vitamin D intake: Other dementias: 1.01 (1.00–1.02) AD: 0.99 (0.98–0.99) Adjusted OR (95% CI) of highest quintile of vitamin D intake (>44 IU/day) compared to lower 4 quintiles combined for AD: 0.23 (0.08–0.69)
								of sample mean (816–820) 1.7% of sample mean (816–820) 1.1.3% of sample mean (816–820) 1.64% 20–<30 ng/mL: 1.13 (0.91–1.41) Trails B (n=3973) <10 ng/mL: 1.00 (0.64–1.56) 10–<20 ng/mL: 0.93 (0.70–1.23) 20–<30 ng/mL: 0.83 (0.64–1.09)
								Change in 3MS score were –1.0, –0.8 and –0.2 points in 25 (OH)D <20, 20–<30, and 30 ng/mL,
Wilson, 2014 (79)	USA	2777 (48.8%)	70–79 years (73.6 years)	Health ABC: population-based study of well-functioning community dwelling older adults; 1997–98	4 years follow-up	Serum 25(OH)D: <20 ng/mL 20–<30 ng/mL 30 ng/mL	Change in 3MS score (n=2207) Change in DSST score (n=2175)	Change in 3MS score were –1.0, –0.8 and –0.2 points in 25 (OH)D <20, 20–<30, and 30 ng/mL,

First author, year (ref)	Country	No. of participants (% female)	Age range (mean age)	Population; baseline year	Follow-up duration	Vitamin D exposure	Outcome measures: overall prevalence	Main findings
Toffanello, 2014 (78)	Italy	1927 (62.7%)	65 years (73.9 years)	Pro.V.A: population-based study of community-dwelling older adults; 1995–97	4.4-year follow-up	Serum 25(OH)D: <20 ng/mL 20–30 ng/mL 30 ng/mL	Cognitive decline; decline in MMSE score of 3 points	Adjusted OR (95% CI) vs. 25(OH)D 30 ng/mL (n=1329): <20 ng/mL: 1.40 (1.11–1.74) 20–30 ng/mL: 1.24 (1.00–1.60)
Littlejohns, 2014 (84)	US	1658 (69.2%)	65 years (73.6 years)	CHS subset: community-dwelling older adults free of dementia, CVD and stroke; 1992–3	5.6 years	Serum 25(OH)D: <10 ng/mL 10–<20 ng/mL 20 ng/mL	Clinical diagnosis of all-cause dementia (10.3%) and AD (6.2%) using the NINCDS-ADRDA working group criteria	Adjusted HR (95% CI) vs. 25 (OH)D of 20 ng/mL: All-cause dementia: <10 ng/mL: 2.25 (1.23–4.13) 10–<20 ng/mL: 1.53 (1.06–2.21) AD: <10 ng/mL: 2.22 (1.02–4.83) 10–<20 ng/mL: 1.69 (1.06–2.69)
Schneider, 2014 (81)	USA	1652 (60%)	55 years (62 years)	ARIC Brain MRI Study: community-dwelling white and black adults; 1993–95	3- and 10-year follow-up; hospitalizations followed through 2010 (median 16.6 years)	Race-specific serum 25(OH)D tertiles (in whites: <21.8, 21.8–<28.3, 28.3 ng/mL; in blacks: <14, 14–<19.3, 19.3 ng/mL)	Hospitalization for dementia (ICD-9 codes 290.0–290.4, 290.9, 294.1, 294.2, 294.8, 294.9, 331.0–331.2, 331.8); 8.6% in	Adjusted HR (95% CI) vs. 25(OH)D in the upper tertile for whites (n=852): <21.8 ng/mL: 1.32 (0.69–2.55) 21.8–

First author, year (ref)	Country	No. of participants (% female)	Age range (mean age)	Population; baseline year	Follow-up duration	Vitamin D exposure	Outcome measures: overall prevalence	Main findings
							whites, 9.0% in blacks; 8.3 ng/mL; whites, 9.0% in blacks; 8.4 (0.95–3.18) Cognitive decline in the top quintile of test scores for: DWRT, DSST, and WFT	Adjusted HR (95% CI) vs. 25(OH)D in the upper tertile for blacks (n=800): <14 ng/mL: 1.53 (0.84–2.79) 14–<19.3 ng/mL: 1.22 (0.68–2.19) Lower 25(OH)D was not associated with greater DWRT, DSST, or WFT decline at 3- or 10-year follow-up (n=467–766 in whites; n=448–663 in blacks).

Abbreviations: AD Alzheimer's disease, ARIC Atherosclerosis Risk in Communities, CES-D Center for Epidemiologic Studies Depression Scale, CHS Cardiovascular Health Study, CI Confidence interval, DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th edition, DSST digit symbol substitution test, DWRT Delayed word recall test, EPIDOS Toulouse Epidemiologie de l'Osteoporose Toulouse cohort, GDS Geriatric Depression Scale, Health ABC Health, Aging, and Body Composition cohort, HR Hazard rate, ICD International Classification of Diseases, InCHIANTI Invecchiare in Chianti, aging in the Chianti area, LASA Longitudinal Aging Study Amsterdam, MMSE Mini-Mental State Examination (range, 0–30), mMMSE Modified Mini-Mental State Examination (range, 0–26), MROS Osteoporotic Fractures in Men, NAD Non-Alzheimer dementia, NINCDS-ADDA National Institute of Neurological and Communicative Disorders/Alzheimer's Disease and Related Disorders Association, OR Odds ratio, PPB Physical performance battery, Pro.V.A. Progetto Veneto Anziani cohort, SPPB Short physical performance battery, SOF Study of Osteoporotic Fractures, TCS Timed chair stands, Trails A Trail Making Test, Part A, Trails B Trail Making Test, Part B, TUG Timed Up and Go, WFT Word fluency test, WHAS Women's Health and Aging Study, WHI CaD Women's Health Initiative Calcium and Vitamin D trial, WHI OS Women's Health Initiative Observational Study, 3MS Modified Mini-Mental State exam (range, 0–100)

Table 2

Description of published intervention trials of vitamin D supplementation and mobility, mood, and memory in older adults

First author, year (ref)	Country	No. of participants (% female)	Age range (mean age)	Population	Intervention	Duration	Outcome measures	Main findings
Physical function and mobility								
Pfeifer, 2000 (46)	Germany	148 (100%)	70 year (74 years)	Healthy, ambulatory older women with 25(OH)D <20 ng/mL	800 IU vitamin D ₃ plus 1200 mg calcium or 1200 mg calcium alone daily	8 weeks	Change in body sway	Significant treatment difference in body sway (−1.1 mm vs. +0.4 mm in vitamin D plus calcium vs. calcium alone, $p=0.04$).
Kenny, 2003 (41)	USA	65 (0%)	65–87 years (76 years)	Healthy, community-dwelling older men (mean (SD) 25(OH)D at baseline, 26 (7) ng/mL)	1000 IU vitamin D ₃ plus 500 mg calcium or placebo plus 500 mg calcium daily	6 months	Change in leg extension strength, SPPB, TUG, and timed “supine to stand” test	No time-by-group effect for muscle strength or any physical performance measure ($p>0.10$).
Dhesi, 2004 (39)	United Kingdom	139 (78.4%)	65 years	Community-dwelling older adults referred to a falls clinic with 25(OH)D 12 ng/mL	Single intramuscular injection of 600,000 IU vitamin D ₂ or placebo	6 months	Change in Aggregate Functional Performance Time (AFPT; time to complete a 50 ft walk, rise from a chair, ascent and descent of 13 steps), body sway, and quadriceps strength	Significant treatment difference in AFPT (−2.0 s in vitamin D vs. +6.6 s in placebo, $p<0.01$) and body sway (−0.0138 vs. +0.0025, respectively, $p=0.02$). No difference in quadriceps strength by treatment group.
Bunout, 2006 (47)	Chile	96 (89.6%)	70 year (76 years)	Healthy, community-dwelling older adults with 25(OH)D <16 ng/mL	Resistance training (RT) plus calcium (800 mg/day); RT plus calcium and vitamin D ₃ (400 IU/day); no RT plus calcium; no RT plus calcium and vitamin D ₃	9 months	Change in grip strength, quadriceps strength, distance walked in 12 min, TUG, SPPB, and body sway	Change in TUG improved more in trained subjects supplemented with vitamin D ₃ than without.
Brunner, 2008 (42)	USA	3137 (100%)	50–79 years	WHI CaD subset: community-dwelling post-menopausal women	400 IU vitamin D ₃ and 1000 mg of calcium carbonate or placebo daily	5 years	Change in grip strength, timed 6-m walk, and number of chair stands in 15 s	No difference in change in grip strength, timed 6-m walk, or chair stands by group over 5 years.
Pfeifer, 2009 (40)	Germany & Austria	242	70 year (77 years)	Healthy ambulatory older men and	800 IU vitamin D ₃ plus 1000 mg calcium or 1000	20 months (12 months on	Change in body sway, TUG, and quadriceps strength	The vitamin D plus calcium group had better quadriceps

First author, year (ref)	Country	No. of participants (% female)	Age range (mean age)	Population	Intervention	Duration	Outcome measures	Main findings
Lips, 2010 (43)	North America and Europe (multicenter)	226	70 years (~78 years)	Women with 25(OH)D <32 ng/mL women with 25(OH)D <32 ng/mL women with 25(OH)D <32 ng/mL	8400 IU vitamin D ₃ or placebo weekly	16 weeks	Change in body sway and SPPB	strength and faster TUG at 12 months and 20 months compared to calcium only ($p<0.05$). Body sway was lower at 20 months (but not 12) in the vitamin D plus calcium compared to calcium only ($p<0.05$). There was no difference in change in body sway or SPPB score by treatment group. In post hoc analyses, body sway was reduced in the vitamin D ₃ group compared to placebo among those with higher baseline sway (0.46 cm; $p=0.047$).
Zhu, 2010 (44)	Australia	302 (100%)	70–90 years	Community-dwelling, ambulatory older women with 25(OH)D <24 ng/mL	1000 IU D ₂ plus 1000 mg calcium or 1000 mg calcium alone daily	1 year	Change in ankle dorsiflexion, knee flexor and extensor, hip abductor, flexor, extensor, and adductor strength, and TUG	No between-group treatment effects for any strength measures or TUG. In those in the lowest tertile of strength and TUG, hip extensor and adductor strength were significantly higher ($p<0.05$) and TUG was faster ($p=0.02$) in the vitamin D plus calcium vs. calcium alone group.
Glendenning, 2012 (45)	Australia	686 (100%)	70 years (76.7 years)	Community-dwelling, ambulatory older women	150,000 vitamin D ₃ or placebo every 3 months	3-, 6-, and 9-month follow-up	Change in grip strength and TUG	No between-group treatment effects for grip strength or TUG.
Depressive symptoms and depressed mood Bertone-Johnson, 2011 (67)	USA	2263 (100%)	50–79 years	WHI CaD subset: community-dwelling postmenopausal women	400 IU vitamin D ₃ and 1000 mg of calcium carbonate or placebo daily	2 years	Change in 8-item Burnam scale for depressive disorders score Depressive symptoms (Burnam scale for depressive disorders score: 0.06); 9.4% of treatment group and 9.9% of placebo group	No difference in change in Burnam score by treatment group. No difference in odds of depressive symptoms by treatment group: Adjusted OR (95% CI) 1.41 (0.97–2.05)

First author, year (ref)	Country	No. of participants (% female)	Age range (mean age)	Population	Intervention	Duration	Outcome measures	Main findings
Sanders, 2011 (66)	Australia	118 (100%)	70 years	Vital D subset: community-dwelling women	500,000 IU vitamin D ₃ or placebo annually	3–5 years	Change in 5-item WHO Well-Being Index score Depression: WHO Well-Being Index score <13 or answer of 0 or 1 on any of the 5 items	No difference in WHO Well-Being Index scores by treatment group ($p=0.47$). No difference in odds of depression by treatment group: OR (95% CI) 0.85 (0.45–1.61)
Cognitive function and dementia								
Rossom, 2012 (85)	USA	4143 (100%)	65 years (71 years)	WHI CaD and WHI WHIMS subset: community-dwelling post-menopausal women	400 IU vitamin D ₃ and 1000 mg of calcium carbonate or placebo daily	8 years	Adjudicated probable dementia (based on DSM-IV criteria) or MCI (performance in 10th percentile on a least one CERAD test based on CERAD norms): 4.8% of treatment group and 5.1% of placebo group Change in 3MS ($n=4143$) and domain-specific cognitive function in a subset ($n=1420$)	No difference in incident dementia or MCI by treatment group: HR (95% CI) 0.94 (0.72–1.24) No difference in mean 3MSE scores ($p=0.30$) or domain-specific cognitive function ($p=0.15$) over 8 years by treatment group.

Abbreviations: CERAD Consortium to Establish a Registry for Alzheimer's Disease, CI confidence interval, DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th edition, HR hazard rate, MCI mild cognitive impairment, OR odds ratio, RM repetition maximum, RT resistance training, SF-36 Short Form 36, SPPB short physical performance battery, TUG Timed Up and Go, WHI CaD Women's Health Initiative Calcium and Vitamin D trial, WHIMS Women's Health Initiative Memory Study, WHO World Health Organization, 3MS modified mini-mental state exam (range, 0–100)