Vitamin D Status and Falls among Older Adults

by

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Submitted in partial fulfillment of the requirements for the degree

Master of Science in Dietetics

Mount Mary University

December 2018

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ABSTRACT

Background: Vitamin D plays an important role in bone metabolism and is associated with bone density and fractures among older adults. Many older adults have poor vitamin D status due to lack of the vitamin in the diet and lack of sun exposure. Falls are a major concern among older adults, as injuries can result in social isolation, decreased quality of life, declining health, institutionalization and death. A major focus in preventing falls among older adults has been optimizing bone health. This systematic review analyzed the effect of vitamin D status on fall rates among older adults (ages 60 and older) in multiple settings (both independent living and in care facilities).

Methods: This project used the Academy of Nutrition and Dietetics Evidence Analysis Library methodology to define a question, analyze research, summarize results, and formulate a conclusion statement that is applicable to practice.

Results: A total of 7 primary research articles met the criteria and were included in the analysis. Mixed results were obtained from the prospective cohort and cross-sectional studies. Snijder et al. found that low vitamin D status (<10 ng/ml) was associated with an almost doubled risk of falling (OR 1.78 (95%CI[1.06-2.99])(2006) compared to those with normal vitamin D status. Peterson et al. (2012) found similar results, where fallers had a significantly lower average serum vitamin D concentration (32.9 ng/ml) compared to non-fallers (39.2 ng/ml) ($p<0.01$). In contrast, Larocque et al. found that vitamin D status was noncontributory to falls (2015). Ghafouri et al. (2016) also found no association between mean serum 25-hydroxy vitamin D levels and the number of recurrent falls. Suzuki et al. only found a significant association between low 25-hydroxy vitamin D levels and a high prevalence of falls among women (2008). Among the randomized controlled trials, there were mixed results as well, with Law et al. (2006) finding that there were no statistically significant differences in falls among a vitamin D supplementation group versus a placebo group. However, Bischoff et al. (2003) found that the calcium plus vitamin D supplementation had a 49% reduction in falls (95% CI, 14–71%; $p < 0.01$) compared to a calcium only supplementation group.

Conclusion: The majority of studies (4 out of 7) found adequate vitamin D status among older adults (ages 60 and older) is associated with a reduced risk in falls, especially among women. Three studies found no association between vitamin D status and risk of falls. Vitamin D supplementation is recommended to increase levels to be within normal limits if older adults (over the age of 60) are deficient, especially among women, to aid in reducing the risk of falling. Whether the relationship between vitamin D status and risk of falls is direct and causal remains to be seen. Randomized controlled trials are needed to clarify whether interventions to improve vitamin D status could reduce risk of falls in adults over age 60 in multiple settings.

CHAPTER 1: INTRODUCTION

Background

There are numerous studies that have clearly shown the positive relationship between bone density and vitamin D status. Especially for the older adult population ages 65 years and older, bone density is a critical component of maintaining strength and independence. With age, falls become a hindrance on independence and quality of life. This population has a critical need for strong bones, as falls are the leading cause of fatal and nonfatal injuries (Bergen, Stevens, & Burns, 2016). Injuries from a fall can result in loss of confidence, social isolation, decreased quality of life, declining physical health, institutionalization and death (Meuleners, et al., 2016). In nursing homes, vitamin D deficiency and secondary hypoparathyroidism is high, which also correlates with a larger risk of hip fracture (Shinkov, et al., 2016).

Multiple factors affect bone health including dietary calcium intake, physical activity, gender, size, age, race, family history, hormone levels, medical status, and certain medications. A diet that is low in calcium contributes to a lower bone density, early bone loss and an increased risk of fractures. When a person is less physically inactive, there is a higher risk of osteoporosis compared to others that are more active. Also, a person is at greater risk of osteoporosis if they are a female, because females have less bone tissue than do males. Bones become thinner and weaker as a person ages. A person is at greater risk of osteoporosis if they are white or of Asian descent. In addition, having a parent or sibling who has osteoporosis leads to a greater risk, especially if there is a family history of fractures. People who have anorexia or bulimia are at risk of bone loss. In addition, gastrectomy, weight-loss surgery and conditions

such as Crohn's disease, celiac disease and Cushing's disease can affect the body's ability to absorb calcium. Certain medications can affect bone health such as long-term use of corticosteroid medications including prednisone, cortisone, prednisolone and dexamethasone, which are damaging to the bone. Other drugs that may increase the risk of osteoporosis include aromatase inhibitors to treat breast cancer, selective serotonin reuptake inhibitors, methotrexate, some anti-seizure medications, such as phenytoin (Dilantin) and phenobarbital, and proton pump inhibitors (Mayo Clinic Staff, 2016).

Vitamin D supplementation, in particular, is of special consideration with the older adult population since many do not consume adequate levels of vitamin D from diet alone. Overall, a significantly lower serum vitamin D concentration and higher prevalence of deficiency has been observed in institutionalized subjects compared to community-dwelling subjects (95% vs. 75%) (Shinkov, et al, 2016). The consequences from inadequate vitamin D levels include secondary hyperparathyroidism and bone loss, leading to osteoporosis, fractures, and mineralization defects, which may lead to osteomalacia in the long term (Spencer & Wong, 2014). Clearly vitamin D status is key among this population in maintaining bone density and strength, and falls can cause a major hindrance in independence and quality of life.

Rationale/Significance

Vitamin D plays such a crucial role in bone health, which is especially important for older adults considering their increased likelihood of falling; therefore, it is important to research whether adequate vitamin D status may prevent falls in the older adult population. Evidence will point to a conclusion of whether or not adequate vitamin D status is associated

with and/or effective in preventing falls among older adults due to its relationship with bone health. If adequate vitamin D status is found to decrease fall rates among older adults, protocols for screening for deficiency of vitamin D and supplementation, as needed, could be implemented.

Problem Statement

Does adequate vitamin D status prevent falls among the older adult population (>60 years-old) living in both free living and institutionalized settings? The objectives of this evidence analysis project are to determine whether there is an association between increased falls and low vitamin D status among older adults (<25 ng/ml for adults, DHHS, 2007) living in both free living and institutionalized settings and to determine whether rates of falls decrease with vitamin D supplementation.

Sub-problems

Sub-problems included in this research are whether vitamin D supplementation is necessary for older adults, and which population of older adults, since vitamin D in the diet alone is often inadequate to meet recommended serum levels. Do other factors affect falls rates that can make it difficult to determine the direct correlation of vitamin D status on falls? How do other health risks and factors play into the affect that vitamin D status may play on falls rates in older adults? How does vitamin D supplementation compare in affecting serum vitamin D levels against vitamin D obtained from dietary sources or the sun?

Limitations

Some limitations of this research include that participants receive varying levels of vitamin D from other sources including food and the sun. There are other factors can influence falls rather than determining vitamin D is the cause of the fall. Also, individual responses to vitamin D supplementation can vary based on their health history including other medications and supplements, health conditions, and exercise.

Delimitations

Delimitations to the study include a sample population of older adults that are ages 65 years and older and limiting samples to individuals in an institutional rather than community setting where diet, supplementation administration and falls can be more closely and easily monitored.

Assumptions

It is assumed that participants' dietary intake is accurately recorded and that they take supplementation in the quantity and on a consistent basis as recommended. It is assumed that serum vitamin D levels are obtained accurately and therefore, results of vitamin D levels are accurate as well. It is also assumed that data is reported accurately regarding dietary intake, supplementation and falls by institutions involved in the studies.

List of Definitions

Older adult**:** encompasses individuals ages 60 and older for this project

Fall: unintentionally coming to rest on the ground, floor, or other lower level, but not as a result of an overwhelming external force (Department of Health & Human Services, Center for Medicare & Medicaid Services, 2007)

Osteomalacia**:** marked softening of bones, most often caused by severe vitamin D deficiency (Mayo Clinic, 2017)

Osteoporosis: a bone disease that occurs when the body loses too much bone, makes too little bone, or both. As a result, bones become weak and may break from a fall or, in serious cases, from sneezing or minor bumps (National Osteoporosis Foundation, 2018)

Dual Energy X-ray Absorptiometry (DXA): an imaging test that measures bone density (the amount of bone mineral contained in a certain volume of bone) by passing x-rays with two different energy levels through the bone. It is used to diagnose osteoporosis (decrease in bone mass and density). Also called BMD scan, bone mineral density scan, DEXA, DEXA scan, dual energy x-ray absorptiometric scan, and DXA. (National Cancer Institute, 2018)

Polymerase Chain Reaction (PCR)**:** sometimes called “molecular photocopying”, the polymerase chain reaction (PCR) is a fast and inexpensive technique used to “amplify” small segments of DNA. Because significant amounts of sample of DNA are necessary for molecular and genetic analyses, studies of isolated pieces of DNA are nearly impossible without PCR amplification (National Human Genome Research Institute, 2015).

Restriction Fragment Length Polymorphism (RFLP): a difference in homologous DNA sequences that can be detected by the presence of fragments of different lengths after digestion of the DNA samples in question with specific restriction endonucleases. RFLP, as a molecular marker, is specific to a single clone/restriction enzyme combination (The National Center for Biotechnology Information, 2017).

Mendelian Randomization**:** uses genetic variation as a natural experiment to investigate the causal relations between potentially modifiable risk factors and health outcomes in observational data (BMJ, 2018).

CHAPTER II: LITERATURE REVIEW

Introduction

One of the major influences on mortality risk in the elderly population is falls. With age, falls become a hindrance in independence and quality of life. Fall preventions is a major focus in healthcare facilities including hospitals, nursing homes, assisted living centers, and senior living facilities since falls are strongly linked with mortality. A large portion of healthcare dollars goes to elderly persons that experience falls and have to rehab or recover from complications. According to Bergen et al., falls are the leading cause of fatal and nonfatal injuries among adults ages 65 and older (2016). Furthermore, approximately 27,000 older adults died because of falls, 2.8 million were treated in emergency departments due to falls and injuries, and approximately 800,000 patients were subsequently hospitalized in 2014. Injuries from a fall may result in loss of confidence, social isolation, decreased quality of life, declining physical health, institutionalization and death (Meulener et al., 2016). Clearly falls have a major impact on the health of older adults and the US healthcare industry in general.

Optimizing bone health has been a major focus in fall prevention efforts. Bone health is mediated by numerous factors including the amount of dietary calcium, physical activity, gender, size, age, race, family history, hormone levels, medical status, and certain medications. Bone health can be improved through ensuring that plenty of calcium and vitamin D in the diet and including physical activity as a part of a daily routine. The recommended daily allowance (RDA) of calcium intake for adults, ages 19 to 50 years, and men, ages 51 to 70 years, is 1,000

mg per day and 1,200 mg per day for women older than 50 years of age and men older than 70 years of age (Institute of Medicine of the National Academies, 2011).

Bone density is a critical component of maintaining strength and independently functioning for older adults. Many older adults have also been found to have low serum vitamin D levels from diet alone. Shinkov et al., found that in nursing homes, vitamin D deficiency and secondary hypoparathyroidism is high, which also correlates with a larger risk of hip fracture (2016). Vitamin D deficiency can also lead to increased fracture risk, muscle dysfunction in the elderly, increased cardiovascular morbidity, and higher rates of some cancers and autoimmune diseases (Shinkov, et al., 2016). Vitamin D status correlates with bone density and thus risk of fracture. If bone health is improved, overall strength and the risk of falls decreases. Optimal vitamin D status could aid in preventing falls in the elderly by increasing bone density and overall strength.

The purpose of this evidence analysis is to critically analyze the relationship between vitamin D status and the risk for falls among the elderly.

Background

Vitamin D

Vitamin D plays an important role in bone metabolism in the body by regulating the main mineral component of the skeleton, calcium. It also controls calcium absorption into the intestine, its excretion through the kidneys and its storage in the bone. When vitamin D is deficient in the body, it causes decreased calcium and phosphate absorption. The subsequent suboptimal bone mineralization may lead to the bone loss disease, or osteomalacia. Another

critical component of bone metabolism is parathyroid stimulating hormone, or PTH. Vitamin D stimulates the production of PTH in the body, which causes increased bone turnover and bone loss. As people get older, kidney function decreases and causes excess PTH to be produced, which also leads to increased bone loss. Prolonged decreased serum vitamin D concentrations ultimately lead to low bone mineral density, falls and fractures (Spencer & Wong, 2014).

Sources of Vitamin D

Vitamin D deficiency is common in the elderly population, since it is difficult for this population to get much sun exposure, which is the number one source of vitamin D. Very few foods in nature contain vitamin D, and these food sources of vitamin D include fatty fish such as tuna, salmon, or mackerel, fish liver oils, beef, liver, cheese, and egg yolks. Fortified foods such as milk, orange juice, and yogurt provide most of the vitamin D in the American diet (Office of Dietary Supplements, 2018). The major source of vitamin D is the sun: upon exposure to ultraviolet light, provitamin D in the skin is synthesized from 7-dehydrocholesterol and converted to vitamin D3, or cholecalciferol. Cholecalciferol undergoes hydroxylation to first 25-hydroxyvitamin D (25OHD) to form the major circulating form and then again to become the active form, 1,25-Di-hydroxyvitamin D [1,25(OH)2D]. 25-hydroxyvitamin D has a fairly long circulating half-life in contrast to circulating 1,25(OH)2D, which is generally not a good indicator of vitamin D status because of its short half-life. Based on a review of estimated serum vitamin D needs, the Institute of Medicine concluded that persons are at risk of vitamin D deficiency with serum concentrations of 25OHD <30 nmol/L (<12 ng/ml). Some are potentially at risk for

inadequacy at levels ranging from 30-50 nmol/L (12-20 ng/ml), and practically all people are sufficient at levels ≥50 nmol/L (≥20 ng/mL) (Office of Dietary Supplements, 2018).

Table 1: Serum 25-hydroxyvitamin D[25OHD] Concentrations and Health

nmol/L**	**ng/mL***	**Health Status**
<30	<12	Associated with vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults
30- <50	12 to <20	Generally considered inadequate for bone and overall health in healthy individuals
≥50	≥20	Generally considered adequate for bone and overall health in healthy individuals
>125	>50	Emerging evidence links potential adverse effects to such high levels, particularly >150 nmol/L (>60 ng/mL)

*Serum concentrations of 25OHD are reported in both nanomoles per liter (nmol/L) and nanograms per milliliter (ng/mL)
**1 nmol/L = 0.4 ng/mL
(National Institutes of Health: Office of Dietary Supplements, 2018)

Oral formulations of vitamin D_2 and D_3 have been regarded as equivalent in their clinical activity for a long time. However, recent studies indicate that ergocalciferol (vitamin D_2) is much less potent and has a shorter duration of action than cholecalciferol (vitamin D3) (Hulisz, 2011).

Vitamin D Status and Its Relation to Falls

The prevalence of vitamin D deficiency and fracture history in nursing home residents and community-dwelling subjects in a study by Shinkov et al. (2016). This cross-sectional study showed that the nursing home residents were significantly older than the community-dwelling residents, and thus all further analyses were adjusted for age. Overall, a significantly lower vitamin D level was observed in the institutionalized subjects compared to community-dwelling subjects (95% vs. 75%, $p < 0.001$). There was no association between vitamin D levels or PTH and fracture prevalence; hip fracture was associated with elevated PTH and not directly to the

vitamin D levels. Therefore, hip risk fracture risk was associated with elevated PTH and not directly with vitamin D levels or the residency status (nursing home vs. community-dwelling). (Shinkov, et al., 2016).

Skin capacity for cholecalciferol synthesis decreases with age. Many older adults have to take vitamin D supplements in order to have an adequate vitamin D status, since they often do not get enough regular exposure to sunlight and have trouble synthesizing vitamin D upon exposure to UV light from the sun. According to the Food and Nutrition Board, Institute of Medicine, National Academies (2011) the recommended amount of vitamin D is 600 international units (IU) for ages 1 to 70 and 800 IU for people over ages of 70 years.

Serum Vitamin D and Genetics

Genetics also plays an important role in vitamin D status and its relation to bone health. It is linked to vitamin D status and bone health in various ways. A study conducted by Ormsby et al. (2013) found that there is a complex relationship between vitamin D metabolism and gene expression in human bones. The expression of the gene CYP27B1 metabolizes 25-hydroxyvitamin D to active 1, 25-dihydroxyvitamin D (1,25 [OH]2D) by endogenous expression. This study focused on examining relationships between this gene expression in bone and its potential function in vivo by looking at the expression of this gene in human trabecular bone samples and comparing them with linear regression analysis with the expression of osteoblast, osteoclast and osteocyte-related gene markers, genes associated with osteoblast/osteoclast control of osteoclastogenesis and transcription factors. Researchers found that the CYP27B1 gene was not associated with genes expressed in bone that are known to be 1,25 (OH)2D

responsive. The authors concluded that the major implication of these relationships in gene expression is that endogenous 1,25 (OH)2D synthesis and the response to 1,25 (OH)2D in human trabecular bone is linked with coordinated functions in both osteoclastic and osteoblastic compartments towards the control of bone remodeling.

Genetic polymorphisms play an interesting role in the risk of fractures among older adults, specifically when looking at the vitamin D receptor (VDR) gene. One observational study took a look at how the VDR gene affects bone mineral density and the presence of vertebral/non-vertebral fractures in a group of post-menopausal Polish women with osteoporosis (Horst-Sikorska, et al., 2013). The mean age of the group was 66.4 ± 8.9 years (n=501). Researchers specifically looked at three alleles on the VDR gene, *Bsm*I*, Apa*I*, and Taq*I, and the association between polymorphisms and risk of fracture. The three polymorphisms were determined by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP). The bone mineral density of subjects was tested at both the lumbar spine and femoral neck through the use of dual energy x-ray absorptiometry (DXA). Among the group, 285 fractures were reported, including 168 vertebral and 117 non-vertebral). Of the carriers of single alleles *a* of *Apa*I, *b* of *Bsm*I and *T* of *Taq*I VDR gene polymorphisms, the incidence of non-vertebral fractures was significantly higher compared to non-carrier (77 B allele vs. 157 b allele, 95 A allele vs. 139 a allele, and 159 T allele vs. 75 t allele, p=0.021, 0.032, and 0.020 respectively). There were no significant associations between the allele variants of the noted polymorphisms and bone mineral density. Authors concluded that the presence of the single alleles a, b and T of *ApaI, BsmI* and *TaqI* polymorphisms of the VDR gene may be related to low-energy fractures, since there were results of significant numbers of non-

vertebral fractures among the single allele variants. The results of a lack of association between the VDR gene polymorphisms and bone mineral density suggest that VDR contributes to low-energy fractures also through other ways (Horst-Sikorska, 2013).

Serum Vitamin D and Bone Metabolism

In a non-controlled experimental trial, researchers attempted to determine the serum 25OHD concentration that has the greatest benefit on bone calcium flux in postmenopausal women through the application of the highly sensitive ^{41}Ca skeletal labeling technique and the measurement of urinary ^{41}Ca:^{40}Ca ratios. This was accomplished through the administration of a mean intravenous ^{41}Ca dose of 870 pmol to healthy postmenopausal women without osteoporosis. The sample size of this group of 24 women aged 64 ± 6.0 y was recruited from the program for elderly citizens at the University of Zurich and by local newspaper advertisements. After 6 months, each of the women were directed to consume daily oral cholecalciferol supplements. The amount consumed increased at 3-month intervals in the following order: 10, 25, and 50 µg per day. Serum 25OHD concentrations were assessed monthly and urinary ^{41}Ca:^{40}Ca ratios were assessed biweekly. ^{41}Ca:^{40}Ca ratios were measured with low-energy accelerator mass spectrometry. The effect of varying serum 25 OHD concentrations on ^{41}Ca transfers were determined with the use of pharmacokinetic analysis. Supplementation of cholecalciferol was associated with a downward shift in the urinary ^{41}Ca:^{40}Ca compared with the predicted ^{41}Ca:^{40}Ca ratio without cholecalciferol supplementation. The increase in serum 25OHD was a transfer from the central compartment to a fast exchanging compartment in the most likely site of action, or in other words, there was a transfer of calcium from the blood or

extracellular space to the fast-exchanging compartment, likely the bone surface. This is also consistent with one of the recognized sites of action of 1,25-dihydroxyvitamin D to maintain plasma calcium concentrations, meaning that there is stimulated bone uptake and release of calcium. A serum 25OHD concentration of ~40 μg/L achieves ~90% of the expected maximal effect on this transfer rate (Schild, A et al., 2015).

Vitamin D and Fractures

One study attempted to ascertain whether the associations between low serum 25 hydroxyvitamin D (25OHD) and osteoporosis and osteoporotic fractures are causal. In this observational study of the Chinese population, Mendelian randomization analysis was used to assess genetic variants predicted risk factors to screen their causal effects on the outcomes of interest (Li, et al., 2016). The authors concluded in a previous study of 2,897 healthy Chinese subjects that the *GC, CYP2R1* and *NADSYN1* polymorphisms within the vitamin D metabolic pathway are genetic determinants of variations in serum 25OHD levels. First the observational associations between the total serum 25OHD and bone mineral density and bone metabolism markers, including intact parathyroid hormone (PTH), Beta-CrossLaps of type I collagen containing cross-linked C-telopeptide (Beta-CTX) and procollagen type 1 N-terminal propeptide (P1NP) were established. Next, researchers calculated the free and bioavailable 25OHD levels by using the Vermeulen formulas based on directly measured values of the total serum 25OHD, vitamin D binding protein (DBP) and albumin levels. From that information, it was determined whether the bioavailable and free 25OHD levels were more closely associated with bone mineral density and bone metabolism markers. The verified observational associations were

determined to be positively causally related. There was a total of 1,824 participants with the average age of 65.5 years (+ 8.9), an average BMI of 23.5 kg/m^2 (+/- 3.3), and the median (25^{th} and 75^{th} percentiles) total serum 25OHD level of 18.3 (13.3, 23.8) ng/ml. Researchers found that the total serum 25OHD levels were positively associated with the serum PTH and PINP levels. Also, the serum levels of the bioavailable or free 25OHD were not associated with any of the tested bone mineral density sites or bone metabolism markers. Lastly, the Mendelian randomization analyses showed that genetically low serum 25OHD levels (controlling for the selection of participants having one of four single nucleotide polymorphisms, *GC*-rs2282679, *NADSYN1*-rs12785878, *CYP2R1*-rs10741657 and *CYP24A1*-rs6913897) were not associated with decreased bone mineral density or with elevated serum PTH or P1NP levels. Ultimately, the total serum 25OHD levels were determined to be unlikely have a robust causal effect on bone mineral density or bone metabolism markers, but they could serve as a marker of 25OHD status (Li, et al., 2016). Authors concluded that their analysis provided no evidence of a causal role of genetically low serum 25OHD levels in either decreased bone mineral density or elevated serum PTH or P1NP levels.

Overall, the evidence suggests that there are mixed results regarding whether vitamin D plays a critical role in bone metabolism in the elderly. Some studies have their strength in numbers, including the study done by Li, et al., (2016) on relating bone mineral density to serum 25OHD levels. They found that 25OHD status can be marked by total 25OHD levels among a sample of 1,824 Chinese older adults through Mendelian randomization. Although this study had a large sample size to increase validity, it was an observational study which limits the conclusions that can be made. Other studies did not have quite as large of numbers in the

sample population. In the study conducted by Shinkov, et al., (2016), just 139 community-dwelling elderly subjects participated in the study that aimed to assess the prevalence of vitamin D deficiency and fractures. This study cross-sectional study found a lower vitamin D level was observed in institutionalized subjects compared to community-dwelling subjects as well as a higher prevalence of vitamin D deficiency. Since institutionalization is so common among the elderly population, it was important to take a look at how that plays a role in vitamin D status and fracture risk as well. Further research with more participants in controlled, experimental studies will increase the validity of the findings.

Researchers in the study conducted by Horst-Sikorska, et al. (2012) wanted to take a look at the vitamin D receptor in particular and its role in bone mineral density. They showed that the presence of the single alleles a, b and T of *ApaI, BsmI*and *TaqI* polymorphisms of the VDR gene may be a predictor of low-energy fractures. Genetics came into play as well in this study of alleles, which other studies do not take into account. Again, it was an observational study, so the methods could have been changed to increase the validity of the results. There was a decent sample size of people, though, with a total of 501 postmenopausal elderly women participating in the study.

One of the studies answered an important question that is still a topic of debate today among health professionals on the appropriate serum levels of vitamin D for adequate health in the elderly. The study by Schild, et al. (2015) revealed that A serum 25OHD concentration of ∼40 μg/L achieves ∼90% of the expected maximal effect on bone mineralization. The validity of this study was increased by the fact that it was experimental in design, although it was non-controlled, so there was no control group for comparison.

Since falls have such a large role in the health outcomes of the elderly population, the risk associated with bone mineral density and falls should be further studied to bridge the gaps in research. Since vitamin D status has been shown to affect bone mineral density, then vitamin D levels and supplementation would be hypothesized to correlate with risk of falls.

Vitamin D Status and Falls Research

There are mixed results regarding vitamin D status among older adults and risk of falls. Multiple study designs with few randomized control trials have shown that in certain circumstances, adequate vitamin D status decreases risk of falls. Other studies, however, showed no correlation. Each study was conducted in a variety of locations, with a variety of sample sizes, and using a variety of methods.

Cross Sectional Studies

Many observational studies have been conducted to research whether there is a correlation between risk of falls and vitamin D status in older adults. Among observational studies, much evidence supports the conclusion that adequate serum vitamin D status does play a role in preventing falls. These studies strengthen the body of evidence, however, do not provide any causal evidence.

Some studies conclude that vitamin D status is, indeed, a key factor in preventing falls among the older adult population. A study conducted by Peterson et al. (2012), used a cross sectional design to elucidate the mechanism through which vitamin D is associated with decreased risk of falls. This study, in particular, looked at an age group on the higher end of the

spectrum with participants ages 70 and older. They did, however, only include participants that were living independently, not demented with a Clinical Dementia Rating score <0.5, Mini Mental State Examination (MMSE) score >24, and being of average health for age. Falls were self-reported to researchers via weekly, computerized questionnaires. Serum vitamin D status was determined through blood draws. Researchers also identified participant characteristics that could possibly confound results including physical, neurological health status and cognitive function, BMI, depression, autonomy, grip strength, and race. This study had a decent-sized sample population with a total of 159 participants that were largely white and generally highly educated (average of 15 years of education) from the Portland, Oregon metropolitan area. They found that fallers had a significantly lower vitamin D level (32.9 ng/ml) as compared to non-fallers (39.2 ng/ml) ($p<0.01$). A 5 ng/ml increase in vitamin D corresponded to a 20% decrease in the odds of falling. It was also interesting that cognitive status did not modify the relationship between vitamin D and falls risk ($p=0.12$). Although this study found significant results with increased vitamin D status correlating with decreased falls, there were limitations in the fact that the falls were self-reported by participants and once again, this was an observational study that could not prove causality. It is interesting that the vitamin D levels of fallers was classified as significantly lower at 32.9 ng/ml, when the National Institutes of Health: Office of Dietary Supplements classified a 25OHD level of 20 ng/mL or higher to be generally considered adequate for bone and overall health in healthy individuals. Of course, this population may have an adjusted scale of vitamin D status, but participants of this study were of fair health, since they were only included if they were living independently, not demented, and were of average health for age based on questionnaires.

Another observational study showed similar results with risk of falls correlating with a decreased vitamin D status that was conducted by Suzuki et al. (2008) in Tokyo, Japan. This study aimed to study the association between serum 25OHD levels and falls among Japanese community-dwelling elderly. This group of participants was slightly younger in age, including participants of 65 years or older. To be included in the study, they also had to be essentially ambulatory, living independently in their homes and of "sound functional capacity". Age, physical activity, and chronic disease conditions of the subjects were obtained through interviews conducted with the participants. Falls were self-reported, as they were asked to report on falls during the previous year. Researchers also chose to study handgrip strength with a dynamometer and the time taken to walk 5 meters. Blood samples measured both serum 25OHD and albumin in a non-fasting state.

Interestingly, the results showed that low 25OHD levels (<25 ng/ml) were significantly associated with a high prevalence of falls only among the Japanese elderly women ($p<0.001$). Researchers came to this conclusion since mean 25OHD concentration was significantly lower in women than in men ($p < 0.001$) and women also showed significant declines in all three fall-related physical performance tests. The validity of these results lacked due to the fact that much of the information was self-reported by participants. However, it does agree with the other observational study by Peterson et al. in concluding that risk of falls is associated with adequate vitamin D levels among the elderly.

Both of these studies found that adequate serum levels of vitamin D is associated with a reduced risk of falls. Even though these studies were conducted with different populations from locations in Portland, Oregon to Tokyo, Japan, they both concluded that falls were higher

among participants with lower serum vitamin D levels. There were a few differences among the studies, with the Peterson et al. including a slightly older population of ages 70 and older compared to ages 65 and older in the Suzuki et al. study. Also, the Suzuki et al. study found that falls were higher among participants with lower serum vitamin D levels only among women compared to men. Both of these studies also included self-reported information on falls that could be inaccurate due to reporting bias. The population of these studies also included independently living seniors who were fairly high functioning, which could have attributed to the results. Although these studies are strong in design as observational studies, their results only add to the literature regarding the association between vitamin D and falls and cannot prove causality.

Prospective Cohort Studies

There are multiple prospective cohort studies that have been completed on vitamin D status and its relation to falls among older adults. These studies have yielded mixed results regarding whether vitamin D status is associated with risk of falls.

One study conducted by Snijder et al. (2006), looked to prospectively investigate the association between serum 25-hydroxyvitamin D 25OHD levels and risk of recurrent falling in both older men and women. This study included 3,107 participants ages 65 and older in the Netherlands. For this study, respondents were asked to report on their falls weekly and mail them into the research center every 3 months. Vitamin D status and PTH were measured with blood samples. Researchers also investigated characteristics of participants including age, sex, season, region, education, lifestyle variables, weight, BMI, number of chronic diseases and

serum creatinine level that were measure due to their effect as confounding variables that might be associated with both vitamin D status and falls. Physical performance was also assessed as a potential mediator with various tests performed.

The results of this study showed that low 25OHD (<10 ng/ml) was associated with an increased risk of falling. There was a statistically significant effect modification by age, and stratified analyses (<75 and ≥ 75 years) showed that the associations were particularly strong in the younger age group; the odds ratios were 5.21 (95% CI 2.03–13.40) for two falls or more and 4.96 (1.52–16.23) for three falls or more.

The strengths of this study were that the population size was fairly large, serum blood samples were taken, and it included both men and women. However, as with most of the other studies, participants were asked to self-report falls, and mail in their results with this study in particular, which could have led to reporting errors if the fall information was not accurate.

Another study by Larocque et al. (2015) was completed by four clinical centers across the U.S. to examine both serum vitamin D status and vitamin D intake with falls in a sample of postmenopausal women from the Study of Osteoporotic Fractures. The sample size of this study included 4,369 females ages 65 years and older that completed the Block Food Frequency Questionnaire (FFQ) that consisted of 109 food items that included questions regarding alcohol intake and vitamin and mineral supplementation. Protein, calcium, and vitamin D intakes were estimated using these FFQ's completed by the participants. Fall incidence was captured by post card and telephone calls every four months. Confounding variables that were assessed included history of previous falls, age, number of alcoholic drinks per week, depressive symptoms, number of items out of six Instrumental Activities of Daily Living, count of total medications,

average of right and left isometric handgrip strength, BMI, current smoking status, number of hours of sleep per night, visual acuity of 50 or better for both eyes, and physical activity factors. Subjects self-rated their health by answering several questions.

This study found that in separate, unadjusted models, dietary protein (per 1 g/kg increase) and vitamin D (per 100 International Unit (IU) increase) significantly increased the odds ratio (OR) of falling (OR 1.35, 95% CI 1.15–1.59; OR 1.11, 95% CI 1.03–1.19, respectively). Once fall-related covariates were added to each model, however, dietary protein and vitamin D were noncontributory to falls. This study found contradicting results to the previous study, but the strength was that covariates were added into statistical analysis to evaluate whether it was protein and/or vitamin D status alone that contributed to falls. Once again, many items were reported based on the participants self-reporting information, so there could be reporting error with these results. Protein was also included as an independent variable in this study, so vitamin D was not isolated to assess for its affects alone in relation to falls.

Yet another prospective cohort study conducted by Ghafouri et al. analyzed the association between serum vitamin D concentration and falls among Iranian older (2016). There was a total of 82 participants over the age of 60 years from the emergency departments of the Rasoul Akram and Sina hospital located in Iran. A structured, self-administered checklist was given to participants to complete that included demographic information (age, gender, level of education and marital status). Past medical history and serum 25OHD concentrations of the participants were obtained at the time of hospitalization. Researchers also asked about any recurrent fall experiences during the six-month follow-up. The self-administered checklist was completed during admission and in a six-month follow-up through telephone calls to the

patients, their family, or caregivers who were aware of the patients' conditions. The researchers also asked about any recurrent fall experience during the six-month follow-up. Those who reported recurrent falls were asked about the frequency of their falls.

Researchers of this study found no association between the mean serum 25OHD levels and the number of recurrent falls in elderly patients irrespective of their age, gender, or physical activity groups. Although this study found that vitamin D status was not associated with risk of falls among older adults, the sample size of this study was much smaller than the other studies completed regarding the subject. This study was also completed in Iran, and had a population that greatly varies as far as location, latitude, and diet compared to other studies conducted. Strengths of this study include that fact that they obtained serum vitamin D levels and past medical history that the hospitals had in their records.

There are many similarities, and some differences among the design and data collection of the prospective cohort studies that investigated vitamin D status and falls among the elderly population. Studies have been conducted in a wide range of locations, from the United States, to the Netherlands, to Iran, with a wide range of sample sizes. Some of the studies simply focused on vitamin D as the independent variable with the outcome of falls, while others focused on other items along with vitamin D status, such as protein, to see their effect on falls. Ages among participants of these studies were fairly similar, ranging between 65-70 years and older. Some studies focused on both genders, but other studies simply focused on women, since they tend to have a lower physical activity status and higher rates of vitamin D and calcium status. Another difference among the studies, however, is the living situation and health status of the participants. Some studies only included participants that were

independently living and physically able to complete certain tasks, while others did not focus on these factors as much when choosing inclusion and exclusion criteria. There were mixed results of the studies, with one of the studies concluding that vitamin D status does, indeed, contribute to falls with a higher rate of falls among participants with a lower vitamin D status. On the other hand, two of the studies concluded that there was no significant relationship between serum vitamin D status and risk of falls. Although the validity of these prospective cohort studies is fairly high, there was room for reporting error, since all three studies had participants self-report information, especially falls, which may have led to some inaccurate data used.

Based off the results of these prospective cohort studies, there is no one specific conclusion that can be reached since conflicting results were obtained. The strength of the Snijder et al. and Larocque et al. can be noted on higher worth compared to the Ghafouri et al. study, simply due to the size of the population sizes, however, these two studies found opposing results, causing no conclusive evidence to be found. Even with the strength in sample sizes and methods, no causality can be made due to the study design as a prospective cohort study that did not include any controls or blinding.

Randomized Controlled Trials

This evidence analysis of vitamin D status and its relation to falls among older adults includes two randomized controlled trials. There were differences in the methods of how these studies were conducted, and two very different conclusions were reached.

One study was conducted by Law et al. in 2006 that aimed to determine whether vitamin D supplementation reduces the risk of fracture or falls in elderly people in care home accommodation in the south of England. The 3,717 participants of this study were ages 60 years

and older that did not include temporary residents admitted for respite care, residents who were already taking calcium/vitamin D or drugs that increase bone density (such as bisphosphonates), or residents or residents who had sarcoidosis or malignancy of other life-threatening illness. This was a cluster randomized control trial that was completed by the computer based on 223 living units. Residents in the units were either allocated to receive vitamin D tablets containing ergocalciferol 2.5 mg every three months, or the control group units received no vitamin D (there was no placebo). The care home staff also recorded any falls that occurred and were not told that falls were measured as the primary outcome of the study. Blood samples were collected in the care homes from 18 treated group participants (a 1% sample) on three occasions- immediately before the first dose of vitamin D, 1 month after the first dose and 3 months after the first dose (immediately before the second dose. Blood samples measured 25-hydroxyvitamin D, PTH and calcium (adjusted for albumin). Although vitamin D intake was not specifically measured, all residents were served relatively the same diet based off the facility menus for the duration of the study.

The results of this study found that risk of falls between the vitamin D and control groups were not statistically significantly different. The researchers concluded that vitamin D supplementation alone failed to reduce the incidence of fractures or reported falls, despite the fact that the vitamin D supplement effectively raised the serum 25-hydroxy vitamin D concentration. Of course, it is hard to determine whether the amount of vitamin D supplementation was a therapeutic dose, especially since dietary vitamin D intake was not recorded for participants of the study. A limitation of this study was that there was not much information on the selection of participants and the non-availability of data on residents who

declined to join the trial or were excluded. There is strength in the fact that there was a control group in this study, and the cluster design was appropriate so that each unit of residents received the same treatment with less chance for error in the caregivers giving the wrong treatments to various participants. There was no blinding in the administration of the vitamin D, which decreased the validity of the results, though.

The other randomized controlled trial was conducted by Bischoff et al. in 2003 that looked to test the hypothesis that vitamin D and calcium supplementation would affect calcium homeostasis and increase muscle strength, which would reduce the risk of falling. This study included 89 participants of ages 60 and older who were cared for in a long-stay geriatric-care units in Switzerland. This study was a double-blinded randomized control trial that included a 6-week pretreatment period and a 12-week treatment period. The subjects were randomly assigned to the vitamin D plus calcium group that received two tablets containing 600 mg of calcium carbonate and 400 IU of cholecalciferol per tablet. Subjects that were randomly assigned to the calcium group received two tablets containing 600 mg of calcium per tablet. The tablets given in both groups had identical appearance and patients, administrators and all investigators were all blinded to the treatment assignments throughout the study. Tablets were administered twice per day with breakfast and dinner, and they were swallowed in the presence of the study nurse to ensure compliance. The number of drugs each participant took was recorded and the diet was overall the same for all participants. Musculoskeletal function was also assessed by summed score including four physical tests. Fasting blood samples measured serum calcium, phosphate, and albumin and total alkaline phosphatase. Serum 25-

hydroxyvitamin D, 1,25-dihydroxyvitamin D, and intact parathyroid hormone (PTH) concentrations were measured by radioimmunoassay.

Key findings of the study found that among subjects in the Cal+D-group, there were significant increases in median serum 25-hydroxyvitamin D (+71%) and 1,25-dihydroxyvitamin D (+8%). After adjustment, Cal+D-treatment accounted for a 49% reduction of falls (95% CI, 14–71%; $p < 0.01$) based on the fall categories stated above. Among fallers of the treatment period, the crude average number of excessive falls (the number of falls during the treatment minus the number of falls during the pre-treatment period) was significantly higher in the Cal-group ($p = 0.045$). Musculoskeletal function improved significantly in the Cal+D-group ($p = 0.0094$). Authors concluded that a single intervention with vitamin D plus calcium over a 3-month period reduced the risk of falling by 49% compared with calcium alone. Over this short-term intervention, recurrent fallers seem to benefit most by the treatment and the impact of vitamin D on falls might be explained by the observed improvement in musculoskeletal function. Vitamin D and calcium supplementation were superior to calcium supplementation alone in regard to fall prevention, musculoskeletal function, and bone function.

This study is a bit different than the other randomized control trial in that the sample size was smaller and both calcium and vitamin D were used as treatments that yielded positive results. There are strengths in the fact that the design of the study has the highest validity with it being a double-blinded randomized controlled trial.

This study, like the other randomized controlled trial by Law et al., was conducted with participants in a long-stay care facility, and they were not independently living. There were strengths in the setup of these two studies, however, since the information was not self-

reported by participants, but rather, witnessed by the caretakers and recorded, yielding results with a higher probability of accuracy. Since caretakers of these facilities were the ones witnessing falls as they occurred, the accuracy of this information is likely higher than that of the self-reported data that participants give on falls that have previously occurred in other studies. There were treatments involved in both of these studies, which was not a part of the design of any of the other studies. These were two very differently designed studies that came up with two very different results. The study by Law et al. concluded that there was no significant impact on falls by vitamin D status, with the independent variable of vitamin D status alone. Although this study had a large sample size, there were weaknesses in the cluster design and no placebo as the control. There was also no blinding involved in this study compared to the Bischoff et al. study. The strengths of the Bischoff study were that the design had very strong validity with blinding involved in the randomized control trial that involved a placebo. It was different than all of the other studies in that it included calcium and vitamin D or calcium as the treatments, so vitamin D was not isolated in order to determine that vitamin D status alone caused the reduced rates of falls. Once again, evidence of these studies are non-conclusive whether vitamin D status is predictive of falls rates since the results obtained are in opposition.

Summary and Conclusions

There is a wide variety in the designs and populations of evidence available regarding research of vitamin D status and its relation to falls among older adults. Although it was hypothesized that falls could be prevented by having adequate serum vitamin D levels, the body of evidence is inconclusive.

The cross-sectional observational studies conducted by Peterson et al. and Suzuki et al. both pointed toward the conclusion that vitamin D status does, in fact, play a role in preventing falls. Although the sample sizes of these two studies are fairly large, there just is not much validity behind these results due to the weakness in design. Both studies are cross-sectional and look at participants that are living independently, of sound cognitive and physical function, for the most part. This information simply adds to the literature regarding vitamin D status and falls, however, there have been other studies conducted with stronger designs that have concluded the opposite of these observational studies.

All of the prospective cohort studies had such conflicting results, that, once again, these studies added to the body of evidence, but they had mixed results that led to an inconclusive conclusion regarding vitamin D status and falls among older adults. The study conducted by Snijder et al. had its strength in a very large sample size of both men and women that found there is a statistically significant increase in rates of falls among older adults ages 65 and older that have a decreased vitamin D status. The Larocque et al. study found results that pointed to just the opposite, but they also assessed vitamin D status and protein status in conjunction, rather than isolating solely vitamin D status' effect on falls. This study sample size was even larger than the Snijder et al. study. The Ghafouri et al. study was interesting in the sense that participants were recruits from patients in emergency departments at hospitals in Iran. These participants were not required to be either independently living or residing at a long-term care facility as with other studies. The validity of this study cannot be compared to that of the Snijder and Larocque studies because of the much smaller sample size of 82 participants. This study is also hard to compare to the other two observational studies, with a vast difference in

diet and differences while being performed in Iran. All of these studies were similar in that they used serum 25OHD levels to measure vitamin D status, which is recommended as it most closely reflects circulating vitamin D (Office of Dietary Supplements, 2018). However, they all have limitations in the fact that the information on falls from participants is self-reported by the participants themselves, and it is impossible to determine their accuracy.

The randomized controlled trials that studied rates of falls with vitamin D supplementation had the highest level of validity, but results were also inconsistent. On one hand, the Law et al. study found that vitamin D supplementation alone failed to prevent falls among participants, even though it successfully raised the serum 25OHD levels of those participants. On the other hand, the Bischoff et al study found that the calcium plus vitamin D supplement group had significantly less falls than the calcium alone supplementation group, pointing to the conclusion that vitamin D plus calcium significantly decreased recurrent falls among participants. Authors concluded that impact of vitamin D on falls might be explained by the observed improvement in musculoskeletal function. While the design of this study is stronger than the Law et al. study, the sample size is also much smaller than the Law et. al study.

Overall, the evidence regarding whether increased vitamin D status can prevent falls among older adults is inconclusive, and therefore, vitamin D cannot be linked in causing the prevention of falls among older adults. Among all the studies, there are some that state that there is no evidence to link vitamin D status in preventing falls among older adults, but other studies conclude that there is evidence to link vitamin D status in preventing falls among older adults. In order to connect a causation with vitamin D status and falls, there would have to be

many more randomized controlled trials that are double-blinded in design with large sample sizes.

CHAPTER 3: METHODS

The Evidence Analysis Library (EAL) was created by the Academy of Nutrition and Dietetics with a process that involves a simple, reliable way for dietetics practitioners to enhance their practice with an array of quality scientific evidence. The Academy developed this tool to conduct systematic reviews that incorporate several models in its own customized process. Methods used in the evidence analysis process are designed specifically to ensure objectivity, transparency and reproducibility. This project used the evidence analysis process as described by the Academy of Nutrition and Dietetics. The EAL process follows five steps: 1) Formulate the Evidence Analysis Question, 2) Gather and Classify Evidence, 3) Critically Appraise Each Article, 4) Summarize the Evidence and, 5) Write and Grade the Conclusion Statement (Academy of Nutrition and Dietetics, 2018). Below they are described in further detail in general and as they apply to this project.

1) Formulate the Evidence Analysis Question

This step describes specifying a focus question in a "defined area of practice". In order to do so, the Academy of Nutrition and Dietetics outlines three key items to generate quality questions including the following: the "PICO" format, an analytical framework that identifies links between factors and outcomes, and uses the Nutrition Care Process to serve as a framework. The PICO format outlines the population, intervention, comparison intervention, and outcomes to formulate the evidence analysis question. In this scenario the population includes older adults ages 65 and older in an institutionalized setting. The intervention is the vitamin D status of participants and ensuring that their vitamin D levels meet the

recommended amount. The comparison intervention looks at participants that do not meet the recommended level for serum vitamin D. The outcome that the question is evaluating is the falls rate that older adults experience. Thus, the research question in this project is, does adequate vitamin D status prevent falls among the older adult population (>60 years-old).

2) Gather and Classify the Evidence

This step includes developing a detailed search plan that enables the conduction of a detailed literature search.

Search Plan & Results

Research Question

Does adequate vitamin D status prevent falls among the older adult population (>60 years-old)?

Inclusion Criteria

The inclusion criteria involved in the search are participants of ages 65 years and older, all study designs, 10 or more subjects, assessment of vitamin D status, assessment of falls, from both free living and institutionalized settings and between the years 2000-2018 conducted in the English language.

Exclusion Criteria

The exclusion criteria of the search are participants of ages 64 or younger, studies conducted in any languages other than English, studies with less than 10 individuals, lack of assessment of vitamin D status and falls, and studies conducted prior to the year 2000.

Search Terms

Search terms include the terms “vitamin D”, “falls”, “older adults”, and “vitamin D supplementation”

Intervention

Vitamin D supplementation

Type of Study Design

Randomized Controlled Trials, Prospective Cohort Studies, Cross Sectional Studies

Electronic Databases

Database*:* PubMed

Hits: 82

Articles to Review: 9

Total Articles Identified to review from electronic databases: 82

Inclusion List

List of Articles Included from Electronic Databases

Bischoff HA, Stahelin HB, Dick W, Akos R, Knecht M, Salis C…&Conzelmann M. (2003). Effects of vitamin D and calcium supplementation on falls: A randomized control trial. Journal of Bone and Mineral Research, 18(2): 343-351.

Ghafouri HB, Zare M, Bazrafshan A, Modirian E, Mousavi A, & Abazarian N. (2016). The association between serum 25-hydroxyvitamin D level and recurrent falls in the elderly population: a cohort study. Electronic Physician, 8(8): 2707-2712.

Hulisz D. (2011). Which is Better: Vitamin D2 or D3? *Medscape.* Retrieved from https://www.medscape.com/viewarticle/746941#vp_2

Larocque SC, Kerstetter JE, Cauley JA, Insogna KL, Ensrud K, Lui LY, & Allore HG. (2015). Dietary protein and vitamin D intake and risk of falls: A secondary analysis of postmenopausal women from the study of osteoporotic fractures. *Journal of Nutrition in Gerontology and Geriatrics*, 34(3): 305-318.

Law M, Withers H, Morris J & Anderson F. (2006). Vitamin D supplementation and the prevention of fractures and falls: results of a randomised trial in elderly people in residential accommodation. Age and Ageing, 35(5)482-486.

Peterson A, Mattek N, Clemons A, Bowman GL, Buracchio T, Kaye J, & Quinn J. (2012). Serum vitamin D concentrations are associated with falling and cognitive function in older adults. The Journal of Nutrition, Health and Aging, 16(10): 898-901.

Snijder MB, van Schoor NM, Plujim SMF, van Dam RM, Visser M & Lips P. (2006). Vitamin D Status in Relation to One-Year Risk of Recurrent Falling in Older Men and Women. *The Journal of Clinical Endocrinology & Metabolism,* 91(8): 2980-5.

Suzuki T, Kwon J, Kim H, Shimada H, Yoshida Y, Iwasa H, & Yoshida H. (2008). Low serum 25-hydroxyvitamin D levels associated with falls among Japanese community-dwelling elderly. Journal of Bone and Mineral Research, 23(8):1309-1317.

List of Articles Included from Hand Search or Other Means

No other articles identified.

List of Excluded Articles with Reason

Excluded Articles	**Reason for Exclusion**
Uusi-Rasi K, Patil R, Karinkanta S, Kannus P, Tokola K, Lamberg-Allardt C, & Sievanen H. (2017). A 2-Year Follow-Up After a 2-Year RCT with Vitamin D and Exercise: Effects on Falls, Injurious Falls and Physical	Addressed exercise benefits with vitamin

Functioning Among Older Women. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences,* 72(9):1239-1245.	D supplementation combined
Dam TT, von Muhlen D, & Barrett-Connor EL. (2009). Sex-specific association of serum vitamin D levels with physical function in older adults. *Osteoporosis International,* 20(5):751-60.	Included physical performance tests including timed up and go (TUG) and timed chair stand (TCS) to determine falls risk
Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B. (2008). Additive benefit of higher testosterone levels and vitamin D plus calcium supplementation in regard to fall risk reduction among older men and women. *Osteoporosis International,* 19(9): 1307-14.	Included only vitamin D combined with calcium as intervention

3) Critically Appraise Each Article

This step includes assessing each research article for methodological quality. Each study design is evaluated for appropriateness and the quality of the conduction of each study using the Quality Criteria Checklist (QCC). The worksheets aide in evaluating the relevance and validity of study design, methods, and conclusions or outcomes found from the study.

4) Summarize the Evidence

This step involves first, extracting key data from the included articles by using the Academy's web-based data extraction template. Second, the evidence extracted is summarized from each study into a brief, coherent, and easy-to-read summary. The end results of this process is the Evidence Summary that includes a synthesis of evidence and identifies similarities and differences among the body of articles. There is a larger emphasis on stronger studies rather than weaker studies that do not carry the same level of validity.

5) Write and Grade the Conclusion Statement

This step involves developing a concise conclusion statement tied to the research question and assigning a grade to this conclusion statement. The grade is determined by the overall strength and weaknesses of evidence in forming the conclusion statement. The grade scale utilized by the Academy is as follows: Grade I (good/strong), II (fair), III (limited/weak), IV (expert opinion only), or V (not assignable).

In researching this topic, there are potential problems that can arise including a lack of validated research, lack of research articles pertaining to the research question, and a lack of research for the population specified.

CHAPTER IV: RESULTS

The evidence analysis included a total of seven studies that varied in study design, including cross-sectional studies, prospective cohort studies, and randomized controlled trials to answer the question "Does adequate vitamin D status prevent falls among the older adult population (>60 years-old)?" A summary of results is shown in Table 1 below.

Table 1: Results Summary

Author, Year, Study Design, Class, Rating	**Study Purpose**	**Study Populations**	**Outcomes**	**Limitations**
Snijder MB, van Schoor NM, Plujim SMF, van Dam RM, Visser M & Lips P, 2006, prospective cohort study, B, +	To prospectively investigate the association between serum 25-hydroxyvitamin D [25OHD] levels and risk of recurrent falling in older men and women	1231 women and men ages 65 years and older participating in the Longitudinal Aging Study Amsterdam	Low 25OHD was associated with and increased risk of falling. After adjustment for age, sex, education level, region, season, physical activity, smoking, and alcohol intake, the odds ratios (95% confidence interval) were 1.78 (1.06-2.99) for subjects who experienced two falls or more as compared with those who did not fall or fell once and 2.23 (1.17-4.25) for subjects who fell three or more times as compared with those who fell two times or less	Fall reports were sent in and monitored by participants (self-reported), no treatments involved with prospective cohort study
Larocque SC, Kerstetter JE, Cauley JA, Insogna KL, Ensrud K, Lui LY, & Allore HG, 2015, prospective cohort study, B, +	to evaluate the association between dietary protein and subsequent falls in a sample of postmenopausal women from the Study of Osteoporotic Fractures (SOF)	4369 Caucasian females ages 65 years and older from 4 clinical centers across the U.S.	In separate, unadjusted models dietary protein (per 1 g/kg increase) and vitamin D (per 100 International Unit (IU) increase) significantly increased the odds ratio (OR) of falling (OR 1.35 95% CI 1.15–1.59, OR 1.11 95% CI 1.03–1.19, respectively). Once fall-	No treatments involved with prospective cohort study

	and examine both serum vitamin D status and dietary viatmin D intake with falls		related covariates were added to each model, dietary protein and vitamin D were noncontributory to falls.	
Peterson A, Mattek N, Clemons A, Bowman GL, Buracchio T, Kaye J, & Quinn J, 2012, D, +	To elucidate the mechanism through which vitamin D is associated with decreased falls.	233 recruits from the Intelligent Systems for Assessment of Aging Changes Study (ISAAC), independently living older adults over age 70	Fallers had a significantly lower vitamin D level (32.9 ng/ml) as compared to non-fallers (39.2 ng/ml) ($p<0.01$). A 5 ng/ml increase in vitamin D corresponds to a 20% decrease in odds of falling. Cognitive status (CDR=0 vs. 0.5) did not modify the relationship between vitamin D and falls risk ($p=0.12$).	No controls or causation made
Ghafouri HB, Zare M, Bazrafshan A, Modirian E, Mousavi A, & Abazarian N, 2016, prospective cohort study, B, +	To examine the association between serum vitamin D concentration and recurrent falls in Iranian older adults.	140 participants (47 males and 35 females), elderly over the age of 60	A small, but insignificant association was found between the mean serum 25OHD levels and the number of recurrent falls in elderly patients irrespective of their age, gender, or physical activity groups (OR=1.008, $p=0.992$)	Self-reported falls data, no causation could be made
Suzuki T, Kwon J, Kim H, Shimada H, Yoshida Y, Iwasa H, & Yoshida H, 2008, cross sectional, D, +	To study the association of serum 25OHD levels and falls among Japanese community-dwelling elderly	2957 (950 males and 2007 females) Japanese participants ages 65 and older	Low 25OHD level was significantly associated with a high prevalence of falls in Japanese elderly women because of their inferior physical performance.	No causation proved with cross sectional observational design
Law M, Withers H, Morris J & Anderson F, 2006, Randomized Control Trial, A, +	to determine whether vitamin D supplementation reduces the risk of fracture or falls in elderly people in care home accommodation	3717 (892 males and 2825 females) ages 60 and older	The differences between the vitamin D and control groups were not statistically significant. Vitamin D supplementation alone failed to reduce the incidence of fractures or reported falls in our trial, despite the fact that the vitamin D effectively raised the serum 25-	Selection of participants and recruitment not explained in detail

			hydroxy vitamin D concentration in a representative 1% sample from the treated group.	
Bischoff HA, Stahelin HB, Dick W, Akos R, Knecht M, Salis C,…&Conzelmann M, 2003, Randomized Control Trial, A, +	To test the hypothesis that vitamin D and calcium supplementation would affect calcium homeostasis and increase muscle strength, which would reduce the risk of falling.	122 females age 60 and older	Among subjects in the Cal+D-group, there were significant increases in median serum 25-hydroxyvitamin D (+71%) and 1,25-dihydroxyvitamin D (+8%). After adjustment, Cal+D-treatment accounted for a 49% reduction of falls (95% CI, 14–71%; $p < 0.01$) based on the fall categories stated above. Among fallers of the treatment period, the crude average number of excessive falls was significantly higher in the Cal-group ($p = 0.045$).	Only shows results among females, relatively small samples size

Cross-Sectional Studies

The cross-sectional studies conducted in this evidence analysis had similar conclusions in that older adults that have adequate vitamin D status (>25 ng/ml) experienced a decreased incidence of falls. Both studies received a positive rating and provided evidence supporting the relationship between adequate vitamin D status and decreased risk of falls. However, because of the cross-sectional nature of these studies, causal relationships between adequate vitamin D status and decreased risk of falls cannot be determined. Therefore, due to the lack of strength of study design, these studies only received a D class rating.

Peterson et al. designed a cross sectional study to discover the mechanism through which vitamin D is associated with decreased falls (2012). Participants of this largely Caucasian

study had to be over the age of 70, living independently and of sound cognitive function (determined by the Clinical Dementia Rating score and Mini Mental State Examination). Key findings of this study included that fallers had significantly lower serum vitamin D levels (average of 32.9 ng/ml) compared to non-fallers (average of 39.2 ng/ml) ($p < 0.01$).

In the Suzuki et al. cross-sectional study (2008), researchers looked serum 25OHD levels and falls among Japanese community-dwelling elderly ages 65 and older. These participants were also living independently and were of sound physical capacity (determined by peak hand force grip measured with a dynamometer, measured time taken to walk 5m, and stork standing test measuring standing time on one foot with eyes open). In this study, a low serum 25-hydroxy vitamin D (25OHD) level (mean 24.2 +/- 4.9 ng/ml) was found specifically to be associated with a high prevalence of falls among women (men's mean 28.5 +/- 5.0 ng/ml, $p<0.001$). Researchers concluded this was due to their inferior physical performance measured in the hand grip test (male 37.1 +/-22.5, female 35.8 +/-23.3, $p<0.001$), stork standing test (male 37.1 +/- 22.1, female 35.8 +/- 23.3, $p = 0.152$) and walking test (male 1.23 +/-0.26, female 1.18 +/- 0.29, $p<0.001$). The mean serum 25OHD concentration was significantly lower ($p<0.01$) in women than in men. Multiple logistic regression analysis showed significant and independent association between 25OHD levels and experience of falls among women only.

Prospective Cohort Studies

There are mixed results among the two prospective cohort studies included in this evidence analysis. These studies with positive quality ratings provide more evidence for causality in concluding whether or not vitamin D status impacts falls rates among older adults.

The study conducted by Snijder et al. (2006) looked to prospectively investigate the association between serum 25OHD levels and risk of recurrent falls in men and women of the ages 65 years and older in the Netherlands. Among this relatively large sample size of 3,107 participants, researchers found that low serum 25OHD (<10 ng/ml) was associated with an increased risk of falling. However, after adjustment for age, sex, education level, region, season, physical activity, smoking, and alcohol intake, the odds ratio (95% confidence interval) was 1.78 (1.06-2.99) for subjects who experienced two or more falls compared to those who did not fall or fell once and 2.23 (1.78-4.25) for subjects who fell three or more times compared to those who fell two times or less. There was also a statistically significant effect modification by age with stratified analyses of those less than 75 years of age and those equal to or greater than 75 years of age that showed the associations were particularly strong in the younger age group with odds ratios of 5.21 (2.03-13.40) for 2 falls or more and 4.96 (1.52-16.23) for three falls or more. Therefore, researchers concluded that poor vitamin D status is independently associated with an increased risk in falling, especially among those aged 65-75 years-old.

The Larocque et al. study (2015) aimed to evaluate the association between dietary protein and subsequent falls in a sample of postmenopausal women. The participants of this study were taken from a previous study, the Study of Osteoporotic Fractures, an observational study of postmenopausal women that included both prospective data on bone health and aging. This fairly large study comprising of 4,886 Caucasian women found that in separate, unadjusted models, dietary protein (per 1g/kg increase) and vitamin D (per 100 IU increase) significantly increased the odds ratio of falling to 1.35 (1.15-1.59) with a 95% confidence interval and 1.11 (10.3-1.19) with a 95% confidence interval, respectively. Although, once fall-

related covariates were added to each model, dietary protein and vitamin D were noncontributory to falls.

The final prospective study analyzed in this evidence analysis by Ghafouri et al. (2016) was designed to examine the association between serum vitamin D concentration and recurrent falls in Iranian older adults over the age of 60 years. The self-administered checklist was conducted, and serum vitamin D status were measured from participants that entered the emergency departments of Rasoul Akram and Sinai Hospitals and evaluated again 6 months later. Authors found that there was no association between the mean serum 25OHD levels and the number of recurrent falls irrespective of their age, gender, or physical activity groups.

Randomized Controlled Trials

The randomized controlled trials on vitamin D status and its effects on falls among the elderly have mixed results. Although study design was stronger with a class A rating (positive quality rating), it is hard to discern the true effect that vitamin D status has among older adults, especially with two opposing results from the study design that can be thought of as the gold standard.

Law, Withers, Morris & Anderson in 2006 researched whether vitamin D supplementation reduces the risk of fracture or falls in elderly people over the age of 60 (n=3,717) in home care. The intervention group took 2.5 mg ergocalciferol every 3 months and were compared to a control group that did not take any vitamin D supplementation or placebo. 25OHD, PTH and calcium were measured. Participants had an incidence of non-vertebral fractures (3.2% per year) and hip fractures (1.1% per year). Baseline 25OHD was high (median

47 nmol/L for the entire sample). There was no change in PTH nor in serum calcium from baseline to the end of the intervention. The conclusion of this study was that vitamin D supplementation alone failed to reduce the incidence of fractures, despite the fact that the vitamin D supplementation effectively raised the serum 25OHD concentration among the subsample that was tested (18 participants).

The Bischoff et al. randomized control trial (2003) had opposing results. This study aimed to test the hypothesis that vitamin D and calcium supplementation would affect calcium homeostasis and increase muscle strength, which would reduce the risk of falling. The difference in this population of older adults ages 60 and older (n=122) was that they were staying in long-stay geriatric care units in Switzerland. This study found that among the subjects in the 600 mg calcium carbonate and 400 IU cholecalciferol (Cal+D) treatment group, there were significant increases in median serum 25OHD concentration (+71%) and 1,25-dihydroxyvitamin D (+8%) and no change in the control group. After adjustment, the Cal+D group had a 49% reduction in falls (95% confidence interval, 14-71%, $p<0.01$) and no change in the control group. When looking at all falls that occurred during the treatment period, the crude average number of excessive falls was significantly higher in the calcium group of 600 mg dose ($p=0.045$). Authors concluded that vitamin D plus calcium over a 3-month period reduced the risk of falling by 49% compared with calcium alone.

Conclusion Statement

Adequate vitamin D status (>/=50 nmol/L or >/=20 ng/ml) among older adults (ages 60 and older) is associated with a reduced risk in falls, especially among women.

This is a grade III conclusion due to the limited number of studies of weak design, lack of generalizability and flaws amongst study designs. Of the 7 total studies included, mixed results were obtained from the prospective cohort and cross-sectional studies. Snijder et al. found that low vitamin D status (<10 ng/ml) was associated with an almost doubled risk of falling (OR 1.78 (95%CI[1.06-2.99])(2006) compared to those with normal vitamin D status. Peterson et al. (2012) found similar results, where fallers had a significantly lower average serum vitamin D concentration (32.9 ng/ml) compared to non-fallers (39.2 ng/ml) ($p<0.01$). In contrast, Larocque et al. found that vitamin D status was noncontributory to falls (2015). Ghafouri et al. (2016) also found no association between mean serum 25-hydroxy vitamin D levels and the number of recurrent falls. Suzuki et al. only found a significant association between low 25-hydroxy vitamin D levels and a high prevalence of falls among women (2008). Among the randomized controlled trials, there were mixed results as well, with Law et al. (2006) finding that there were no statistically significant differences in falls among a vitamin D supplementation group versus a placebo group. However, Bischoff et al. (2003) found that the calcium plus vitamin D supplementation had a 49% reduction in falls (95% CI, 14–71%; $p < 0.01$) compared to a calcium only supplementation group.

CHAPTER V: DISCUSSION

Vitamin D status is a critical component of health, especially among older adults. Its relation to bone and muscle function has been researched and linked in the past. With the older adult population at an increased risk for falling, vitamin D status has been further researched in regards to its relation to falls among older adults. Articles including a variety of observational studies, cross sectional and prospective cohort in nature, and randomized controlled trials looking at the relationship between vitamin D status and falls among older adults were included as a part of this systematic review.

Overall Summary Statement

Poor vitamin D status, characterized by less than the recommended range (<30 nmol/L or <12 ng/ml), is associated with an increased risk of falls among older adults ages 60 and older. This is especially true for women. However, mixed results were obtained from the variety of research available on this topic. The conclusion that poor vitamin D status is associated with an increased risk of falls was found among a majority of the studies (4 out 7) in this evidence analysis. The studies were designed very differently, so many factors affected the results and led to conflicting conclusions whether vitamin D status did, indeed, affect falls among older adults. Differences included varying levels of vitamin D status (pre- and post-treatment in randomized controlled trials), varying treatments among the randomized controlled trials that included both vitamin D supplementation alone and vitamin D plus calcium supplementation, and differing inclusion and exclusion criteria.

In order to determine whether vitamin D status alone directly and causally impacts risk of falls, more randomized controlled trials need to be conducted among older adults to have a treatment with which to compare pre- and post-vitamin D status results in relation to falls rates.

Comparison of Studies

Vitamin D Levels

Among the randomized controlled trials, each had differing vitamin D levels in the pool of participants based on their pre-treatment levels as a baseline.

The Law et al. (2006) study had a group of participants with higher levels of serum 25-hydroxy vitamin D status, with a median of 47 nmol/l from a subsample of subjects (n=18). The 18 participants were from five homes in different counties in the south of England. This vitamin D level is just below the 30-50 nmol/l range, which is categorized as "generally considered adequate for bone and overall health in healthy individuals" per the National Institutes of Health recommendations (2018). It is not surprising that this study found that vitamin D supplementation alone failed to reduce the incidence of reported falls, despite the fact that vitamin D effectively raised the 25-hydroxyvitamin D concentration, with a median vitamin D level of 74 nmol/l after 3 months of 2.5 mg ergocalciferol tablets every month. It would make sense that there was no significant change in falls rates when the starting vitamin D levels were already almost considered to be in the adequate range.

The other randomized controlled trial conducted by Bischoff et al. (2003) included in this evidence analysis had differing levels of vitamin D that was measured pre-treatment. 50%

of women had serum 25-hydroxyvitamin D concentrations below 12 ng/ml (30 nmol/l), 90% below 31 ng/ml (78 nmol/l), and 95% below 40 ng/ml (100 nmol/l). The calcium plus vitamin D supplementation group had 49% less falls (95% CI, 14-71%, $p<0.01$) than the calcium supplementation only group. Also, among fallers of the treatment period, the average number of excessive falls, which is classified as the number of falls during the treatment minus the number of falls during the pre-treatment period, was significantly higher in the calcium supplementation only group ($p=0.045$). It would make sense why this study saw a significant reduction in falls from the vitamin D+ calcium supplementation, since the baseline vitamin D serum status among participants was much lower than the Law et. al study participant group, and many of the subjects were deficient at baseline. The median serum 25OHD concentration was 47 nmol/L before the first dose of vitamin D and 82 nmol/L 1 month after, an increase of 31 nmol/L. Three months later (immediately before the second dose), the median serum concentration was 74 nmol/L, confirming that 3-monthly dosing is sufficient. There were also marked increases in serum 25-hydroxyvitamin D (71%) and 1,25 dihydroxyvitamin D (8%) from baseline to after the treatment period.

Treatment Types

The treatment types differed between the two randomized controlled trials included in the evidence analysis. The Law et al. study focused on vitamin D supplementation only, with the treatment group receiving 2.5 mg ergocalciferol every 3 months (equal to 1,100 IU of cholecalciferol per day). The placebo group received no vitamin D supplementation. Markers that were also measured included parathyroid hormone, calcium, and phosphate. Results found that parathyroid hormone levels decreased slightly from a mean of 5.1 pmol/l to 4.4 pmol/l,

which are both still within the normal range. However, calcium and phosphate levels remained stable through the treatment course with phosphate levels beginning and ending with a mean of 1.2 mmol/l and calcium levels remaining at a mean of 2.3 mmol/l. On the other hand, the Bischoff et al. study included both calcium plus vitamin D supplementation in the treatment group with a 12-week treatment period. This group received 2 tablets containing 600 mg of calcium carbonate and 400 IU of cholecalciferol per tablet that were administered twice per day. The comparison group received 2 tablets containing 600 mg of calcium two times per day.

The Law et al. study had a slightly higher dose of vitamin D supplementation per day, with 1,100 IU ergocalciferol/day equivalent compared to 800 IU cholecalciferol/day. Both exceeded the RDA for vitamin D supplementation (600 IU vitamin D for people ages 1-70 and 800 IU for people over the age of 70) (reference the IOM's DRI's (the actual source of the recommendations)). In the Bischoff et al. study (2003), of the 1,762 participants that were allocated to the vitamin D treatment group, 42 (2%) stopped taking vitamin D before the end of the trial, 28 because of cancer or other serious illness, 13 refused the tablets, and one was diagnosed with hypercalcemia. In the Law et al. (2006) study, of the 89 participants that completed the study, 10 had decreased compliance with vitamin D and/or calcium treatment.

Inclusion and Exclusion Criteria

There were varying inclusion and exclusion criteria among the studies included in the evidence analysis, ranging in ages, differing groups of gender, living environments, and much more. All participants included among the various studies were at least 60 years of age or older. Both the Law et al. study and Bischoff et al. study included men and women over the age of 60.

However, the Peterson et al. study (2012) only included women over the age of 70. With a wide variety of age ranges included among the various studies from 60 years of age and older to 70 years of age and older, there was also a variety of results based on age inclusion criteria. The Peterson et. al study was the only study included in the evidence analysis to include older adults ages 70 and older, with a result of fallers having a significantly lower vitamin D level (32.9 ng/ml) compared to non-fallers (39.2 ng/ml) ($p<0.01$). Three studies included participants ages 65 years and older, however, there were conflicting results whether vitamin D status affected falls among participants or not. Three of the studies included participants of the age of 60 and older, but those also yielded mixed results as well.

Studies included various gender groups as well, with some studies only focusing on women. The Snijder et al. study (2006) and the Larocque et al. study (2015) only included women over the age of 65 with a prospective cohort design. Lastly, the randomized controlled trial that Bischoff et al. conducted only included women over the age of 60. All three of these studies concluded that a low vitamin D status correlated or caused a decreased risk of falls. Suzuki et al. (2008) included both women and men in their study but found an association between serum vitamin D status and risk of falls only in women. Therefore, women are more likely than men to have an increased risk of falls dependent upon a lower vitamin D status (<30 mg/dl).

Some studies in the evidence analysis included participants that were community-dwelling or independently living, while some studies only included participants living in a medical care facility setting. There was no association between setting and whether or not vitamin D had an effect on risk of falls. The Peterson et al. study included those independently

living over the age of 70 found that fallers had a significantly lower vitamin D status as compared to non-fallers ($p<0.01$). Cognitive status did not play a significant role in modifying the relationship between vitamin D status and falls risk. Among community-dwelling Japanese elderly over the age of 65 in the Suzuki et al. study, there was an association between vitamin D status and falls reported only among women in the cross-sectional observational design. The Law et al. study focused on elderly living in care home accommodation throughout Britain and found that vitamin D supplementation alone failed to reduce the incidence of reported falls when comparing vitamin D plus calcium supplementation versus calcium supplementation alone. There are overall mixed results in regards to the type of setting that was studied in whether vitamin D status affects falls risks among older adults. For example, among settings in a medical care facility, the Law et. al study and Larocque et al. (2015) found no significant associations with vitamin D status and risk of falls. On the other hand, among studies involving participants that were independently living, there were both studies like the Snijder et al. (2006), the Bischoff et al. study (2003), and the Peterson et al. study (2012), found that there was a significant association between vitamin D status and falls. However, Ghafouri et al. (2016) and Suzuki et al. (2008) found no association between vitamin D status and risk of falling.

Limitations

Study Design

Overall, there were a lack of randomized controlled trials to strengthen the research available for this evidence analysis. Of the two randomized controlled trials included, they both had limitations that compromised the validity. Although there was a large sample size of 3,717

males and females in the Law et al. study, researchers only included a 1% subsample (18 participants) when measuring 25-hydroxyvitamin D serum levels. Unfortunately, the selection and recruitment of participants was not reported in this study. The Bischoff et al. study had a relatively smaller sample size of 122 females, and they did not isolate vitamin D supplementation when comparing groups, rather they utilized a calcium plus vitamin D supplement regimen for one group and calcium supplement regimen for the other group, which may have led to the calcium supplementation having an impact on the results. Although there are a larger number of observational studies available that were included in the evidence analysis, both prospective cohort and cross sectional in design, these studies lack strength in validity due to their inability to prove causation.

Future Research

Study Design

Since there was a strong lack of randomized controlled trials available regarding research on vitamin D status and its effects on falls rates among the elderly, the strength of the results found could be improved by more randomized controlled trials to better clarify whether vitamin D has a causal relationship with risk of falls. Not only should there be more randomized controlled trials to strengthen results, but these studies should be designed with a large sample size of both men and women, and they should ideally focus on a population that has a lower pre-treatment vitamin D status to see if supplementation to reach vitamin D sufficiency reduces risk of falls. It would also be best if vitamin D serum samples were taken from all subjects in the sample (or at least ~20% of the sample) at baseline in order to have a larger data set to pull

from in linking vitamin D status with falls. A study that included only vitamin D supplementation as the intervention, and controlling for all potential confounding variables, such as dietary calcium intake, bone density, and strength would aid in identifying vitamin D's exact role in the risk of falls. Once vitamin D's role in risk of falls is clarified, future studies to determine whether there is an interaction among vitamin D and body composition, bone density, calcium intake, to name a few, in relation to the impact on risk of falls, would be helpful to best develop fall prevention protocols.

It would be best to replicate the randomized controlled trials in both community or independent living settings and medical facilities, since results were mixed among the various settings. Since vitamin D status can be impacted by living environment, especially in regards to whether participants are able to get adequate vitamin D levels from sun exposure, it would still be imperative to measure serum vitamin D status to ensure that the participant pool has pre-treatment vitamin D status at lower levels than recommended to be able to see an impact from the intervention.

Gender

Since gender seems to play a large role in vitamin D status and risk of falling among older adults, it would be important to look deeper in how this relationship affects outcomes. These studies have shown that women are affected more when it comes to vitamin D status in its relationship with risk of falling among older adults. Since women are impacted more with a higher risk of falling if vitamin D status is low, there should be more well-designed studies,

including more randomized controlled trials, that look specifically at the relationship between vitamin D status and risk of falling among women.

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Appendix A Evidence Worksheets for Primary RESEARCH Article

Citation:	Bischoff HA, Stahelin HB, Dick W, Akos R, Knecht M, Salis C…,&Conzelmann M. (2003). Effects of vitamin D and calcium supplementation on falls: A randomized control trial. Journal of Bone and Mineral Research, 18(2): 343-351.
Study design:	Randomized Control Trial
Study Class (A,B,C,D)	A
Research Quality Rating	+Positive
Purpose/Population Studied/Practice Studied	
Research purpose:	To test the hypothesis that vitamin D and calcium supplementation would affect calcium homeostasis and increase muscle strength, which would reduce the risk of falling.
Inclusion criteria:	Elderly persons who are not living independently and awaiting placement, are cared for in a long-stay geriatric care units in Switzerland, 60 years of age or older, ability to walk 3m with or without a walking aid
Exclusion criteria:	primary hyperparathyroidism, hypocalcemia, hypercalcuria, renal insufficiency (creatinine>117 um), and fracture or stroke within the last 3 months, those who had received any treatment with hormone replacement therapy, calcitonin, fluoride, or bisphosphonates during the previous 24 months
Recruitment:	elderly persons, who are not able to live independently and awaiting placement, and are cared for in long-stay geriatric care units in Switzerland
Blinding used:	tablets given in both groups had identical appearance , patients administrators and all investigators were all blinded to the treatment assignment throughout the study. The treatment allocation was kept in sealed envelopes to which the physician in charge of the patient only had access to in case of emergency.
Description of study protocol:	double-blinded randomized control trial with 6-week pre-treatment period and a 12-week treatment period Tablets were administered twice per day with breakfast and dinner and swallowed in the presence of the study nurse to ensure compliance. Number of drugs was recorded and the diet was overall the same for all participants. Overall musculoskeletal function was assessed by summed score including the timed up & go (TUG test), knee flexor strength, knee extensor strength, and grip strength. Fasting blood samples were collected for the measurement of serum calcium, phosphate, and albumin and total alkaline phosphatase. Serum 25-hydroxyvitamin D, 1,25-

	dihydroxyvitamin D, and intact parathyroid hormone (PTH) concentrations were measured by radioimmunoassay.
Intervention:	subjects randomly assigned to the vitamin D plus calcium group received two tablets containing 600 mg of calcium carbonate and 400 IU of cholecalciferol per tablet. Subjects randomly assigned to the calcium group received two tablets containing 600 mg of calcium per tablet.
Statistical analysis:	For group comparison at baseline, the two sample t-tests, Wilcoxon rank sums test, Chi-square, and Fisher's exact tests were used. Wilcoxon rank sums test were used to evaluate median difference from baseline for laboratory investigations. A crude comparison of the mean number of excessive falls (number of falls during the treatment − falls during the pretreatment period) among subjects who fell during the treatment period was carried out by a two-sample t-test. The main adjusted analysis used the Poisson regression to compare the number of falls in the two treatment groups.
Timing of measurements:	November 1999 and March 2000. Assessments took place at the beginning of treatment period and after 12 weeks.
Dependent variables:	number of falls per person
Independent Variables:	vitamin D and calcium supplementation
Control Variables:	Calcium
Description of Actual Data Sample:	Initial: 130 (130 females, 0 males) Attrition (Final N): 89 Age: 60 and older (average age of 85 Ethnicity: N/A Other relevant demographics: N/A Anthropometrics: average BMI of 24.7 Location: Switzerland
Summary of Results:	Among subjects in the Cal+D-group, there were significant increases in median serum 25-hydroxyvitamin D (+71%) and 1,25-dihydroxyvitamin D (+8%). Before treatment, mean observed number of falls per person per week was 0.059 in the Cal+D-group and 0.056 in the Cal-group. In the 12-week treatment period, mean number of falls per person per week was 0.034 in the Cal+D-group and 0.076 in the Cal-group. After adjustment, Cal+D-treatment accounted for a 49% reduction of falls (95% CI, 14–71%; $p < 0.01$) based on the fall categories stated above. Among fallers of the treatment period, the crude average number of excessive falls was significantly higher in the Cal-group ($p = 0.045$). Musculoskeletal function improved significantly in the

	Cal+D-group (p = 0.0094). A single intervention with vitamin D plus calcium over a 3-month period reduced the risk of falling by 49% compared with calcium alone. Over this short-term intervention, recurrent fallers seem to benefit most by the treatment.
Author Conclusion:	The impact of vitamin D on falls might be explained by the observed improvement in musculoskeletal function.
Reviewer Comments:	*The strength in the design of this study makes the results causative and holds a high validity. This study differs from others, with its use of vitamin D and calcium supplementation as controls.*
Funding Source:	International Foundation for the Promotion of Nutrition Research and Nutrition Education, Swiss Orthopedic Society, and Swiss Foundation for Nutrition Research

Quality Criteria Checklist- Primary Research

Symbols Used	Explanation
+	**Positive**- Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis
-	**Negative**- Indicates that these issues have not been adequately addressed
⦸	**Neutral**- Indicates that the report is neither exceptionally strong nor exceptionally weak

Relevance Questions

1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA from some epidemiological studies)	4	Yes

If the answers to all of the above relevance questions are "Yes", the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.

Validity Questions

1. Was the <u>research question</u> clearly stated?	1	Yes

1.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3. Were the target population and setting specified?	1.3	Yes
2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Unclear
2.1. Were inclusion/exclusion criteria specified (e.g. risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
2.2. Were criteria applied equally to all study groups?	2.2	Yes
2.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes

3. Were <u>study groups comparable</u>?	3	Yes
3.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Unclear
3.2. Were distribution of disease and status, prognostic factors, and other factors (e.g. demographics) similar across study groups at baseline?	3.2	Unclear
3.3. Were concurrent controls used? (Concurrent preferred over historical controls)	3.3	N/A
3.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	Unclear
3.5. If case control study, were potential confounding factors comparable for cases and controls? (If series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. “gold standard”)?	3.6	N/A
4. Was method of handling <u>withdrawals</u> described?	4	Yes
4.1. Were follow up methods described and the same for all groups?	4.1	Yes
4.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Yes
4.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes

4.4. Were reasons for withdrawals similar across groups?	4.4	Yes
4.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5. Was <u>blinding</u> used to prevent introduction of bias?	5	No
5.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	No
5.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as lab value, this criterion is assumed to be met?	5.2	No
5.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	Unclear
5.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
5.5. IN diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
6. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Yes
6.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	N/A
6.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A
6.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	N/A
6.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	N/A
6.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	N/A
6.6 Were extra or unplanned treatments described?	6.6	N/A
6.7. Was the information for 6.4. 6.5, and 6.6 assessed the same way for all groups?	6.7	N/A
6.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable?</u>	7	Yes
7.1. Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
7.2. Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
7.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
	7.4	Yes

7.4. Were the observations and measurements based on standard, valid and reliable data collection instruments/tests/procedures?	7.5	Yes
7.5. Was the measurement of effect at an appropriate level of precision?	7.6	Yes
7.6. Were other factors accounted for (measured) that could affect outcomes?	7.7	Yes
7.7. Were the measurements conducted consistently across groups?		
8. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
8.1. Were statistical analyses adequately described the results reported appropriately?	8.1	Yes
8.2. Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
8.3. Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
8.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	Yes
8.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	Yes
8.6. Was clinical significance as well as statistical significance reported?		
8.7. If negative findings, was a power calculation reported to address type 2 error?	8.6	Yes
	8.7	N/A
9. Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?	9	Yes
9.1. Is there a discussion of findings?	9.1	Yes
9.2. Are biases and study limitations identified and discussed?	9.2	No
10. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Yes
10.1. Were sources of funding and investigators' affiliations described?	10.1	Yes
10.2. Was there no apparent conflict of interest?	10.2	Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No", the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (⦸) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (⦸) symbol on the Evidence Worksheet.*		
PLUS/POSITIVE (+)		

If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7, and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.

Evidence Worksheet for Primary RESEARCH Article

Citation:	Ghafouri HB, Zare M, Bazrafshan A, Modirian E, Mousavi A, & Abazarian N. (2016). Electronic Physician, 8(8): 2707-2712.
Study design:	Prospective cohort
Study Class (A,B,C,D)	B
Research Quality Rating	+Positive
Purpose/Population Studied/Practice Studied	
Research purpose:	To examine the association between serum vitamin D concentration and recurrent falls in Iranian older adults.
Inclusion criteria:	Elderly participants over age 60 who suffered from an unintentional episode of falling
Exclusion criteria:	Use of vitamin D supplements, anti-seizure medications, or glucocorticoids
Recruitment:	Conducted in the emergency departments (EDs) of Rasoul Akram and Sina Hospitals
Blinding used:	N/A
Description of study protocol:	A structured, self-administered checklist was developed to obtain the participants' demographic and clinical information. The questionnaire included demographic information (age, gender, level of education, and marital status), past medical history, and serum 25OHD concentration of included participants at the time of hospitalization. Researchers also asked about any recurrent fall experience during the six-month follow-up. A serum 25OHD sample was obtained from all of the patients who participated in the study.
Intervention:	N/A
Statistical analysis:	Descriptive statistics (mean, median, SD, and range) were used to present the overall characteristics of the participants. Spearman's regression coefficient was used to measure the associations between the quantitative variables. In order to compare the mean serum 25OHD concentration between different categorical variables, the Mann-Whitney U and Kruskal-Wallis tests were used.
Timing of measurements:	March 2012-January 2013
Dependent variables:	Falls

Independent Variables:	vitamin D status
Control Variables:	N/A
Description of Actual Data Sample:	Initial: 120 (47 males, 35 females) Attrition (Final N): 82 Age: 60 and older, mean age was 75 Ethnicity: Iranian Other relevant demographics: about 80% lived in private homes Anthropometrics: 8 participants with BMI<20, 38 participants with BMI 20-24.9, 31 participants with BMI 25-29.9, and 5 with BMI>30. Location: Iran (Rasoul Akram and Sina Hospitals)
Summary of Results:	A small, but insignificant association was found between the mean serum 25OHD levels and the number of recurrent falls in elderly patients irrespective of their age, gender, or physical activity groups (OR=1.008, p=0.992) An inverse, but insignificant, association was found between the age of participants and their serum 25OHD levels (r-0.03, p=0.07).
Author Conclusion:	No significant association was observed between their serum 25OHD concentrations and recurrent falls. In addition, mean serum 25OHD concentration was not associated with muscle weakness and balance in older adults. In this study, no significant association of 25OHD was found with incidence of one or more recurrent falls.
Reviewer Comments:	*This was a smaller prospective cohort study that found no evidence of association between serum vitamin D levels and falls. Although the study was conducted thoroughly and methodically, a larger sample of a randomized control trial would be optimal for increased validity and strength of results.*
Funding Source:	Iran University of Medical Sciences

Quality Criteria Checklist- Primary Research

Symbols Used	Explanation
+	**Positive**- Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis
-	**Negative**- Indicates that these issues have not been adequately addressed
⦸	**Neutral**- Indicates that the report is neither exceptionally strong nor exceptionally weak

Relevance Questions

1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	No
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA from some epidemiological studies)	4	Yes

If the answers to all of the above relevance questions are "Yes", the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.

Validity Questions

1. Was the <u>research question</u> clearly stated?	1	Yes
1.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3. Were the target population and setting specified?	1.3	Yes
2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1. Were inclusion/exclusion criteria specified (e.g. risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
2.2. Were criteria applied equally to all study groups?	2.2	Yes
2.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes

3. Were <u>study groups comparable</u>?	3	N/A
3.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	N/A
3.2. Were distribution of disease and status, prognostic factors, and other factors (e.g. demographics) similar across study groups at baseline?	3.2	N/A
	3.3	N/A

3.3. Were concurrent controls used? (Concurrent preferred over historical controls)	3.4	Unclear
3.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.5	N/A
3.5. If case control study, were potential confounding factors comparable for cases and controls? (If series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.6	N/A
3.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. "gold standard")?		
4. Was method of handling <u>withdrawals</u> described?	4	Yes
4.1. Were follow up methods described and the same for all groups?	4.1	Yes
4.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Yes
4.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
4.4. Were reasons for withdrawals similar across groups?	4.4	Yes
4.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5. Was <u>blinding</u> used to prevent introduction of bias?	5	No
5.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	No
5.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as lab value, this criterion is assumed to be met?	5.2	No
5.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	Unclear
5.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
5.5. IN diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
6. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Yes
6.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	N/A
6.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A

6.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	N/A
6.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	N/A
6.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	N/A
6.6 Were extra or unplanned treatments described?	6.6	N/A
6.7. Was the information for 6.4. 6.5, and 6.6 assessed the same way for all groups?	6.7	N/A
6.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable?</u>	7	Yes
7.1. Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
7.2. Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
7.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
7.4. Were the observations and measurements based on standard, valid and reliable data collection instruments/tests/procedures?	7.4	Yes
7.5. Was the measurement of effect at an appropriate level of precision?	7.5	Yes
7.6. Were other factors accounted for (measured) that could affect outcomes?	7.6	Yes
7.7. Were the measurements conducted consistently across groups?	7.7	Yes
8. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
8.1. Were statistical analyses adequately described the results reported appropriately?	8.1	Yes
8.2. Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
8.3. Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
8.4. Was “intent to treat” analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	Yes
8.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	Yes

8.6. Was clinical significance as well as statistical significance reported?	8.6	Yes
8.7. If negative findings, was a power calculation reported to address type 2 error?	8.7	No
9. Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?	9	Yes
9.1. Is there a discussion of findings?	9.1	Yes
9.2. Are biases and study limitations identified and discussed?	9.2	Yes
10. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Yes
10.1. Were sources of funding and investigators' affiliations described?	10.1	Yes
10.2. Was there no apparent conflict of interest?	10.2	Yes

MINUS/NEGATIVE (-)

If most (six or more) of the answers to the above validity questions are "No", the report should be designated with a minus (-) symbol on the Evidence Worksheet.

NEUTRAL (⦸)

If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (⦸) symbol on the Evidence Worksheet.

PLUS/POSITIVE (+)

If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7, and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.

Evidence Worksheet for Primary RESEARCH Article

Citation:	Larocque SC, Kerstetter JE, Cauley JA, Insogna KL, Ensrud K, Lui LY, & Allore HG. (2015). Dietary protein and vitamin D intake and risk of falls: A secondary analysis of postmenopausal women from the study of osteoporotic fractures. Journal of Nutrition in Gerontology and Geriatrics, 34(3): 305-318.
Study design:	prospective cohort
Study Class (A,B,C,D)	B
Research Quality Rating	+ Positive
Purpose/Population Studied/Practice Studied	
Research purpose:	to evaluate the association between dietary protein and subsequent falls in a sample of postmenopausal women from the Study of Osteoporotic Fractures (SOF) and examine both serum vitamin D status and dietary vitamin D intake with falls
Inclusion criteria:	Caucasian women older than 65 years of age
Exclusion criteria:	Subjects with missing data
Recruitment:	Participants are from SOF, an observational study of postmenopausal women that includes prospective data on bone health and aging. Enrollment began in 1986 in four U.S. clinical centers, and clinical visits occurred approximately every two years
Blinding used:	N/A
Description of study protocol:	For the purpose of this study, data from visit 6 (V6, years 1997-1998) were utilized because 4886 participants completed the Block Food Frequency Questionnaire (FFQ) that consisted of 109 food items and inclueded questions on alcohol intake and vitamin and mineral supplementation including calcium. Protein intake from any source was analyzed using the FFQ as g/d and converted to g/kg body weight to compare subjects' intakes with the RDA for protein, 0.8 g/kg. Daily intake through diet and supplemental vitamin D and calcium (mg) were estimated from the FFQ. A subset of women (N=1,171) were randomly chosen to have their vist 6 serum 25-hydroxyvitamin D [25 (OH) D] measured as nano-grams per milliliters. Falls were examined prospectively one year post-V6 and treated as a dichotomous variable. Fall incidence was captured by postcard and telephone calls every 4 months. Candidate fall-related covariates that were previously shown to be associated with falls included history of a previous fall, age,

	number of alcoholic drinks per week, depressive symptoms, number of items out of six Instrumental Activities of Daily Living, count of total medications, average of right and left isometric handgrip strength, BMI, current smoking status, number of hours of sleep per night, visual acuit of 50 or better for both eyes, and physical activity factors. Subjects self-rated their health by answering several questions.
Intervention:	N/A
Statistical analysis:	Baseline characteristics were compared using either ANOVA or chi-square for continuous and categorical data. Unadjusted logistic regression was used to calculate the odds ratio and 95% confidence interval for the occurrence of fall within one year after V6 per 1g/kg or per 50 g/day increase in protein intake and for vitamin D per 100 IU increase in dietary vitamin D or per 1 ng/ mL increase in the serum 25(OH)D. Quadratic regression was performed to assess if there was a curvilinear or linear association between falls and dietary protein and falls and vitamin D.Once each predictor of interest (dietary protein and vitamin D) was added into its own model, to control for confounding, forward stepwise selection of fall-related variables was used. The forward stepwise selection process was also used with dietary protein and vitamin D and all significant potential fall-related confounders selected.
Timing of measurements:	collected during V6 (1997-1998)
Dependent variables:	vitamin D and dietary protein
Independent Variables:	Falls
Control Variables:	history of falls, physical activity, total caloric intake, medications
Description of Actual Data Sample:	Initial: 9704 (0 males, 9704 females), Attrition (final N): 4369 Age: 65 and older Ethnicity: Caucasian Anthropometrics: N/A Location: Four clinical centers across the U.S.
Summary of Results:	In separate, unadjusted models dietary protein (per 1 g/kg increase) and vitamin D (per 100 International Unit (IU) increase) significantly increased the odds ratio (OR) of falling (OR 1.35 95% CI 1.15–1.59, OR 1.11 95% CI 1.03–1.19, respectively). Once fall-related covariates were added to each model, dietary protein and vitamin D were noncontributory to falls.

Author Conclusion:	While we could find no direct association between vitamin D and protein intake and fall prevention, adequate intake of these two nutrients are critical for musculoskeletal health in older adults.
Reviewer Comments:	*While there were strengths in the large population size and methods of data collection, this prospective cohort study could have been strengthened by including a control in the study.*
Funding Source:	National Institutes of Health, National Institute on Aging

Quality Criteria Checklist- Primary Research

Symbols Used	Explanation
+	**Positive**- Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis
-	**Negative**- Indicates that these issues have not been adequately addressed
⦸	**Neutral**- Indicates that the report is neither exceptionally strong nor exceptionally weak

Relevance Questions

1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA from some epidemiological studies)	4	Yes

If the answers to all of the above relevance questions are "Yes", the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.

Validity Questions

1. Was the <u>research question</u> clearly stated?	1	Yes
1.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3. Were the target population and setting specified?	1.3	Yes
2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes

2.1. Were inclusion/exclusion criteria specified (e.g. risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
2.2. Were criteria applied equally to all study groups?	2.2	Yes
2.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes

3. Were <u>study groups comparable</u>?	3	N/A
3.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	N/A
3.2. Were distribution of disease and status, prognostic factors, and other factors (e.g. demographics) similar across study groups at baseline?	3.2	N/A
3.3. Were concurrent controls used? (Concurrent preferred over historical controls)	3.3	N/A
3.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	Yes
3.5. If case control study, were potential confounding factors comparable for cases and controls? (If series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. “gold standard”)?	3.6	N/A
4. Was method of handling <u>withdrawals</u> described?	4	Yes
4.1. Were follow up methods described and the same for all groups?	4.1	Yes
4.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Yes
4.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
4.4. Were reasons for withdrawals similar across groups?	4.4	Yes
4.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5. Was <u>blinding</u> used to prevent introduction of bias?	5	No

5.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	No
5.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as lab value, this criterion is assumed to be met?	5.2	No
5.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	Unclear
5.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
5.5. IN diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
6. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Yes
6.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	N/A
6.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A
6.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	N/A
6.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	N/A
6.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	N/A
6.6 Were extra or unplanned treatments described?	6.6	N/A
6.7. Was the information for 6.4. 6.5, and 6.6 assessed the same way for all groups?	6.7	N/A
6.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable?</u>	7	Yes
7.1. Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
7.2. Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
7.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
7.4. Were the observations and measurements based on standard, valid and reliable data collection instruments/tests/procedures?	7.4	Yes
7.5. Was the measurement of effect at an appropriate level of precision?	7.5	Yes
7.6. Were other factors accounted for (measured) that could affect outcomes?	7.6	Yes

7.7. Were the measurements conducted consistently across groups?	7.7	Yes
8. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
8.1. Were statistical analyses adequately described the results reported appropriately?	8.1	Yes
8.2. Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
8.3. Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
8.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	Yes
8.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	Yes
8.6. Was clinical significance as well as statistical significance reported?	8.6	Yes
8.7. If negative findings, was a power calculation reported to address type 2 error?	8.7	N/A
9. Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?	9	Yes
9.1. Is there a discussion of findings?	9.1	Yes
9.2. Are biases and study limitations identified and discussed?	9.2	Yes
10. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Yes
10.1. Were sources of funding and investigators' affiliations described?	10.1	Yes
10.2. Was there no apparent conflict of interest?	10.2	Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No", the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (⊘) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (⊘) symbol on the Evidence Worksheet.*		
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7, and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*		

Evidence Worksheet for Primary RESEARCH Article

Citation:	Law M, Withers H, Morris J & Anderson F. (2006). Vitamin D supplementation and the prevention of fractures and falls: results of a randomised trial in elderly people in residential accommodation. Age and Ageing, 35(5)482-486.
Study design:	Randomized control trial
Study Class (A,B,C,D)	A
Research Quality Rating	+Positive
Purpose/Population Studied/Practice Studied	
Research purpose:	to determine whether vitamin D supplementation reduces the risk of fracture or falls in elderly people in care home accommodation
Inclusion criteria:	older than 60 years of age
Exclusion criteria:	temporary residents admitted for respite care, residents who were already taking calcium/vitamin D or drugs that increase bone density (such as bisphosphonates), and residents who had sarcoidosis or malignancy of other life-threatening illness
Recruitment:	No information
Blinding used:	Care home staff that recorded falls were not told that falls were an outcome measure
Description of study protocol:	cluster randomisation by computer based on 223 units Blood samples were collected in the care homes from 18 treated group participants (a 1% sample) on three occasions- immediately before the first dose of vitamin D, 1 month after the first dose and 3 months after the first dose (immediately before the second dose. Blood samples measured 25-hydroxyvitamin D, PTH and calcium (adjusted for albumin)
Intervention:	Residents in the units allocated to receive vitamin D were given tablets containing ergocalciferol 2.5 mg every 3 months. Residents in the control group took no vitamin D (no placebo).
Statistical analysis:	Relative risk estimates of fractures and falls in the treated group compared with the control group were calculated using a Poisson regression model, which took into account age, sex, the length of time a person was in the trial and the cluster randomisation of the trial. The measurements on the serum samples were analysed non-parametrically using Wilcoxon's matched pairs signed rank test

Timing of measurements:	7-14 months duration (10 month mean and median duration)
Dependent variables:	non-vertebral fractures and falls
Independent Variables:	vitamin D status/supplementation
Control Variables:	not taking vitamin D
Description of Actual Data Sample:	Initial: 3717 (892 males, 2825 females) Attrition (Final N): 3717 Age: average of 85 years of age (all over 60 years of age) Ethnicity: N/A Other relevant demographics: N/A Anthropometrics: N/A Location: the south of England
Summary of Results:	The differences between the vitamin D and control groups were not statistically significant. The incidence of all non-vertebral fractures in the care homes (3.2% per year) and of hip fractures (1.1% per year) was low, similar to rates in elderly people in sheltered accommodation, and the pre-treatment serum 25-hydroxy vitamin D concentration was high [median 47 nmol/l, measured in a 1% (n = 18) sample]. There was no change in parathyroid hormone, as expected in view of the relatively high pre-treatment serum 25-hydroxy vitamin D (Table 2) [24]. There were no material changes on average in the serum concentrations of calcium or phosphate, or of protein or liver function tests (not shown).
Author Conclusion:	Vitamin D supplementation alone failed to reduce the incidence of fractures or reported falls in our trial, despite the fact that the vitamin D effectively raised the serum 25-hydroxy vitamin D concentration in a representative 1% sample from the treated group.
Reviewer Comments:	*This trial has the sample size and design for strong validity in its results, however there are weaknesses in the selection of participants and non-availability of data on residents who declined to join the trial or who were excluded.*
Funding Source:	Sir Jules Thorn Charitable Foundation

Quality Criteria Checklist- Primary Research

Symbols Used	**Explanation**

+	**Positive**- Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis
-	**Negative**- Indicates that these issues have not been adequately addressed
⊘	**Neutral**- Indicates that the report is neither exceptionally strong nor exceptionally weak

Relevance Questions

1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA from some epidemiological studies)	4	Yes

If the answers to all of the above relevance questions are "Yes", the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.

Validity Questions

1. Was the <u>research question</u> clearly stated?	1	Yes
1.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3. Were the target population and setting specified?	1.3	Yes
2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1. Were inclusion/exclusion criteria specified (e.g. risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
2.2. Were criteria applied equally to all study groups?	2.2	Yes
2.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes

3. Were <u>study groups comparable</u>?	3	N/A

3.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	N/A
3.2. Were distribution of disease and status, prognostic factors, and other factors (e.g. demographics) similar across study groups at baseline?	3.2	N/A
3.3. Were concurrent controls used? (Concurrent preferred over historical controls)	3.3	N/A
3.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	Yes
3.5. If case control study, were potential confounding factors comparable for cases and controls? (If series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. "gold standard")?	3.6	N/A
4. Was method of handling <u>withdrawals</u> described?	4	No
4.1. Were follow up methods described and the same for all groups?	4.1	Yes
4.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	No
4.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
4.4. Were reasons for withdrawals similar across groups?	4.4	N/A
4.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5. Was <u>blinding</u> used to prevent introduction of bias?	5	No
5.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	No
5.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as lab value, this criterion is assumed to be met?	5.2	No
5.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	Unclear
5.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
5.5. IN diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A

6. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Yes
6.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	N/A
6.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A
6.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	N/A
6.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	N/A
6.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	N/A
6.6 Were extra or unplanned treatments described?	6.6	N/A
6.7. Was the information for 6.4. 6.5, and 6.6 assessed the same way for all groups?	6.7	N/A
6.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable?</u>	7	Yes
7.1. Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
7.2. Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
7.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
7.4. Were the observations and measurements based on standard, valid and reliable data collection instruments/tests/procedures?	7.4	Yes
7.5. Was the measurement of effect at an appropriate level of precision?	7.5	Yes
7.6. Were other factors accounted for (measured) that could affect outcomes?	7.6	Yes
7.7. Were the measurements conducted consistently across groups?	7.7	Yes
8. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
8.1. Were statistical analyses adequately described the results reported appropriately?	8.1	Yes
8.2. Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
8.3. Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes

8.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	Yes
8.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	Yes
8.6. Was clinical significance as well as statistical significance reported?	8.6	Yes
8.7. If negative findings, was a power calculation reported to address type 2 error?	8.7	N/A
9. Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?	9	Yes
9.1. Is there a discussion of findings?	9.1	Yes
9.2. Are biases and study limitations identified and discussed?	9.2	Yes
10. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Yes
10.1. Were sources of funding and investigators' affiliations described?	10.1	Yes
10.2. Was there no apparent conflict of interest?	10.2	Yes

MINUS/NEGATIVE (-)

If most (six or more) of the answers to the above validity questions are "No", the report should be designated with a minus (-) symbol on the Evidence Worksheet.

NEUTRAL (⦸)

If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (⦸) symbol on the Evidence Worksheet.

PLUS/POSITIVE (+)

If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7, and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.

Evidence Worksheet for Primary RESEARCH Article

Citation:	Peterson A, Mattek N, Clemons A, Bowman GL, Buracchio T, Kaye J, & Quinn J. (2012). Serum vitamin D concentrations are associated with falling and cognitive function in older adults. The Journal of Nutrition, Health and Aging, 16(10): 898-901.
Study design:	cross-sectional study
Study Class (A,B,C,D)	D
Research Quality Rating	+Positve
Purpose/Population Studied/Practice Studied	
Research purpose:	To elucidate the mechanism through which vitamin D is associated with decreased falls.
Inclusion criteria:	age of 80 years and older (70 years and older for minorities and spouses of participants), living independently, not demented with a Clinical Dementia Rating score <0.5, Mini Mental State Examination (MMSE) score >24, and being of average health for age
Exclusion criteria:	younger than 80 years of age (younger than 70 years of age for minorities and spouses of participants), demented with Clinical Dementia Rating score of >0.5, and score<24 on Mini Mental State Examination (MMSE)
Recruitment:	Participants were recruited from the Intelligent Systems for Assessment of Aging Changes Study (ISAAC), a community-based cohort study that examines changes in motor and cognitive function among independently living older adults over age 70
Blinding used:	N/A
Description of study protocol:	Participants were assessed with standardized health and function questionnaires, physical and neurological examinations, and a variety of tests of motor and cognitive function. Falls were self-reported via weekly, computerized questionnaires. Health status was documented
Intervention:	N/A
Statistical analysis:	Participant characteristics of fallers and non-fallers were compared using Student's t-test or Wilcoxon Rank Sum Test for continuous variables and Pearson Chi-square test for categorical variables. Multivariate logistic regression was used to estimate risk of falls by vitamin D level, controlling for gender and supplementation use. Analysis of variance was used to compare vitamin D concentration among three fall categories (non-faller, single faller, multiple faller. Correlations between vitamin D

	concentration and clinical variables are reported as Spearman's or Pearson's coefficient as appropriate. Multivariate linear regression was used to model the relationships between vitamin D level and each cognitive domain z-score, after adjusting for age, sex, and education.
Timing of measurements:	Blood draws were all completed between 9/26/08 and 2/11/09. Participants were assess with standardized health and function questionnaires, phsical and neurological examinations, and a variety of tests of motor and cognitive function. Falls were self-reported via weekly, computerized questionnaires. Health status was documented via the modified Cumulative Illness Rating Scale. The number of falls each subject reported were summed for the 3 months before, and the 3 months after the date of the vitamin D blood draw. Vitamin D was measured as 25-hydroxy vitamin D in the serum using radioimmunoassay (RIA) from IDS (Immunodiagnostic Systems Inc).
Dependent variables:	Falls
Independent Variables:	Vitamin D status
Control Variables:	physical, neurological health status and cognitive function, BMI, depression, autonomy, grip strength and race
Description of Actual Data Sample:	Initial: 233 Attrition (Final N): 159 Age: average age of 85 y.o. Ethnicity: largely white Other relevant demographics: generally highly educated (average of 15 years of education) Anthropometrics: N/A Location: Portland, Oregon metropolitan area
Summary of Results:	Fallers had a significantly lower vitamin D level (32.9 ng/ml) as compared to non-fallers (39.2 ng/ml) ($p<0.01$). A 5 ng/ml increase in vitamin D corresponds to a 20% decrease in odds of falling. Cognitive status (CDR=0 vs. 0.5) did not modify the relationship between vitamin D and falls risk ($p=0.12$). Fallers had a significantly lower vitamin D level (32.9 ng/ml) as compared to non-fallers (39.2 ng/ml) ($p<0.01$). A 5 ng/ml increase in vitamin D corresponds to a 20% decrease in odds of falling. Cognitive status (CDR=0 vs. 0.5) did not modify the relationship between vitamin D and falls risk ($p=0.12$).
Author Conclusion:	These data are consistent with other studies showing that higher plasma vitamin D concentrations are associated with reduced falls. In this study, fallers had a significantly lower vitamin D

	concentration than non-fallers. The data also showed a significant correlation of vitamin D concentration with MMSE scores and cognitive status.
Reviewer Comments:	*While this data is by no means conclusive, there is strong evidence to suggest that vitamin D status reduces falls rates, with the mechanism still unknown. A study using a control would produce causation, and therefore strengthen the validity of the findings.*
Funding Source:	The National Institutes of Health, the Department of Veterans Affairs, and Intel Corporation

Quality Criteria Checklist- Primary Research

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-	**Negative**- Indicates that these issues have not been adequately addressed
⦸	**Neutral**- Indicates that the report is neither exceptionally strong nor exceptionally weak

Relevance Questions

1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA from some epidemiological studies)	4	Yes

If the answers to all of the above relevance questions are "Yes", the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.

Validity Questions

1. Was the <u>research question</u> clearly stated?	1	Yes
1.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3. Were the target population and setting specified?	1.3	Yes

2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1. Were inclusion/exclusion criteria specified (e.g. risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
2.2. Were criteria applied equally to all study groups?	2.2	Yes
2.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes

3. Were <u>study groups comparable</u>?	3	N/A
3.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	N/A
3.2. Were distribution of disease and status, prognostic factors, and other factors (e.g. demographics) similar across study groups at baseline?	3.2	N/A
3.3. Were concurrent controls used? (Concurrent preferred over historical controls)	3.3	N/A
3.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	Yes
3.5. If case control study, were potential confounding factors comparable for cases and controls? (If series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. “gold standard”)?	3.6	N/A
4. Was method of handling <u>withdrawals</u> described?	4	Unclear
4.1. Were follow up methods described and the same for all groups?	4.1	Yes
4.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Unclear
4.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
4.4. Were reasons for withdrawals similar across groups?	4.4	Unclear
4.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5. Was <u>blinding</u> used to prevent introduction of bias?	5	No

5.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	No
5.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as lab value, this criterion is assumed to be met?	5.2	No
5.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	Unclear
5.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
5.5. IN diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
6. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Yes
6.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	N/A
6.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A
6.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	N/A
6.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	N/A
6.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	N/A
6.6 Were extra or unplanned treatments described?	6.6	N/A
6.7. Was the information for 6.4. 6.5, and 6.6 assessed the same way for all groups?	6.7	N/A
6.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable?</u>	7	Yes
7.1. Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
7.2. Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
7.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
7.4. Were the observations and measurements based on standard, valid and reliable data collection instruments/tests/procedures?	7.4	Yes
7.5. Was the measurement of effect at an appropriate level of precision?	7.5	Yes
7.6. Were other factors accounted for (measured) that could affect outcomes?	7.6	Yes

7.7. Were the measurements conducted consistently across groups?	7.7	Yes
8. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
8.1. Were statistical analyses adequately described the results reported appropriately?	8.1	Yes
8.2. Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
8.3. Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
8.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	Yes
8.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	Yes
8.6. Was clinical significance as well as statistical significance reported?	8.6	Yes
8.7. If negative findings, was a power calculation reported to address type 2 error?	8.7	N/A
9. Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?	9	Yes
9.1. Is there a discussion of findings?	9.1	Yes
9.2. Are biases and study limitations identified and discussed?	9.2	Yes
10. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Yes
10.1. Were sources of funding and investigators' affiliations described?	10.1	Yes
10.2. Was there no apparent conflict of interest?	10.2	Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No", the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (⊘) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (⊘) symbol on the Evidence Worksheet.*		
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7, and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*		

Evidence Worksheet for Primary RESEARCH Article

Citation:	Snijder MB, van Schoor NM, Plujim SMF, van Dam RM, Visser M & Lips P. (2006). Vitamin D Status in Relation to One-Year Risk of Recurrent Falling in Older Men and Women
Study design:	Prospective Cohort Study
Study Class (A,B,C,D)	B
Research Quality Rating	+ Positive
Purpose/Population Studied/Practice Studied	
Research purpose:	To prospectively investigate the association between serum 25-hydroxyvitamin D (25OHD) levels and risk of recurrent falling in older men and women
Inclusion criteria:	participants born on or before 1930 (ages 65 years or older as of Jan. 1, 1996), and participated in a follow-up examination which took place 1995-1996
Exclusion criteria:	Subjects with missing data on serum PTH, serum 25OHD, lifestyle (smoking, physical activity, and alcohol), education level, body mass index BMI), serum creatinine and three or four periods (of 3 months) of fall follow-up
Recruitment:	random sample of older men and women (aged 55-85 yr), stratified by age, sex, urbanization, and expected 5-yr mortality, was drawn from the population of registers of 11 municipalities in the areas in the west (Amsterdam and its vicinity), northeast (Zwolle and vicinity), and south (Oss and vicinity) of the Netherlands
Blinding used:	N/A
Description of study protocol	Respondents were asked to report their falls weekly and mail into research center every 3 months. There were two groups including those who have not fallen or have fallen once (most likely coincidental falls with extrinsic cause) and those who fall recurrently (two or more falls during the study period, more likely associated with an intrinsic cause). Vitamin D status was measured with blood samples that were obtained in the morning and immediately centrifuged and frozen. PTH was measured by means of immunoadiometric assay, and serum 25OHD was determined according to a competitive protein binding assay. Age, sex, season, region, education level, lifestyle variables, weight, BMI, number of chronic diseases, and serum creatinine level were measured as confounding factors because these variable might be associated with both vitamin D status and

	falling. Physical performance was assessed as a potential mediator with three tests including: the walking test, chair stands, and the tandem test.
Intervention:	N/A
Statistical analysis:	Baseline characteristics of the population are shown stratified for the number of falls, and differences between the groups were tested by Student's t test for normally distributed variables and by Mann-Whitney's test. Differences in proportion were tested by the x^2 test. Logistic regression analyses were performed to study the association between the low (<10 ng/ml) serum 25OHD (independent variable) and the incidence of falls (dependent variable). Results are expressed as odds ratios (OR) with a 95% confidence interval (CI)
Timing of measurements:	Unclear
Dependent variables:	incidence of falls
Independent Variables:	serum 25(OH)D
Control Variables:	age, sex, season, region, educational levels, lifestyle variables, weight, BMI, number of chronic diseases, serum creatinine level
Description of Actual Data Sample:	Initial: 3107 Attrition (final N): 1231 Age: 65 and older Ethnicity: Dutch Anthropometrics: unclear Location: Netherlands
Summary of Results:	Low 25OHD (<10 ng/ml) was associated with an increased risk of falling. After adjustment for age, sex, education level, region, season, physical activity, smoking, and alcohol intake, the odds ratios (95% confidence interval) was 1.78 (1.06–2.99) for subjects who experienced two falls or more as compared with those who did not fall or fell once and 2.23 (1.17–4.25) for subjects who fell three or more times as compared with those who fell two times or less. There was a statistically significant effect modification by age, and stratified analyses (<75 and ≥ 75 yr) showed that the associations were particularly strong in the younger age group; the odds ratios (95% confidence interval) were 5.21 (2.03–13.40) for two falls or more and 4.96 (1.52–16.23) for three falls or more
Author Conclusion:	Poor vitamin D status is independently associated with an increased risk of falling in the elderly, particularly in those aged 65–75 yr

Reviewer Comments:	*The validity of this study could have been strengthened through the use of a control rather than the prospective cohort design. Other characteristics that strengthened the study included population size, use of serum vitamin D levels, and taking into account multiple confounding variables.*
Funding Source:	Merck & Co.

Quality Criteria Checklist- Primary Research

Symbols Used	Explanation
+	**Positive**- Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis
-	**Negative**- Indicates that these issues have not been adequately addressed
⦸	**Neutral**- Indicates that the report is neither exceptionally strong nor exceptionally weak

Relevance Questions

1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA from some epidemiological studies)	4	Yes

If the answers to all of the above relevance questions are "Yes", the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.

Validity Questions

1. Was the <u>research question</u> clearly stated?	1	Yes
1.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3. Were the target population and setting specified?	1.3	Yes
2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
	2.1	Yes

2.1. Were inclusion/exclusion criteria specified (e.g. risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?		
2.2. Were criteria applied equally to all study groups?	2.2	Yes
2.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes

3. Were <u>study groups comparable</u>?	3	Yes
3.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Yes
3.2. Were distribution of disease and status, prognostic factors, and other factors (e.g. demographics) similar across study groups at baseline?	3.2	Yes
3.3. Were concurrent controls used? (Concurrent preferred over historical controls)	3.3	Yes
3.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	N/A
3.5. If case control study, were potential confounding factors comparable for cases and controls? (If series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. “gold standard”)?	3.6	N/A
4. Was method of handling <u>withdrawals</u> described?	4	No
4.1. Were follow up methods described and the same for all groups?	4.1	Unclear
4.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Unclear
4.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	No
4.4. Were reasons for withdrawals similar across groups?	4.4	Unclear
4.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5. Was <u>blinding</u> used to prevent introduction of bias?	5	Yes

5.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	No
5.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as lab value, this criterion is assumed to be met?	5.2	Yes
5.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	N/A
5.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
5.5. IN diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
6. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Yes
6.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	Yes
6.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A
6.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
6.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	N/A
6.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	N/A
6.6 Were extra or unplanned treatments described?	6.6	N/A
6.7. Was the information for 6.4. 6.5, and 6.6 assessed the same way for all groups?	6.7	N/A
6.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable?</u>	7	Yes
7.1. Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
7.2. Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
7.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
7.4. Were the observations and measurements based on standard, valid and reliable data collection instruments/tests/procedures?	7.4	Yes
7.5. Was the measurement of effect at an appropriate level of precision?	7.5	Yes
7.6. Were other factors accounted for (measured) that could affect outcomes?	7.6	Yes

7.7. Were the measurements conducted consistently across groups?	7.7	Yes
8. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
8.1. Were statistical analyses adequately described the results reported appropriately?	8.1	Yes
8.2. Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
8.3. Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
8.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	Yes
8.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	Yes
8.6. Was clinical significance as well as statistical significance reported?	8.6	Yes
8.7. If negative findings, was a power calculation reported to address type 2 error?	8.7	N/A
9. Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?	9	Yes
9.1. Is there a discussion of findings?	9.1	Yes
9.2. Are biases and study limitations identified and discussed?	9.2	Yes
10. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Yes
10.1. Were sources of funding and investigators' affiliations described?	10.1	Yes
10.2. Was there no apparent conflict of interest?	10.2	Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No", the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (⊘) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (⊘) symbol on the Evidence Worksheet.*		
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7, and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*		

Evidence Worksheet for Primary RESEARCH Article

Citation:	Suzuki T, Kwon J, Kim H, Shimada H, Yoshida Y, Iwasa H, & Yoshida H. (2008). Low serum 25-hydroxyvitamin D levels associated with falls among Japanese community-dwelling elderly. Journal of Bone and Mineral Research, 23(8):1309-1317.
Study design:	Cross-sectional
Study Class (A,B,C,D)	D
Research Quality Rating	+Positive
Purpose/Population Studied/Practice Studied	
Research purpose:	To study the association of serum 25(OH)D levels and falls among Japanese community-dwelling elderly
Inclusion criteria:	65 years of age and older, living in Itabashi ward of Tokyo, Japan, essentially ambulatory, lived independently in their homes, and had sound functional capacity
Exclusion criteria:	History of malignant diseases, current treatment of vitamin D, chronic renal failure, or other serious diseases affecting vitamin D regulation.
Recruitment:	Participants of mass health checkups for the community elderly
Blinding used:	N/A
Description of study protocol:	Interviews were conducted to assess the age, physical activity, and chronic disease conditions of the subjects. History of chronic diseases were self-reported. The subjects were asked about their falls over the previous year. Those who reported one or more falls were asked about the circumstances and consequences of each fall. The peak handgrip force (kg) was measured by Smedley's hand dynamometer. A stopwatch measured the time taken to walk 5m, from the time when a foot first touched the ground after the 3-m line to when a foot touched the ground after the 8-m line. Blood samples of serum 25OHD and serum albumin levels were collected in a nonfasting state and in a sitting position.
Intervention:	N/A
Statistical analysis:	Means and SDs (for continuous variables) along with proportions (for categorical variables) were calculated for all participants. Differences between men and women were assessed using t-tests for continuous variables and Chi-square tests for categorical data. Differences in 25OHD levels were analyzed among the four age groups by one-way ANOVA in both sexes. Comparisons of fall-

	related variables by 25(OH)D level were performed using analysis of covariance (ANOVA) controlled for age in continuous variables, and Mantel-Haenszel Chi-square tests were used to adjust for age in categorical variables in both sexes. Multiple regression analyses were conducted with age adjustment to analyze the association of serum albumin and 25OHD level with physical performance. Logistic regression analysis was conducted to study the association of falls and 25OHD levels.
Timing of measurements:	October/November of 2004 and 2005
Dependent variables:	Falls
Independent Variables:	vitamin D status
Control Variables:	age, physical performance test, serum albumin
Description of Actual Data Sample:	Initial: 2957 (950 males, 2007females) Attrition (Final N): 2957 Age: 65 years and older Ethnicity: Asian Other relevant demographics: N/A Anthropometrics: N/A Location: Itabashi ward of Tokyo, Japan
Summary of Results:	Low 25OHD level was significantly associated with a high prevalence of falls in Japanese elderly women because of their inferior physical performance. Mean 25OHD concentration was significantly lower in women than in men ($p < 0.001$). Women showed a significant decline of 25OHD level with increased age ($p < 0.001$). There was also a significant difference in the prevalence of 25OHD insufficiency (25OHD level < 20 ng/ml) between the sexes ($p < 0.001$). The rate of falls was significantly higher in the lowest quartile of 25OHD level in women ($p = 0.02$) and in women with 25OHD insufficiency ($p = 0.001$). Women also showed significant declines in all three fall-related physical performance tests. Multiple logistic regression analysis showed significant and independent associations between 25OHD level and experience of falls in women only ($p = 0.01$).
Author Conclusion:	a lower serum 25OHD level was significantly associated with fall experience over the previous year and with fall-associated variables in Japanese women whose fall rate has been reported to be about one half that of white women. This indicates that serum 25OHD level has a common and positive relationship with the occurrence of falls in elderly women, and probably beyond

	any genetic background represented by VDR phenotype differences and anthropometric and nutritional differences.
Reviewer Comments:	*Although there were some limitations in the validity of this cross-sectional study, the results support evidence that vitamin D status does play an impact on falls in elderly women. Further studies involving randomized control trials are needed to increase the validity of the results*
Funding Source:	Ministry of Education and Culture of Japan, Research Society for Metabolic Bone Diseases in Japan

Quality Criteria Checklist- Primary Research

Symbols Used	Explanation
+	**Positive**- Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis
-	**Negative**- Indicates that these issues have not been adequately addressed
⦸	**Neutral**- Indicates that the report is neither exceptionally strong nor exceptionally weak

Relevance Questions

1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA from some epidemiological studies)	4	Yes

If the answers to all of the above relevance questions are "Yes", the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.

Validity Questions

1. Was the <u>research question</u> clearly stated?	1	Yes
1.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3. Were the target population and setting specified?	1.3	Yes

2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1. Were inclusion/exclusion criteria specified (e.g. risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
2.2. Were criteria applied equally to all study groups?	2.2	Yes
2.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes

3. Were <u>study groups comparable</u>?	3	Yes
3.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Yes
3.2. Were distribution of disease and status, prognostic factors, and other factors (e.g. demographics) similar across study groups at baseline?	3.2	Yes
3.3. Were concurrent controls used? (Concurrent preferred over historical controls)	3.3	Yes
3.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	N/A
3.5. If case control study, were potential confounding factors comparable for cases and controls? (If series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. “gold standard”)?	3.6	N/A
4. Was method of handling <u>withdrawals</u> described?	4	Yes
4.1. Were follow up methods described and the same for all groups?	4.1	Yes
4.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Yes
4.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
4.4. Were reasons for withdrawals similar across groups?	4.4	Yes
4.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5. Was <u>blinding</u> used to prevent introduction of bias?	5	Yes

5.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	Yes
5.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as lab value, this criterion is assumed to be met?	5.2	Yes
5.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	N/A
5.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
5.5. IN diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
6. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Yes
6.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	Yes
6.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A
6.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
6.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	Yes
6.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	Yes
6.6 Were extra or unplanned treatments described?	6.6	Yes
6.7. Was the information for 6.4. 6.5, and 6.6 assessed the same way for all groups?	6.7	Yes
6.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable?</u>	7	Yes
7.1. Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
7.2. Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
7.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
7.4. Were the observations and measurements based on standard, valid and reliable data collection instruments/tests/procedures?	7.4	Yes
7.5. Was the measurement of effect at an appropriate level of precision?	7.5	Yes
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9. Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?	9	Yes
9.1. Is there a discussion of findings?	9.1	Yes
9.2. Are biases and study limitations identified and discussed?	9.2	Yes
10. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Yes
10.1. Were sources of funding and investigators' affiliations described?	10.1	Yes
10.2. Was there no apparent conflict of interest?	10.2	Yes
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