Published in final edited form as:

Osteoporos Int. 2009 May ; 20(5): 751–760. doi:10.1007/s00198-008-0749-1.

Sex Specific Association of Serum 25-Hydroxyvitamin D Levels with Physical Function in Older Adults

Thuy-Tien L. Dam, MD¹, Denise von Mühlen, MD, PhD², and Elizabeth L. Barrett-Connor, MD²

¹ Division of Hospital Medicine, Department of Medicine, University of California San Diego, San Diego, CA

² Division of Epidemiology, Department of Family and Preventive Medicine, University of California San Diego, San Diego, CA

Abstract

Introduction—Preserved physical function may explain how 25(OH)D supplementation reduces falls and fractures.

Methods—A total of 1065 community dwelling men and women (mean age 74.6 years) with 25-hydroxyvitamin D [25(OH)D] levels and performance on timed up and go (TUG) and timed chair stand (TCS) were seen in 1997–1999; 769 (72%) participants returned for follow-up. Associations were examined using generalized linear models.

Results—25(OH)D levels were higher in men than women, but the prevalence of vitamin D insufficiency defined as 25(OH)D <75 nmol/L was 14%. There were no baseline sex differences in TUG or TCS. However, after 2.5 years, decline in TCS and TUG was greater in women than men (11% vs. 3%; $P < .001$). Women in the lowest 25(OH)D quartile (<80 nmol/L) compared to the highest quartile had an accelerated rate of functional decline on the TUG and TCS independent of covariates. No significant associations were seen in men.

Conclusion—In women, but not men, lower 25(OH)D levels were associated with impaired performance on two lower extremity function tests in both cross-sectional and prospective analyses. These results provide additional evidence that 25(OH)D is associated with physical function, which may explain how vitamin D supplementation reduces falls and fractures.

Keywords

25-hydroxyvitamin D; elderly; physical function; vitamin D

INTRODUCTION

Vitamin D maintains serum calcium levels by increasing intestinal calcium and phosphorous absorption. Vitamin D stimulates stem cells in the bone to become mature osteoclasts, which mobilize calcium from the bone into the circulation for bone mineralization. (1) 25-hydroxyvitamin D levels decline with age due to several mechanisms including decreased ultraviolet light exposure, decreased Vitamin D₃ skin conversion, decreased oral intake, and decreased hydroxylation in the liver. Serum 25(OH)D concentrations vary with latitude,

Corresponding author: Thuy-Tien Dam, MD, University California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0659, Phone: 858-534-8060, Fax: 858-534-4952, e-mail: tldam@ucsd.edu.

Alternate corresponding author: Elizabeth Barrett-Connor, MD, University California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0607, Phone: 858-534-0511, Fax: 858-534-8625, e-mail: ebarrettconnor@ucsd.edu

season, race, age, and dietary intake. (2) Prevalence of vitamin D deficiency/insufficiency ranges between 7 to 80% depending on the defined cutpoint. (3–10) Suggested minimal 25 (OH)D levels whereby parathyroid hormone secretion is minimized and intestinal calcium absorption is maximized range between 40 to 122 nmol/L. (11–14)

Several studies have examined the effects of vitamin D on fractures and falls. In a meta-analysis, Bischoff Ferrari et al (15) found that the usual recommended dose of vitamin D (400–600IU daily) was ineffective for reducing fractures, but fracture prevention was demonstrated in persons taking more than 800 IU daily; suggesting that higher doses of vitamin D intake are necessary for fracture prevention. Although most of the protective effects of vitamin D on fractures have been attributed to its effect on BMD, vitamin D may also mediate fracture risk by decreasing falls. Broe and colleagues randomly assigned 124 nursing home residents to four vitamin D supplement doses for five months and found that participants randomized to the 800 IU group had a 72% lower incidence rate of falls compared to participants on placebo. (16) Additionally, a meta-analysis by Bischoff Ferrari which included five randomized controlled trials of 1237 participants showed that subjects taking vitamin D supplements were significantly less likely to have at least one fall (relative risk reduction 22%) (17). A similar meta-analysis by Jackson and colleagues also showed that the pooled relative risk for preventing falls was 0.88 (95% CI 0.78–1.00) in the vitamin D supplemented group compared to placebo. (18)

In addition to the benefits on bone health and falls, vitamin D has a less well-known effect on muscle metabolism. Knockout mice without vitamin D receptors (VDR) demonstrated altered muscle development (19) and prolonged vitamin D deficiency in adults has been associated with severe muscle weakness, that improved after vitamin D supplementation. (20–22) Some epidemiologic studies have shown a correlation between low 25(OH)D levels and physical performance, (23–27) while other studies found no association. (28) Results of vitamin D supplementation in clinical trials have also been contradictory. Some trials observed no effect of vitamin D supplements on muscle strength (23,29,30) or disability in activities of daily living; (31) while a beneficial effect on muscle function was observed by others. (32,33) The majority of these studies were small and examined mostly women with very low levels of 25 (OH)D. None of these studies, evaluated the association of 25(OH)D levels with muscle strength in a population with high 25(OH)D levels or a low prevalence of vitamin D deficiency. The present study of community dwelling men and women is the largest prospective study to examine sex specific differences between serum 25-hydroxyvitamin D insufficiency and declining performance on physical function tests.

MATERIALS AND METHODS

Study population

The Rancho Bernardo Study (RBS) is a longitudinal observational cohort study, based in a southern California community. Eighty two percent of the adults who were at least 30 years of age were enrolled in the RBS from 1972 to 1974. A high proportion of the surviving participants have been followed for various exposures and common diseases, using annual mailers and clinical evaluations repeated approximately every 4 years.

For the current analysis, we studied 1065 community-dwelling ambulatory Caucasian men and women who had serum 25-hydroxyvitamin D assays and physical function tests measured in 1997–1999. Of these participants, 72% (769) returned for a clinic visit in 1999–2002, an average of 2.5 years later (median 2.5 years, range 0.4 to 5 years), and had repeat physical function measures. Of the 237 subjects who did not participate in the follow-up visit, 99 (42%) had died. Participants gave written informed consent. The University of California San Diego Institutional Review Board approved the study.

Covariates

At both visits, participants completed a self-administered questionnaire that included personal and family medical history (including fractures), medication and supplement use, and lifestyle factors (physical activity, smoking and alcohol intake). Baseline physical activity level was ascertained from participants' response to "Do you exercise 3 or more times a week?" A registered nurse confirmed medication use by examining pills and prescriptions brought to the clinic. Participants were asked if they used calcium or vitamin D supplements; use of each supplement was categorized yes/no. Height and weight were measured in the clinic with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as body weight (kilograms) divided by height (meters²). Comorbidities such as history of hypertension, diabetes cardiovascular disease, congestive heart failure, and stroke were obtained by self-report.

Blood samples

At the baseline visit, blood for 25(OH)D was obtained between 8 and 12 AM from fasting participants in tubes that were protected from sunlight. Serum was stored at -70 degrees C within 30 minutes of processing. Serum 25(OH)D levels were analyzed by a competitive protein binding assay (CPBA) in the Vitamin D research laboratory of Dr. Michael Holick (Boston University), as described by Chen et al. (34) The intra- and inter-assay coefficients of variation were 8% and 10%, respectively. The limit of detection was 12.5 nmol/L and the reference range was 25–130 nmol/L. The results obtained from the CPBA have good agreement with those obtained by liquid chromatography/mass spectrometry. (35) Intact PTH values were determined in the same laboratory using a chemiluminescence assay kit (Nichols Institute Diagnostics, San Juan Capistrano, California). The assay has both intra- and inter-assay coefficients of variation of 6% and a reference of 10–65 ng/L.

Serum creatinine levels were measured by Smith Kline Beecham clinical laboratories. Creatinine clearance was calculated by the modified Cockcroft-Gault formula [$140 - \text{age (in years)}$] multiplied by weight (in kilograms) divided by [$72 \times \text{serum creatinine (mg/dl)}$] and multiplied by 0.85 (correction factor for females). (36) Creatinine clearance levels <30 mg/ml were considered to represent 'moderate' or 'severe' renal insufficiency.

Physical function measures

At both visits, lower extremity function was assessed using the timed up and go test (TUG) and timed chair stands (TCS); upper extremity strength was assessed using grip strength (GS) test.

TUG measures the amount of time it takes to rise from a chair, walk 3 meters, and return to a sitting position. Two trials of the TUG were performed by each participant and recorded to the tenth of a second. Increasing time to perform these activities reflect worse performance and a decline in function at the follow-up visit. Overall 96% (n=1030) of the participants were able to complete this test.

For the TCS, participants were seated with their arms folded across their chests in a straight-backed chair and asked to stand up and sit down as quickly as possible five times without stopping or using their arms to push off. The time to complete the TCS from initial seating to final standing position was recorded in seconds. Increasing time to complete the TCS reflect poorer performance and a decline in function at the follow-up visit. Overall 90% (n=962) of the participants were able to perform the TCS.

Grip strength was measured in each hand using a Jamar dynamometer. A trained examiner adjusted the handle so that the dynamometer was held comfortably in the hand with the

elbow flexed at 90 degrees and the forearm parallel to the floor. The dynamometer was squeezed maximally while simultaneously lowering the arm on a 3 second count. GS was recorded to the nearest 0.5 kg. Higher values reflect better performance. Approximately 95% (n=1020) participants were able to complete the GS test.

Statistical analysis

Participant baseline characteristics were summarized using means ($\pm$ standard deviation) for continuous variables and counts and percentages for categorical variables. For continuous variables with normal distributions, Student *t* tests were used. Differences in categorical variables were examined using Chi-square test. Vitamin D deficiency was defined as 25(OH)D levels less than 50 nmol/L, while vitamin D insufficiency was defined as 25(OH)D levels less than 75 nmol/L. Serum 25(OH)D concentrations were analyzed by sex-specific quartiles. The presence of a nonlinear (quadratic) effect of 25(OH)D concentration was examined but was not apparent, so only the linear associations were modeled.

The average of the two TUG results are presented. The average grip strength was analyzed to reduce confounding due to hand dominance. Separate analyses were performed for the each different physical function outcome (TCS, TUG, and GS). Percent change in physical function was calculated as the difference between baseline and follow-up values divided by baseline physical performance.

Generalized linear models were used to examine the independent association between 25(OH)D levels and each measure of physical function. Known factors associated with 25(OH)D levels and/or physical function were examined for inclusion in multivariate models. Covariates with a *p*-value <0.10 in the bivariate analysis were added to the final model. Potential confounders included in the multivariate models were age, sex, BMI, baseline physical activity level, alcohol and estrogen use (only in women). Initially, analyses combining the two sexes showed a significant interaction (*p* value <0.05) between 25(OH)D levels, physical function and sex. Therefore, all analyses were stratified by sex. All analyses were performed using SAS version 8.2 (Cary NC: SAS institute). All statistical tests were two-tailed and statistical significance was defined as a *p*-value <0.05 .

RESULTS

Sex-specific baseline characteristics of the 1065 participants are shown in Table 1. Their mean $\pm$ SD age was 74.6 ± 10.3 years; 61% were women and 98% were Caucasian. About 72% exercised three or more times per week; 50% were previous smokers, but only 4.5% smoked at baseline.

In this cohort, 58.5% of women and 21.9% of men were taking calcium supplements, while fewer participants were taking vitamin D supplements (28.6% women and 9.3% men). Even though three times more women were taking vitamin D supplements, the mean serum 25(OH)D concentrations were higher in men (107.6 ± 29.2 nmol/L) than women (100.8 ± 33.1) (*p* <0.0001). Vitamin D supplement users had higher levels of 25(OH)D than non-users. Mean 25(OH)D levels did not vary by each 5-year age group in either men or women. Only 5 (1.2%) men and 19 (2.9%) women were vitamin D deficient defined as 25(OH)D <50 nmol/L; while 31 (7.6%) men and 113 (17.2%) women were vitamin D insufficient. The mean PTH level in the vitamin D deficient subjects was 63.8 ± 38.3 ng/dl compared to 50.5 ± 25.4 ng/dl in non-vitamin D deficient subjects. The PTH levels were significantly higher in the vitamin D deficient compared to the non-vitamin D deficient subjects (*p* $=0.01$). However, there was no statistically significant difference in the proportion of subjects who had hyperparathyroidism (PTH >65 ng/ml).

Except for grip strength, which was better for men, baseline TCS and TUG measures were similar for men and women. After 2.5 years, the absolute change in grip strength was the same in both sexes ($p=0.4$) and the relative difference in grip strength was -0.76% in women and -0.89% in men. (Table 1). However, the relative decline on the TCS and TUG test was greater in women than men (11% vs. 3% for each test).

In bivariate analyses, lower 25(OH)D levels were associated with female sex and increasing age, higher BMI and greater alcohol intake. Levels of 25(OH)D were lower in those who did not exercise and in smokers. Lower GS was associated with increased age, alcohol use and lower BMI. Older age, smoking and lower baseline physical activity were associated with poorer TUG and TCS.

Association between 25(OH)D levels and physical performance

In cross-sectional analyses, women in the lowest 25(OH)D quartile had the poorest performance on the TUG and TCS tests even after adjusting for age and other confounders (Table 2). Lower extremity function was 7.2% poorer for women in the lowest 25(OH)D quartile (≤ 80 nmol/L) compared to women in the highest quartile (≥ 115 nmol/L). All of the associations were independent of age, BMI, baseline physical activity level, alcohol, estrogen use (in women), and comorbidities including diabetes, hypertension, stroke, coronary artery disease, and congestive heart failure.

Prospectively, women in the lowest quartile performed more poorly and had a larger mean percent decrease on the TCS and TUG tests compared to women in the highest 25(OH)D quartile (20% vs. 8%) (Table 3). Women with 25(OH)D levels ≤ 80 nmol/L had about 3 fold greater change in lower extremity physical function compared to women with 25(OH)D levels >80 nmol/L (Figure 1).

25(OH)D levels in the lowest quartile (≤ 80 nmol/L) were associated with lower grip strength in men at baseline (p -value= 0.04), but, TCS and TUG was not. However, grip strength was not associated with 25(OH)D levels in either sex longitudinally.

Additional analyses

Analyses comparing vitamin D insufficiency vs. sufficiency (25(OH)D levels <75 vs. >75 nmol/L) showed similar associations cross-sectionally and prospectively as the vitamin D quartile analysis. Women with vitamin D insufficiency had slower TCS and TUG at baseline and almost a 3-fold greater percent change on the TCS and TUG during follow-up compared to vitamin D sufficient women (25% vs. 8% , $p<.0001$). When we examined vitamin D deficiency, vitamin D deficient women (25(OH)D <50 nmol/L) had a mean 39% change in TCS and TUG compared to 10% in non-vitamin D deficient women. Physical function measures were not significantly different in men with vitamin D insufficiency or deficiency. Analyses comparing severe vitamin D deficiency (25(OH)D levels <25 nmol/L) showed no cross-sectional or prospective associations with any of the physical function measures. However, this lack of an association is probably due to the small sample size, since less than 1% of the patients had 25(OH)D levels <25 nmol/L.

To examine the effect of non-participation at the follow-up visit on these results, we compared the baseline characteristics of those who did or did not return to the second visit. Table 4 demonstrates that, at baseline, participants who did not return to the clinic were older, thinner with lower 25(OH)D levels and physical performance as compared to participants who were seen at both visits (all comparisons between participants and non-participants were statistically significant at the $p<.001$ level). Therefore the magnitude of the associations observed here was likely attenuated by the selective attrition of those with lower 25(OH)D levels and poorer

physical function at baseline, a conservative bias. Relatively few participants had missing data for GS (5.3%), TUG (4.5%) or TCS (10.8%). Baseline characteristics were not different between participants with missing data versus no missing data. Finally we determined whether impaired renal function explained our findings. Only 56 (5.2%) men and women in this cohort had creatinine clearance less than 30mg/ml. Results excluding these participants were unchanged.

DISCUSSION

We found a significant cross-sectional association between lower 25(OH)D concentrations and poorer lower extremity function in community dwelling elderly women. Likewise, low 25(OH)D levels independently predicted the decline in TUG and TCS in women over a 2.5-year follow-up. No associations were observed in men, who were less likely than women to have vitamin D insufficiency. The observed associations are likely underestimated, in that they were attenuated by the selective loss of older participants with lower 25(OH)D levels and poorer function at baseline.

Our findings are consistent with other cross-sectional studies. Significant correlations between vitamin D metabolites and leg extension power have been found, (26) as well as with arm muscle strength, ability to climb stairs, physical activity and the absence of falls. (25) Additionally, circulating calcitriol [1,25(OH)₂D] has also been positively associated with leg extension power, physical activity and falls. (25) In another study, both men and women with 25(OH)D levels less than 40 nmol/L were found to have reduced handgrip strength and walking distance. (24) In addition, effects on gait speed and thigh muscle strength were confirmed in two randomized clinical trials of vitamin D supplements. (32,33)

Two similar prospective studies of serum 25(OH)D and change in physical function has been published. One study of elderly men and women in the Longitudinal Aging Study Amsterdam showed that adults with serum 25(OH)D up to 50 nmol/L had a higher risk for decline in physical performance over 3 years of follow-up. (27) However, the study by Verrault and colleagues did not find an association between vitamin D deficiency and muscle strength, walking speed or chair stands. Vitamin D deficient participants from the Women's Health and Aging Study (WHAS) had an annual 1.17 kg (5.5% compared to baseline) decline in grip strength and an annual 3.3 sec (15.9% compared to baseline) increase in TCS. (28) Women in the RBS had lower rates of functional decline: approximately 0.2 kg (1% compared to baseline) in grip strength and approximately 0.5 sec (4% compared to baseline) on TCS and TUG tests.

The differences between these two cohorts may be explained by the fact that the participants in the WHAS were moderately to severely disable, unlike the RBS participants who were generally healthy with little to no disabilities. This led the authors to speculate that the WHAS women were already below a threshold of strength where vitamin D could have an impact.

The association between 25(OH)D and physical function in the Rancho Bernardo cohort was observed only in women. This sex difference is unlikely explained by the slightly higher 25(OH)D levels in men. Selective attrition of men is also unlikely since there were no differences in rates of follow-up or mortality by sex. A more likely explanation is that men retained their strength and had a smaller degree of functional decline compared to women of the same age (3% vs. 11%). Rancho Bernardo men likely had more preserved muscle strength compared to women due to their higher reported physical activity. Other potential mechanisms such as differences in vitamin D receptor gene polymorphisms might also explain the sex specific differences. (37,38)

There is increasing evidence suggesting that vitamin D intakes higher than those currently recommended are associated with better outcomes. Some suggest that older adults should be

supplemented to maintain 25(OH)D levels at a minimum of 70nmol/L, with optimal values between 90 to 100nmol/L. (39) In this cohort, women with 25(OH)D levels below 80 nmol/L had clinically significant more functional decline. However, levels greater than 80 nmol/L did not confer additional benefit. The vitamin D threshold demonstrated in this study is consistent with previously suggested optimal levels, however, determining the exact level is confounded by assay differences. Recent methodological comparisons have demonstrated that CPBA overestimates 25(OH)D concentrations compared to radioimmunoassay (RIA) or high protein liquid chromatography (HPLC). (40) Although the exact levels would differ by assays, methodology differences would not affect the linear association seen between 25(OH)D with physical function.

Limitations to the present study should be noted. Specifically, the 2.5 years follow-up was a short duration to show a large change in physical function in men. Nevertheless, it was of sufficient duration to show a clinically meaningful loss of function in women. Generalizability is a potential limitation, in that the Rancho Bernardo cohort was largely middle to upper middle class, Caucasian, and lived in a warm sunny climate where outdoor physical activity is almost always possible, and where there was a low prevalence of vitamin D deficiency/insufficiency. Any bias should have caused a conservative estimate on the magnitude of the association, as a larger effect would be expected in a population with more vitamin D deficiency. Participation bias likely attenuated the results, since those who did not return to the follow-up evaluation had lower 25(OH)D levels and poorer physical function at baseline. Other residual confounders and causes of reduced physical function may have contributed to this association. As noted above, differences in 25(OH)D assay methods make it difficult to define optimal levels when comparing results from different studies.

In conclusion, our findings support the hypothesis that 25(OH)D levels are associated with muscle function, and supports recent data that higher 25(OH)D levels are beneficial for various outcomes. Future studies evaluating different cutpoints with different 25(OH)D assays and longer follow-up are necessary to determine the optimal 25(OH)D level and dose for supplementation.

Acknowledgements

Funding: This work was supported by the National Institutes of Health, National Institute on Aging, NIH/NIA Contracts 5 R37 AG007181. This study was partially supported by an unrestricted grant by the Alliance for Better Bone Health: Procter & Gamble Pharmaceuticals and Sanofi-Aventis Pharmaceuticals. Dr. Dam is recipient of the HRSA Geriatric Academic Career Award.

Financial Disclosures: All authors should indicate financial support for research, consultations, and speakers forum, as well as having any company holdings (e.g. stocks) or patents.

Thuy-Tien Dam: Research Support: Alliance for Better Bone Health

Denise von Mühlen: (none)

Elizabeth Barrett-Connor: Consulting contracts and Research Support: Eli Lilly & Company, Merck & Company

References

1. Holick, MF. Vitamin D: Photobiology, Metabolism, Mechanism of Action and Clinical Applications. In: Favus, MJ., editor. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. American Society for Bone and Mineral Research; Washington DC: 2003. p. 129-136.
2. Mitra, D.; Bell, NH. Racial, geographic, genetic and body habits effects on Vitamin D. In: Feldman, D.; Glorieux, FH.; Pike, JW., editors. Vitamin D. Academic Press; San Diego: 1997. p. 521-532.
3. Chapuy, MC.; Meunier, PJ. Vitamin D insufficiency in adults and the elderly. In: Feldman, D.; Glorieux, FH.; Pike, JW., editors. Vitamin D. San Diego: 1997. p. 679-693.

4. Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, Meunier PJ. Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos Int* 1997;7:439–443. [PubMed: 9425501]
5. Gloth FM 3rd, Gundberg CM, Hollis BW, Haddad JG Jr, Tobin JD. Vitamin D deficiency in homebound elderly persons. *Jama* 1995;274:1683–1686. [PubMed: 7474272]
6. Lamberg-Allardt CJ, Outila TA, Karkkainen MU, Rita HJ, Valsta LM. Vitamin D deficiency and bone health in healthy adults in Finland: could this be a concern in other parts of Europe? *J Bone Miner Res* 2001;16:2066–2073. [PubMed: 11697803]
7. Scharla SH. Prevalence of subclinical vitamin D deficiency in different European countries. *Osteoporos Int* 1998;8 Suppl 2:S7–12. [PubMed: 10197176]
8. Tareen N, Martins D, Zadshir A, Pan D, Norris KC. The impact of routine vitamin supplementation on serum levels of 25 (OH) D3 among the general adult population and patients with chronic kidney disease. *Ethn Dis* 2005;15:S5-102–106.
9. van der Wielen RP, Lowik MR, van den Berg H, de Groot LC, Haller J, Moreiras O, van Staveren WA. Serum vitamin D concentrations among elderly people in Europe. *Lancet* 1995;346:207–210. [PubMed: 7616799]
10. Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, Vamvakas EC, Dick IM, Prince RL, Finkelstein JS. Hypovitaminosis D in medical inpatients. *N Engl J Med* 1998;338:777–783. [PubMed: 9504937]
11. Kinyamu HK, Gallagher JC, Rafferty KA, Balhorn KE. Dietary calcium and vitamin D intake in elderly women: effect on serum parathyroid hormone and vitamin D metabolites. *Am J Clin Nutr* 1998;67:342–348. [PubMed: 9459385]
12. Lips P. Vitamin D deficiency and osteoporosis: the role of vitamin D deficiency and treatment with vitamin D and analogues in the prevention of osteoporosis-related fractures. *Eur J Clin Invest* 1996;26:436–442. [PubMed: 8817154]
13. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. *Lancet* 1998;351:805–806. [PubMed: 9519960]
14. Need AG, Horowitz M, Morris HA, Nordin BC. Vitamin D status: effects on parathyroid hormone and 1, 25-dihydroxyvitamin D in postmenopausal women. *Am J Clin Nutr* 2000;71:1577–1581. [PubMed: 10837301]
15. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B. Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. *Am J Med* 2004;116:634–639. [PubMed: 15093761]
16. Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, Kiel DP. A higher dose of vitamin D reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. *J Am Geriatr Soc* 2007;55:234–239. [PubMed: 17302660]
17. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, Wong JB. Effect of Vitamin D on falls: a meta-analysis. *Jama* 2004;291:1999–2006. [PubMed: 15113819]
18. Jackson C, Gaugris S, Sen SS, Hosking D. The effect of cholecalciferol (vitamin D3) on the risk of fall and fracture: a meta-analysis. *Qjm* 2007;100:185–192. [PubMed: 17308327]
19. Endo I, Inoue D, Mitsui T, Umaki Y, Akaka M, Yoshizawa T, Kato S, Matsumoto T. Deletion of vitamin D receptor gene in mice results in abnormal skeletal muscle development with deregulated expression of myoregulatory transcription factors. *Endocrinology* 2003;144:5138–5144. [PubMed: 12959989]
20. Mingrone G, Greco AV, Castagneto M, Gasbarrini G. A woman who left her wheelchair. *Lancet* 1999;353:806. [PubMed: 10459963]
21. Prabhala A, Garg R, Dandona P. Severe myopathy associated with vitamin D deficiency in western New York. *Arch Intern Med* 2000;160:1199–1203. [PubMed: 10789615]
22. Ziambaras K, Dagogo-Jack S. Reversible muscle weakness in patients with vitamin D deficiency. *West J Med* 1997;167:435–439. [PubMed: 9426489]
23. Kenny AM, Biskup B, Robbins B, Marcella G, Burleson JA. Effects of vitamin D supplementation on strength, physical function, and health perception in older, community-dwelling men. *J Am Geriatr Soc* 2003;51:1762–1767. [PubMed: 14687355]
24. Mets T. Calcium, vitamin D, and hip fractures. Incidence of falls may have decreased. *Bmj* 1994;309:193. [PubMed: 8044104]

25. Mowe M, Haug E, Bohmer T. Low serum calcidiol concentration in older adults with reduced muscular function. *J Am Geriatr Soc* 1999;47:220–226. [PubMed: 9988294]
26. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlson EW, Dawson-Hughes B. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. *Am J Clin Nutr* 2004;80:752–758. [PubMed: 15321818]
27. Wicherts IS, van Schoor NM, Boeke AJ, Visser M, Deeg DJ, Smit J, Knol DL, Lips P. Vitamin D status predicts physical performance and its decline in older persons. *J Clin Endocrinol Metab* 2007;92:2058–2065. [PubMed: 17341569]
28. Verreault R, Semba RD, Volpato S, Ferrucci L, Fried LP, Guralnik JM. Low serum vitamin d does not predict new disability or loss of muscle strength in older women. *J Am Geriatr Soc* 2002;50:912–917. [PubMed: 12028180]
29. Gloth FM 3rd, Smith CE, Hollis BW, Tobin JD. Functional improvement with vitamin D replenishment in a cohort of frail, vitamin D-deficient older people. *J Am Geriatr Soc* 1995;43:1269–1271. [PubMed: 7594162]
30. Johnson KR, Jobber J, Stonawski BJ. Prophylactic vitamin D in the elderly. *Age Ageing* 1980;9:121–127. [PubMed: 7395656]
31. Corless D, Dawson E, Fraser F, Ellis M, Evans SJ, Perry JD, Reisner C, Silver CP, Beer M, Boucher BJ, et al. Do vitamin D supplements improve the physical capabilities of elderly hospital patients? *Age Ageing* 1985;14:76–84. [PubMed: 4003187]
32. Dhesei JK, Jackson SH, Bearne LM, Moniz C, Hurley MV, Swift CG, Allain TJ. Vitamin D supplementation improves neuromuscular function in older people who fall. *Age Ageing* 2004;33:589–595. [PubMed: 15501836]
33. Verhaar HJ, Samson MM, Jansen PA, de Vreede PL, Manten JW, Duursma SA. Muscle strength, functional mobility and vitamin D in older women. *Aging (Milano)* 2000;12:455–460. [PubMed: 11211956]
34. Chen TC, Turner AK, Holick MF. Methods for the determination of the circulating concentration of 25-hydroxyvitamin D. *J Nutr Biochem* 1990;1:315–319. [PubMed: 15539221]
35. Holick M, Chen T, Jamieson D, Lu Z, Mathieu J. Evaluation of Precision and Accuracy of Nichols Advantage 25-Hydroxyvitamin D Assay for 25-Hydroxyvitamin D2 and 25-Hydroxyvitamin D3: In Comparison to Four Other Assays Methods Including Liquid Chromatography-Mass Spectrometry. *J Bone Mineral Res* 2004;19:S343.
36. Papaioannou A, Ray JG, Ferko NC, Clarke JA, Campbell G, Adachi JD. Estimation of creatinine clearance in elderly persons in long-term care facilities. *Am J Med* 2001;111:569–573. [PubMed: 11705434]
37. Geusens P, Vandevyver C, Vanhoof J, Cassiman JJ, Boonen S, Raus J. Quadriceps and grip strength are related to vitamin D receptor genotype in elderly nonobese women. *J Bone Miner Res* 1997;12:2082–2088. [PubMed: 9421241]
38. Grundberg E, Brandstrom H, Ribom EL, Ljunggren O, Mallmin H, Kindmark A. Genetic variation in the human vitamin D receptor is associated with muscle strength, fat mass and body weight in Swedish women. *Eur J Endocrinol* 2004;150:323–328. [PubMed: 15012617]
39. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 2006;84:18–28. [PubMed: 16825677]
40. Lips P, Chapuy MC, Dawson-Hughes B, Pols HA, Holick MF. An international comparison of serum 25-hydroxyvitamin D measurements. *Osteoporos Int* 1999;9:394–397. [PubMed: 10550457]

Figure 1. 25-hydroxyvitamin D quartiles and Change in Physical Function (%)

Figure 1 depicts the percent change in physical function by quartiles of 25-hydroxyvitamin D over a 2.5 year follow-up period in older men and women. Physical function were measured by two physical performance tests: 1) Timed Chair Stands (TCS) and 2) Timed Up and Go (TUG). Timed Chair Stands is the time (seconds) it takes to complete 5 chair stands without stopping or using arms to push off. Timed Up & Go is the amount of time (seconds) it takes to rise from a chair, walk 3 meters, and return to a sitting position. Increase time to perform these tests reflected poorer physical performance. Women in the lowest quartile of 25-hydroxyvitamin D had the largest relative increase on the physical function measures.

Comparison of Demographics, Vitamin D and Physical Performance Measures by Sex in 1065 Participants from the Rancho Bernardo Study

Table 1

	Men (n=409)	Women (n=656)	P -value
Demographics			
Age (years), mean $\pm$ SD	74.5 $\pm$ 9.5	74.7 $\pm$ 10.8	.80
Weight (kg), mean $\pm$ SD	80.5 $\pm$ 12.6	63.5 $\pm$ 12.1	<.001
BMI (kg/m ²), mean $\pm$ SD	26.1 $\pm$ 3.6	24.8 $\pm$ 4.2	<.001
Exercise 3 times per week, n(%)	320 (77.5)	457 (68.9)	<.001
Alcohol intake > 1–2 times per week, n(%)	131 (31.7)	188 (28.3)	<.001
Calcium supplements use, n(%)	89 (21.9)	386 (58.5)	<.001
Vitamin D supplements use, n(%)	38 (9.3)	187 (28.6)	<.001
Diabetes, n(%)	36 (8.8)	38 (5.8)	<.001
Congestive Heart Failure, n(%)	16 (3.9)	9 (1.4)	<.001
Stroke, n(%)	18 (4.4)	12 (1.8)	<.001
Creatinine (mg/dl), mean $\pm$ SD	1.1 $\pm$ 0.3	0.9 $\pm$ 0.4	.50
Parathyroid Hormone (ng/dl), mean $\pm$ SD	51.6 $\pm$ 26.8	50.4 $\pm$ 25.4	.47
Parathyroid Hormone (>65 ng/dl), n(%)	69 (16.9)	120 (18.3)	.55
25(OH)D (nmol/L), mean $\pm$ SD	107.6 $\pm$ 29.2	100.8 $\pm$ 33.1	<.001
25(OH)D <75 nmol/L, n(%)	31 (7.6)	113 (17.2)	<.001
25(OH)D <50 nmol/L, n(%)	5 (1.2)	19 (2.9)	.50
Baseline physical performance measures			
Grip strength (kg), mean $\pm$ SD	32.5 $\pm$ 7.9	17.6 $\pm$ 5.0	<.001
Timed Chair Stands ^a (sec), mean $\pm$ SD	10.9 $\pm$ 2.9	10.9 $\pm$ 3.1	.40
Timed Up & Go ^b (sec), mean $\pm$ SD	10.8 $\pm$ 2.8	10.9 $\pm$ 3.1	.40
Absolute change in physical performance measures			
Grip strength (kg), mean $\pm$ SD	−26 $\pm$ 4.1	−43 $\pm$ 3.0	.40
Timed Chair Stands (sec), mean $\pm$ SD	.22 $\pm$ 2.4	1.17 $\pm$ 3.1	<.001
Timed Up & Go (sec), mean $\pm$ SD	.22 $\pm$ 2.4	1.19 $\pm$ 3.1	<.001
Percent change in physical performance measures			
Grip strength (%), mean $\pm$ SD	−76 $\pm$ 13.0	−89 $\pm$ 25.0	.50
Timed Chair Stands (%), mean $\pm$ SD	3.3 $\pm$ 20.1	11.1 $\pm$ 26.6	<.001

	Men (n=409)	Women (n=656)	P -value
Timed Up & Go (%), mean ± SD	3.3 ± 20.1	11.2 ± 26.6	<.001

^aTimed Chair Stands is the time (seconds) it takes to complete 5 chair stands without stopping or using arms to push off.

^bTimed Up & Go is the amount of time (seconds) it takes to rise from a chair, walk 3 meters, and return to a sitting position. Increased time to perform these tests reflected poorer physical function.

Table 2
Cross-sectional Age and Multivariate^a adjusted Means (95% Confidence Intervals) for Physical Function by 25-Hydroxyvitamin D Quartiles

WOMEN		Quartile 1 range 10-80 n=159	Quartile 2 range 82.5-97.5 n=181	Quartile 3 range 100-112.5 n=153	Quartile 4 range 115-337.5 n=163	p-trend
Grip Strength (kg)						
Age-adjusted		17.34 (16.65, 18.03)	17.55 (16.92, 18.18)	17.92 (17.24, 18.60)	17.57 (16.90, 18.24)	.50
Multivariate-adjusted		17.40 (16.63, 18.17)	17.72 (17.05, 18.40)	18.13 (17.41, 18.86)	17.92 (17.22, 18.63)	.24
Timed Chair Stands (sec)						
Age-adjusted		11.28 (10.85, 11.72)*	10.90 (10.50, 11.29)	10.81 (10.39, 11.23)	10.47 (10.06, 10.88)	.009
Multivariate-adjusted		11.03 (10.60, 11.47)*	10.78 (10.41, 11.15)	10.72 (10.32, 11.12)	10.28 (9.90, 10.66)	.009
Timed Up and Go (sec)						
Age-adjusted		11.28 (10.84, 11.72)*	10.90 (10.50, 11.29)	10.81 (10.39, 11.23)	10.46 (10.05, 10.87)	.01
Multivariate-adjusted		11.03 (10.60, 11.47)*	10.78 (10.41, 11.15)	10.72 (10.32, 11.11)	10.26 (9.88, 10.65)	.01
MEN		Quartile 1 range 10-90 n=114	Quartile 2 range 92.5-102.5 n=86	Quartile 3 range 105-120 n=110	Quartile 4 range 122.5-262.5 n=99	p-trend
Grip Strength (kg)						
Age-adjusted		31.89 (30.72, 33.06)*	32.04 (30.69, 33.38)	32.46 (31.29, 33.63)	33.67 (32.43, 34.91)	.04
Multivariate-adjusted		32.09 (30.83, 33.34)*	31.95 (30.55, 33.36)	32.75 (31.55, 33.95)	34.12 (32.83, 35.41)	.02
Timed Chair Stands (sec)						
Age-adjusted		11.18 (10.68, 11.68)	11.00 (10.42, 11.58)	10.57 (10.07, 11.07)	10.71 (10.19, 11.24)	.12
Multivariate-adjusted		10.90 (10.42, 11.37)	10.76 (10.22, 11.30)	10.56 (10.10, 11.02)	10.82 (10.33, 11.31)	.69
Timed Up and Go (sec)						
Age-adjusted		11.18 (10.70, 11.65)	11.01 (10.47, 11.56)	10.40 (9.92, 10.88)	10.69 (10.20, 11.19)	.07
Multivariate-adjusted		10.91 (10.47, 11.35)	10.76 (10.26, 11.26)	10.38 (9.95, 10.80)	10.79 (10.34, 11.24)	.47

^a adjusted for age, BMI, baseline physical activity level, alcohol, estrogen use (in women), comorbidities including diabetes, hypertension, stroke, coronary artery disease, and congestive heart failure

* p-value <.05 compared to quartile 4 (reference category)

Table 3
Longitudinal Age and Multivariate^a adjusted Means (95% Confidence Intervals) Percent Change for Physical Function by 25-Hydroxyvitamin D Quartiles

WOMEN					
	Quartile 1 range 10–80 n=159	Quartile 2 range 82.5–97.5 n=181	Quartile 3 range 100–112.5 n=153	Quartile 4 range 115–337.5 n=163	p-trend
Change Grip Strength (%)					
Age-adjusted	–0.32 (–5.02, 4.37)	–1.87 (–2.24, 5.97)	–2.05 (–6.36, 2.26)	–3.42 (–7.64, 0.81)	.19
Multivariate-adjusted	–0.78 (–4.76, 6.32)	–3.30 (–1.34, 7.95)	–2.01 (–6.85, 2.83)	–2.33 (–7.10, 2.45)	.22
Change Timed Chair Stands (%)					
Age-adjusted	19.97 (14.86, 25.07)**	9.04 (4.66, 13.43)	9.09 (4.46, 13.71)	8.15 (3.53, 12.78)	.002
Multivariate adjusted	21.98 (16.28, 27.67)**	7.38 (2.70, 12.06)	8.51 (3.51, 13.51)	7.70 (2.58, 12.62)	.0007
Change Timed Up and Go (%)					
Age-adjusted	19.93 (14.82, 25.03)†	9.03 (4.65, 13.41)	9.08 (4.46, 13.71)	8.52 (3.86, 13.19)	.002
Multivariate adjusted	21.92 (16.22, 27.62)**	7.37 (2.69, 12.04)	8.48 (3.48, 13.48)	8.13 (3.16, 13.10)	.001
MEN					
	Quartile 1 range 10–90 n=114	Quartile 2 range 92.5–102.5 n=86	Quartile 3 range 105–120 n=110	Quartile 4 range 122.5–262.5 n=99	p-trend
Change Grip Strength (%)					
Age-adjusted	–0.62 (–3.26, 2.01)	–0.79 (–3.88, 2.30)	–0.67 (–1.92, 3.25)	–2.43 (–5.12, 0.26)	.52
Multivariate-adjusted	–0.71 (–2.12, 3.54)	–0.64 (–3.91, 2.63)	–0.37 (–2.34, 3.07)	–2.34 (–5.15, 0.48)	.22
Change Timed Chair Stands (%)					
Age-adjusted	2.84 (–1.25, 6.93)	2.67 (–2.16, 7.50)	5.34 (1.35, 9.33)	1.99 (–2.19, 6.17)	.99
Multivariate adjusted	3.36 (–1.11, 7.82)	3.52 (–1.75, 8.79)	4.95 (0.69, 9.21)	1.42 (–3.05, 5.90)	.68
Change Timed Up and Go (%)					
Age-adjusted	2.84 (–1.25, 6.93)	2.67 (–2.16, 7.50)	5.34 (1.35, 9.33)	1.99 (–2.19, 6.17)	.99
Multivariate adjusted	3.36 (–1.11, 7.82)	3.52 (–1.75, 8.79)	4.95 (0.69, 9.21)	1.42 (–3.05, 5.90)	.68

^a adjusted for age, BMI, baseline physical activity level, alcohol, estrogen use (in women), comorbidities including diabetes, hypertension, stroke, coronary artery disease, and congestive heart failure

* p-value <.05 compared to quartile 4 (reference category)

** p-value <.05 compared to quartile 4 (reference category)

Comparison of Demographics, Vitamin D and Physical Function Measures by Participant Status at Follow-up Visit in 1999–2002^a

Table 4

	Non-participants (n=237)	Participants (n=828)
Male n(%)	84 (35.4)	329 (39.7)
Female n(%)	153 (64.6)	512 (61.8)
Age (years), mean ± SD	78.7 ± 12.0	73.5 ± 9.5
Weight (kg), mean ± SD	65.4 ± 14.7	71.3 ± 14.6
BMI (kg/m ²), mean ± SD	24.3 ± 4.0	25.8 ± 4.0
25(OH)D (nmol/L), mean ± SD	95.1 ± 26.7	106.9 ± 36.4
25(OH)D <25 nmol/L, n(%)	19 (1)	2 (0)
Grip strength (kg), mean ± SD	20.3 ± 9.5	24.3 ± 9.7
Timed Chair Stands* (sec), mean ± SD	12.1 ± 4.0	10.5 ± 2.7
Timed Up & Go† (sec), mean ± SD	12.0 ± 3.8	10.5 ± 2.8

^a comparisons between participants and non-participants were statistically significant at the p<.001 level