Combined effect of dynapenia (muscle weakness) and low vitamin D status on incident disability

Abstract

Background and objective: There is little epidemiological evidence considering the combined effect of dynapenia and low 25-hydroxyvitamin D [25(OH)D] on incident disability. Our aim was to investigate whether the combination of dynapenia and low 25 (OH) D serum levels increases the risk of activities of daily living (ADL) incident disability. **Design:** Prospective cohort study. **Settings:** English Longitudinal Study of Ageing (ELSA). **Participants:** 4,630 community-dwelling adults aged 50 years and older without ADL disability at baseline. **Measurements:** The baseline sample was categorized into four groups i.e. non-dynapenic/normal 25 (OH) D, low 25 (OH) D only, dynapenic only and dynapenic/low 25 (OH) D according to their handgrip strength (<26 kg for men and <16 kg for women) and 25 (OH) D (≤ 50nmol/L). The outcome was the presence of any ADL disability two years after baseline according to the modified Katz Index. Incidence rate ratios (IRR) adjusted by sociodemographic, behavioral and clinical characteristics were estimated using Poisson regression. **Results:** The fully adjusted model showed that older adults with dynapenia only and those with lower serum levels of 25 (OH) D combined with dynapenia had higher incident ADL disability risk compared to non-dynapenic and those with normal serum levels of 25 (OH) D. The IRRs for lower 25 (OH) D serum levels combined with dynapenia were higher than for dynapenia only, however, the confidence intervals showed similar effect for these two groups. The IRRs were 1.31 for low 25(OH) D only (95% CI = 0.99 - 1.74), 1.77 for dynapenia only (95% CI = 1.08 - 2.88), and 1.94 for combined dynapenia and low 25(OH) D (95% CI = 1.28 - 2.94). **Conclusion:** Dynapenia only and dynapenia combined with low 25 (OH) D serum levels were important risk factors for ADL disability in middle-aged individuals and older adults in two years of follow up.

Key-words: Handgrip, vitamin D, muscle strength, 25(OH) D

Introduction

Low 25 (OH) D status is an increasingly important public health issue worldwide, in all population groups, although more common in older adults[1]. The importance of 25 (OH) D in the absorption and metabolism of calcium for bone health is well known[1] and its deficiency increases osteoporosis, hip fractures risk and it is extremely frequent in chronic obstructive pulmonary disease[2], cardiovascular disease[3–5], cancer[3] and chronic kidney disease[6].

Despite aging related hormonal changes being associated with musculoskeletal changes, the participation of low 25 (OH) D serum levels in muscular strength modulation is still controversial[6–10]. For example, longitudinal data from Dutch adults aged between 55 and 85 showed that 25 (OH) D serum levels lower than 25 nmol/liter increased the risk of loss of handgrip strength (≥ 40%) compared to baseline[9]. On the other hand, Verreault et al.[10], also using three years of follow-up data from American women aged 65 and older, who were Medicare beneficiaries, found that 25 (OH) D deficiency was not associated with loss in muscle strength assessed by grip strength, maximum isometric strength of knee extensor and hip flexor.

Dynapenia, defined as a reduction in muscle strength, has been shown to be associated with declines in physical functioning and is an important risk factor for disability[11,12] and mortality[11,13]. Rantanen et al.[14], using 25 years of follow-up data from Japanese-American participants aged between 45 and 68, found that dynapenia (lowest handgrip tertile < 37 kg) increased the risk of both basic (ADL) and instrumental (IADL) activities of daily living disability. Similarly, Al Snih et al.[15], using 5 years of follow-up data from older Mexican Americans, found that dynapenia (lowest handgrip quartile < 22.01 kg for men and < 14 kg for women), was a strong predictor of mortality.

Data regarding 25 (OH) D serum levels in older adults with dynapenia are scarce and previous studies analyzed low 25 (OH) D serum levels and dynapenia as independent conditions. This analytical approach ignores the fact that both conditions can occur simultaneously in older adults and, therefore, increasing their risk of disability. In addition, dynapenic low 25 (OH) D cases are included separately on either dynapenia

only or low 25 (OH) D only groups, which may lead to an overestimation of the association between dynapenia and low 25 (OH) D with disability.

Therefore, our primary objective was to investigate whether the combination of dynapenia and low 25 (OH) D serum levels can increase the risk of activities of daily living (ADL) incident disability in a large representative sample of community-dwelling English adults aged 50 years and older, who were ADL disability free at baseline.

Methods

Study Population

ELSA is an ongoing prospective observational study of community-dwelling people aged 50 years and older in England that commenced in 2002. The ELSA sample was drawn from participants that had previously participated in the Health Survey for England (HSE); an annual health examination survey, which each year recruits a different nationally representative sample using a multi-staged stratified random probability design[16]. After baseline, follow-up interviews within ELSA occur every two years and health examinations i.e. a nurse visit, every four years. The first health examination was in 2004-05. A detailed description of the study can be found elsewhere[17].

We analysed baseline data from wave 6 (2012-13), as this was the first time that 25 (OH) D serum levels were ascertained in ELSA. The outcome was assessed at wave 7 (2014-15). Wave 6 had 10,601 respondents that also included non-core members, such as partners. Only the 9,169 core sample members eligible for a nurse visit at which blood samples could be taken were included. Of those, 8,054 had a nurse visit. Blood samples were obtained from 6,126 participants, and 25 (OH) D concentrations were ascertained in 6,112. 5,377 participants answered all the questions included in this study and 4,630 had no ADL disability at baseline.

Assessment of 25-hydroxyvitamin D – 25 (OH) D

Blood samples were not taken from those who had a clotting or bleeding disorder (e.g. haemophilia or low platelets), had ever had a seizure, were currently on anticoagulant drugs (e.g. warfarin therapy) or were did not give their consent in writing. The analyses of blood samples were carried out at the Royal Victoria Infirmary (Newcastle-upon-Tyne, UK)[18]. Serum 25 (OH) D levels were measured by the Diasorin Liaison immunoassay that detects both 25 (OH) D2 and 25 (OH) D3 and therefore, provides the total circulating 25 (OH) D level, as previously described (Vitamin D). The assay for 25 (OH) D has an analytical sensitivity (lower detection limit) of 7.5 nmol/L. The detection limit represents the lowest measurable analysis level that can be distinguished from zero. All assays were performed in duplicate. The coefficient of variation ranged from 8.7% to 9.4%. The laboratory performing the 25 (OH) D analyses took part in the Internal and the Vitamin D External Quality Assessment Schemes (DEQAS). Low 25 (OH) D was defined as 25 (OH) D $\leq$ 50 nmol/L[19].

Strength

Grip strength (kg) of the dominant hand was assessed using the Smedley hand-held dynamometer. Maximum strength tests were performed with a one-minute rest between tests and the highest value was used. Dynapenia was defined based on two cutoff points for grip strength: < 26 kg for men and < 16 kg for women[20].

Classification of the groups

We constructed a four-category variable based on participants' dynapenia status and 25 (OH) D serum levels. The categories were as follow: non-dynapenic/normal 25 (OH) D, non-dynapenic/low 25 (OH) D, dynapenic/ normal 25 (OH) D and dynapenic/low 25 (OH) D.

Activities of Daily Living (ADL) disability

Self-reported ADL disability was measured at baseline and two years later. Disability was defined herein as a difficult to perform one of the following six ADL activities: dressing, walking across a room, bathing or showering, eating, getting in or out of bed and using the toilet according to the modified Katz Index[21,22]. Only individuals without

any ADL disability at baseline were included in our study. The outcome was the presence or absence of ADL disability two years after the baseline.

Covariates

Age was coded into four groups. Marital status was classified as single, married, divorced/separated and widowed. Level of education was classified into lower than "O-level" or equivalent (0-11 years of schooling), lower than "A-level" or equivalent (12-13 years) and a higher qualification (>13 years). Total non-pension household wealth included financial wealth, the value of any home and other property, the value of any business assets and physical wealth such as artwork and jewellery, net of debt. Wealth is the most robust indicator of socioeconomic circumstances in ELSA, and has been found to be more strongly associated with the risk of death than any other socioeconomic position indicator at older ages[23].

Smoking status was classified into non-smokers, former smokers or current smokers. Frequency of alcohol consumption was classified as rarely/never (even once a week), frequently (2 - 6 times a week), daily and missing data. Self-reported level of physical activity (PA) included three questions on the frequency of participation in vigorous, moderate, and mild physical activities (more than once per week, once per week, one to three times per month, or hardly ever). PA was categorized into four groups, as previously described: inactive (no activity on a weekly basis); only mild activity at least once a week; at least moderate but no vigorous activity at least once a week; and any vigorous activity at least once a week[24].

Self-reported doctor diagnosed chronic diseases including hypertension, diabetes, osteoporosis, cancer, stroke, arthritis, lung disease and cardiovascular diseases (angina, heart attack, heart failure and heart murmur or heart rhythm) were assessed. Depressive symptoms were measured by the shortened version of the Centre for Epidemiological Studies-Depression (CES-D) Scale[25]. A dichotomous variable was derived using the validated cut point of four or more depressive symptoms to classify depression[26,27]. Cognitive function was measured by a memory test that consisted of 10 randomly selected words that the respondents were asked to recall immediately and five minutes

later. We used the total number of recalled words (possible range: 0 to 20 words) as a marker of memory[28].

Nurses measured participants' body weight to the nearest 0.1 kg using Tanita electronic scales (Tanita Co, IL, USA) without shoes and in light clothing, and height was measured using a Stadiometer with the Frankfurt plane in the horizontal position. Body mass index (BMI) was calculated using the standard formula [weight (kg)/height^2 (m^2)] and used as a continuous variable.

Season of blood sampling was categorized into summer (Jun–Aug), autumn (Sept–Nov), winter (Dec–Feb), and spring (Mar–May).

Statistical analyses

Differences in participants' characteristics according to their follow-up status were analyzed using the Rao and Scott Wald test and the chi-square test with the Rao-Scott correction. For the analysis of associated factors, the outcome was the presence or absence of ADL disability in 2014/15.

Poisson's regression analysis was used to investigate the unadjusted and adjusted association between dynapenia status and 25OHD serum levels and ADL disability. Poisson's regression was performed because it offers better consistency and efficiency than logistic regression to estimate relative risk in longitudinal studies when both are compared with the Mantel-Haenszel method[29]. Following the unadjusted model (model 1), a further model (model 2) was derived to investigate the association between dynapenia status and 25 (OH) D serum levels with the outcome ADL and adjusted for potential confounders.

Poisson post-estimates were calculated in order to confirm the differences found between non-dynapenic/low 25 (OH) D serum levels, dynapenic/normal 25 (OH) D serum levels and dynapenic/low 25 (OH) D serum levels groups in the Poisson models. All the analyses were performed using STATA version 14.0.

Ethics Approval and Informed Consent

All participants gave written informed consent. The National Research Ethics Service (London Multicentre Research Ethics Committee (MREC/01/2/91) has approved the English Longitudinal Study of Ageing.

Results

The average age was 66.2 years (SD = 8.7), 54.2% were female, 68.6% married. 41.6% were non-dynapenic and had normal 25 (OH) D levels, 50.7% were non-dynapenic with low 25 (OH) D, 3.1% dynapenic and normal 25 (OH) D and 4.6% dynapenic and low 25 (OH) D. Baseline characteristics of the 4,630 subjects according dynapenia and 25 (OH) D status are shown in Table 1.

The excluded participants due to missing data on handgrip strength, 25 (OH) D and other covariates (but all ADL disability free at baseline) were older, separated, had a lower level of education and wealth, were sedentary, current smoker, reported more high blood pressure, diabetes, stroke, arthritis and cardiovascular diseases, worse cognitive function, more depressive symptoms and higher BMI ($p < 0.05$ data not shown). The dropout rate between wave 6 and wave 7 was 10%.

Table 2 shows the IRRs for ADL disability risk according to dynapenia and 25 (OH) D status. The fully adjusted models showed that individuals with dynapenia and low 25 (OH) D levels and dynapenic only had higher ADL disability risk than non-dynapenic/non-low 25 (OH) D individuals in two years of follow up. The IRRs were 1.94 for dynapenia and low 25 (OH) D (95% CI = 1.28-2.94) and 1.77 for dynapenia only (95% CI = 1.08-2.88).

Poisson post-estimation showed no significant differences between non-dynapenic/low 25 (OH) D serum levels and dynapenic only individuals ($p=0.21$) as well as between dynapenic only and those dynapenic/low 25 (OH) D ($p=0.72$). However, a significant difference was found between non-dynapenic/low 25 (OH) D serum levels individuals and dynapenic/low 25 (OH) D serum levels ($p=0.04$).

Discussion

In this large nationally representative sample of community-dwelling English adults aged 50 years and older, we demonstrated that those who were dynapenic only and dynapenic with low 25 (OH) D serum levels had a higher risk to develop ADL disability than non-dynapenic/normal 25 (OH) D serum levels in a short two years follow-up period. To the best of our knowledge, this is the first study to analyze the combined effect of dynapenia and low 25 (OH) D serum levels on incident ADL disability.

The findings from the literature investigating the relationship between muscle strength, 25 (OH) D serum levels and disability are conflicting. A study using cross-sectional data from 4,100 American men and women aged 60 and older found that walking speed and chair rise test performance as well as measures of lower extremity function, were associated with 25 (OH) D serum levels[30]. The performance times for both tests were higher for participants with 25 (OH) D levels between 22.5 and 94 nmol/l compared to those individuals with 25 (OH) D levels between 22.5 and 40 nmol/l. Similarly, Wicherts et al[19], analysing cross-sectional data from Dutch men and women aged between 65 and 88 years, found that individuals with serum levels of 25 (OH) D lower than 50 nmol/L had worse physical performance as measured by walking speed and chair rise test compared to those with levels above 75 nmol/L. In addition, the authors demonstrated, longitudinally, that those with serum levels of 25 (OH) D lower than 50 nmol/L had worse physical performance at three years' follow-up compared to those with levels above 75 nmol/L.

Another study analyzing 2,099 men and women aged 70 to 79 years, who were free from disability at baseline as measured by the ability to walk a quarter of a mile or climbing ten steps, also found that levels of 25 (OH) D lower than 50 nmol/L were associated with higher risk to develop mobility limitation and disability[31]. However, a risk, on a smaller scale, was also observed in those with 25 (OH) D levels between 50 and 75 nmol/L. Hirani et al.[32], analyzing data from Australian men aged 70 years, found that 25 (OH) D serum levels lower than 50 nmol/L were associated with incident disability and lower grip strength suggesting that lower levels of 25 (OH) D could be associated with higher risk of loss of muscle mass and strength.

Yet, not all epidemiological evidence reported associations between dynapenia, low 25 (OH) D levels and disability. Verreault et al.[10] analyzing data from 628 American women aged 65 and older, who had moderate to severe disability at baseline, found that 25 (OH) D serum levels lower than 25 nmol/L were not associated with declines in hip flexor strength, knee extensor strength, grip strength, walking speed, time for repeated chair stands and disability in activities involving mobility and upper extremity function. These muscle characteristics were assessed at baseline and during three years of follow-up. However, the analyses were restricted only to women who already had moderate to severe disability which did not demonstrate any effect of low 25 (OH) D levels on the outcome. There were also few participants with low 25 (OH) D in the analyses making it difficult to detect any significant different between the groups. Mathei et al.[33], using cross-sectional data from the Belfrail study to investigate the relationship between 25 (OH) D serum level and muscle performance using both measures of global physical performance and muscle strength among persons aged 80 years and older, could not confirm the findings of previous studies showing an association between serum 25 (OH) D and physical performance in the elderly. In addition, despite critiques about the different samples included and lack of information about previous 25 (OH) D serum levels, the findings from a meta-analysis conducted by Muir and Montero-Odasso, using only data from older adults, did not support the benefits of a daily 25 (OH) D supplement (800 IU to 1000 IU per day) on muscle strength, but only in terms of balance and mobility[34].

Our study has several strengths and potential limitations that need to be considered. A major strength is the large and representative sample of community-dwelling English men and women aged 50 years and older using a wide range of covariates. In addition, certified examiners following standardized protocols, assuring excellent quality of data, performed all examinations and laboratory measurements. We would like to acknowledge some limitations. First, ADL disability was based on a self-report measure. However, the instruments used in this study are the ones used in research investigating disability internationally[17]. Second, the drop-out rate due to follow-up despite being small could be a source of bias. However, this type of bias is unavoidable in longitudinal studies of aging that only include community-dwelling older adults. Third, both 25 (OH) D serum levels and grip strength were measured only at baseline making it difficult to establish whether low 25 (OH) D levels cause muscle weakness

or vice-versa. Furthermore, despite dynapenia combined with low 25 (OH) D levels showed higher IRRs compared to dynapenia only, the 95% CIs and Poisson post-estimation indicated similar effects. However, it is important to highlight that these two groups had fewer individuals which could be an explanation for the similar CIs found. Finally, the individuals excluded from our analyses due to the lack of information could be a source of bias i.e. selection bias. For example, the excluded individuals had more chronic diseases and reported worst health behaviors.

Conclusions/Relevance

In summary, our main findings suggest that dynapenia on its own (handgrip strength ≤ 26 kg for men or ≤ 16 kg for women) and dynapenia combined with low 25 (OH) D serum levels are important risk factors for incident ADL disability in middle-aged and older English adults in a two-year follow-up period. Our findings, along with other recent evidence showing the importance of vitamin D and muscle strength on multiple health outcomes, draw attention to the combined effect of these conditions on incident disability among older adults. Future prospective studies with longer follow-up, examining incident ADL disability in relation to dynapenic and vitamin D are required.

Acknowledgements

We thank all of the staff working on the English Longitudinal Study of Ageing (ELSA) and the participants in the project.

Funding:

The English Longitudinal Study of Ageing is supported by the National Institute on Aging (NIA/NIH) USA (grant number 5 R01 AG017644-16) and a consortium of the United Kingdom government departments coordinated by the Economic and Social Research Council (ESRC). These funding bodies had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Conflict of interest: None declared

References

1. de Oliveira C, Biddulph JP, Hirani V, Schneider IJC. Vitamin D and inflammatory markers: Cross-sectional analyses using data from the English Longitudinal Study of Ageing (ELSA). *J Nutr Sci*. 2017;6(May):1-6. doi:10.1017/jns.2016.37
2. Janssens W, Mathieu C, Boonen S, Decramer M. Vitamin D Deficiency and Chronic Obstructive Pulmonary Disease. In: *Vitamins and Hormones*. Vol 86. ; 2011:379-399. doi:10.1016/B978-0-12-386960-9.00017-4
3. Rosen CJ, Adams JS, Bikle DD, et al. The Nonskeletal Effects of Vitamin D: An Endocrine Society Scientific Statement. *Endocr Rev*. 2012;33(3):456-492. doi:10.1210/er.2012-1000
4. Brøndum-Jacobsen P, Benn M, Jensen GB, Nordestgaard BG. 25-hydroxyvitamin d levels and risk of ischemic heart disease, myocardial infarction, and early death: population-based study and meta-analyses of 18 and 17 studies. *Arterioscler Thromb Vasc Biol*. 2012;32(11):2794-2802. doi:10.1161/ATVBAHA.112.248039
5. Norman PE, Powell JT. Vitamin D and cardiovascular disease. *Circ Res*. 2014;114(2):379-393. doi:10.1161/CIRCRESAHA.113.301241
6. Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. *Lancet Diabetes Endocrinol*. 2014;2(1):76-89. doi:10.1016/S2213-8587(13)70165-7
7. Cohen S, Nathan JA, Goldberg AL. Muscle wasting in disease: molecular mechanisms and promising therapies. *Nat Rev Drug Discov*. 2015;14(1):58-74. doi:10.1038/nrd4467
8. Halfon M, Phan O, Theta D, Teta D. Vitamin D: A review on its effects on muscle strength, the risk of fall, and frailty. *Biomed Res Int*. 2015;2015:1-11. doi:10.1155/2015/953241
9. Visser M, Deeg DJH, Lips P. Low Vitamin D and High Parathyroid Hormone Levels as Determinants of Loss of Muscle Strength and Muscle Mass (Sarcopenia): The Longitudinal Aging Study Amsterdam. *J Clin Endocrinol Metab*. 2003;88(12):5766-5772. doi:10.1210/jc.2003-030604
10. Verreault R, Semba RD, Volpato S, et al. Low serum vitamin D does not predict new disability or loss of muscle strength in older women. *J Am Geriatr Soc*. 2002;50(5):912-917. doi:10.1046/j.1532-5415.2002.50219.x

11. Manini TM, Clark BC. Dynapenia and aging: An update. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2012;67 A(1):28-40. doi:10.1093/gerona/glr010
12. Alexandre TS, Duarte YAO, Wong R, Lebrao ML. Sarcopenia according to the European Working group on sarcopenia in older people versus Dynapenia as a risk factor for disability in elderly. *J Nutr Heal Aging*. 2014;18:547-553.
13. Alexandre TS, Scholes S, Santos JLF, Duarte YAO. Dynapenic abdominal obesity increases mortality risk among english and brazilian older adults: a 10-year follow-up of the ELSA and SABE studies. *J Nutr Health Aging*. 2017;in press. doi:10.1007/s12603-017-0966-4
14. Rantanen T. Midlife Hand Grip Strength as a Predictor of Old Age Disability. *Jama*. 1999;281(6):558. doi:10.1001/jama.281.6.558
15. Snih S Al, Markides KS, Ray L, et al. Handgrip strength and mortality in older Mexican Americans. *J Am Geriatr Soc*. 2002;50(7):1250-1256. doi:10.1046/j.1532-5415.2002.50312.x
16. Mindell J, Biddulph JP, Hirani V, et al. Cohort profile: The health survey for england. *Int J Epidemiol*. 2012;41(6):1585-1593. doi:10.1093/ije/dyr199
17. Steptoe A, Breeze E, Banks J, Nazroo J. Cohort profile: The English Longitudinal Study of Ageing. *Int J Epidemiol*. 2013;42(6):1640-1648. doi:10.1093/ije/dys168
18. Vitamin D Total (25-hydroxyvitamin D) pack insert. Roche diagnostics.
19. Wicherts IS, van Schoor NM, Boeke a JP, et al. Vitamin D status predicts physical performance and its decline in older persons. *J Clin Endocrinol Metab*. 2007;92(6):2058-2065. doi:10.1210/jc.2006-1525
20. Alley DE, Shardell MD, Peters KW, et al. Grip strength cutpoints for the identification of clinically relevant weakness. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2014;69 A(5):559-566. doi:10.1093/gerona/glu011
21. Katz S, Ford AB, Moskowitz RW, et al. Studies of illness in the aged. The Index of ADL: A Standardized Measure of Biological and Psychosocial Function. *J Am Med Assoc*. 1963;185:914-919. doi:10.1001/jama.1963.03060120024016
22. Gale CR, Cooper C, Aihie Sayer A. Prevalence of frailty and disability: findings from the English Longitudinal Study of Ageing. *Age Ageing*. 2015;44(1):162-165. doi:10.1093/ageing/afu148
23. Demakakos P, Biddulph JP, Bobak M, Marmot MG. Wealth and mortality at older ages: a prospective cohort study. *J Epidemiol Community Health*.

2016;70(4):346-353. doi:10.1136/jech-2015-206173

24. Hamer M, de Oliveira C, Demakakos P. Non-Exercise Physical Activity and Survival. *Am J Prev Med*. 2014;47(4):452-460. doi:10.1016/j.amepre.2014.05.044
25. Radloff LS. The CES-D Scale: A Self Report Depression Scale for Research in the General. *Appl Psychol Meas*. 1977;1:385-401. doi:10.1177/014662167700100306
26. Wallace RB, Regula A, Mary H, et al. HRS/AHEAD Documentation Report Documentation of Affective Functioning Measures in the Health and Retirement Study. 2000. http://hrsonline.isr.umich.edu/sitedocs/userg/dr-005.pdf. Accessed May 11, 2018.
27. de Oliveira C, Hirani V, Biddulph JP. Associations Between Vitamin D Levels and Depressive Symptoms in Later Life: Evidence From the English Longitudinal Study of Ageing (ELSA). *Journals Gerontol Ser A*. 2017. doi:10.1093/gerona/glx130
28. Zaninotto P, Batty GD, Allerhand M, Deary IJ. Cognitive function trajectories and their determinants in older people: 8 years of follow-up in the English Longitudinal Study of Ageing. *J Epidemiol Community Health*. April 2018:jech-2017-210116. doi:10.1136/jech-2017-210116
29. Zou G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. *Am J Epidemiol*. 2004;159(7):702-706. doi:10.1093/aje/kwh090
30. Bischoff-Ferrari HA, Dietrich T, Orav EJ, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged ≥60 y. *Am J Clin Nutr*. 2004;80(3):752-758. doi:80/3/752 [pii]
31. Houston DK, Neiberg RH, Tooze JA, et al. Low 25-hydroxyvitamin D predicts the onset of mobility limitation and disability in community-dwelling older adults: The health ABC study. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2013;68(2):181-187. doi:10.1093/gerona/gls136
32. Hirani V, Cumming RG, Naganathan V, et al. Associations between serum 25-hydroxyvitamin D concentrations and multiple health conditions, physical performance measures, disability, and all-cause mortality: The concord health and ageing in men project. *J Am Geriatr Soc*. 2014;62(3):417-425. doi:10.1111/jgs.12693

33. Matheï C, Van Pottelbergh G, Vaes B, et al. No relation between vitamin D status and physical performance in the oldest old: Results from the belfrail study. *Age Ageing*. 2013;42(2):186-190. doi:10.1093/ageing/afs186

34. Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: A systematic review and meta-analysis. *J Am Geriatr Soc*. 2011;59(12):2291-2300. doi:10.1111/j.1532-5415.2011.03733.x