Published in final edited form as:

Vasc Med. 2014 February ; 19(1): 18–26. doi:10.1177/1358863X13518364.

Vitamin D status, functional decline, and mortality in peripheral artery disease

Mary M McDermott¹, Kiang Liu¹, Luigi Ferrucci², Lu Tian³, Jack Guralnik⁴, Peter Kopp¹, Linda Van Horn¹, Yihua Liao¹, David Green¹, Melina Kibbe¹, Robert Sufit¹, Lihui Zhao¹, and Michael H Criqui⁵

¹ Northwestern University's Feinberg School of Medicine, Chicago, IL, USA

² National Institute on Aging, Baltimore, MD, USA

³ Stanford University, Palo Alto, CA, USA

⁴ University of Maryland School of Medicine, Baltimore, MD, USA

⁵ University of California at San Diego, San Diego, CA, USA

Abstract

Associations of vitamin D levels with prospectively measured functional decline and mortality in people with lower extremity peripheral artery disease (PAD) are unknown. We determined whether lower baseline vitamin D levels are associated with a faster decline in functional performance and higher mortality among people with and without PAD. A total of 658 participants (395 with PAD) underwent baseline measurement of 25-hydroxyvitamin D (DiaSorin radioimmunoassay), a 6-minute walk test, 4-meter walking velocity and the Short Physical Performance Battery (SPPB), and were followed annually for up to 4 years. Analyses were adjusted for age, sex, race, body mass index, comorbidities, the ankle-brachial index, and other confounders. Among participants with PAD, lower baseline vitamin D levels were associated with a faster decline in the 6-minute walk (vitamin D < 30 nmol/L: -70.0 feet/year; vitamin D 30 to < 50 nmol/L: -72.3 feet/year; vitamin D 50 to < 75 nmol/L: -35.5 feet/year; vitamin D 75 to < 120 nmol/L: -35.9 feet/year; p trend=0.012). PAD participants with vitamin D < 30 nmol/L had a faster decline in the SPPB and 6-minute walk compared to those with levels of 50 to < 75 (p =0.034 and p =0.04, respectively). Among participants without PAD, lower vitamin D was associated with a faster decline in the fast 4-meter walking velocity (p trend=0.003). There were no significant associations of baseline vitamin D levels with all-cause or cardiovascular disease mortality in PAD or non-PAD participants. In conclusion, among individuals with and without PAD, low vitamin D status was associated with a faster decline in some measures of functional performance but was not related to mortality.

Reprints and permissions: sagepub.co.uk/journalsPermissions.nav

Corresponding author: Mary M McDermott, Northwestern University's Feinberg School of Medicine, 750 Lake Shore Drive, 10th Floor, Chicago, IL 60611, USA, mdm608@northwestern.edu.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

Keywords

exercise; intermittent claudication; peripheral arterial disease; peripheral vascular diseases; walking

Introduction

Basic and animal research suggests that vitamin D is important for maintaining physical function and cardiovascular health.^{1,2} However, a recent systematic review concluded that the association of low vitamin D levels with functional decline in people without lower extremity peripheral artery disease (PAD) is unclear.³ Similarly, associations of low vitamin D levels with cardiovascular events in clinical populations without PAD are inconsistent.⁴⁻⁶

Vitamin D contributes to skeletal muscle health. Vitamin D receptors exist on nuclear and cellular membranes of skeletal muscle cells and vitamin D promotes changes in mRNA transcription and protein synthesis that maintain muscle health.⁷⁻¹⁰ In animals, vitamin D deficiency is associated with myofibrillar protein degradation and adverse alterations in muscle contraction kinetics.^{11,12} Because patients with PAD have more adverse muscle characteristics than individuals without PAD, vitamin D may be particularly important for skeletal muscle health in patients with PAD compared to those without PAD.¹³

People with PAD have greater functional impairment, faster functional decline, and increased cardiovascular event rates compared to individuals without PAD.¹⁴⁻¹⁶ A recent population-based study suggested that men and women with PAD have lower levels of vitamin D than those without PAD.¹⁷ Therefore, we studied associations of baseline vitamin D levels with subsequent functional decline and mortality among individuals with PAD. We hypothesized that lower vitamin D levels are associated with faster functional decline and higher all-cause and CVD mortality among individuals with PAD. In exploratory analyses, we assessed whether lower vitamin D levels were associated with more adverse changes in calf muscle and greater declines in peripheral nerve function among people with PAD. To determine whether our results were unique to PAD, we also studied these associations in individuals without PAD.

Methods

Participant identification

The protocol was Institutional Review Board-approved by Northwestern University Feinberg School of Medicine. Participants gave informed consent. Participants included 395 individuals with PAD and 263 individuals without PAD who were part of the Walking and Leg Circulation Study (WALCS) II cohort,^{13,20} had stored blood samples from their baseline study visit, and had follow-up data available for functional decline or mortality. The WALCS II cohort included participants in the original WALCS cohort who consented to continuing annual follow-up visits and newly identified participants recruited to increase the sample size of WALCS II.^{13,18} Inclusion criteria for WALCS II were identical to those for the original WALCS cohort, except that because all WALCS participants were aged 59 years at the start of WALCS II, newly identified participants for WALCS II were aged 59 and older.

WALCS II PAD participants were identified consecutively from among patients diagnosed with PAD in three Chicago-area non-invasive vascular laboratories. Approximately half of the non-PAD participants were identified from among consecutive patients with normal lower extremity arterial testing in the Chicago-area vascular laboratories. The remainder were identified from consecutive patients in a primary care practice.^{13,18} Participants were aged 59 years and older at baseline. Participants returned annually for up to 4 years after baseline.

Inclusion and exclusion criteria

Inclusion and exclusion criteria for WALCS II have been reported^{14,19} and are summarized here. PAD was defined as an ankle-brachial index (ABI) < 0.90. Absence of PAD was defined as an ABI ≥ 0.90 and ≤ 1.30. Potential patients with a lowest leg ABI > 1.30 were excluded. Patients with dementia, nursing home residents, wheelchair-bound patients, patients with recent major surgery, and patients with foot or leg amputations were excluded. Non-English-speaking patients were excluded.

Ankle-brachial index measurement

After participants had rested supine for 5 minutes, a hand-held Doppler probe (Nicolet Vascular Pocket Dop II; Golden, CO, USA) was used to measure systolic pressures in the right brachial, dorsalis pedis, and posterior tibial arteries and the left brachial, dorsalis pedis, and posterior tibial arteries. Each pressure was measured twice. The ABI was calculated by dividing average pressures in each leg by the average of the four brachial pressures.¹⁹ Average brachial pressures in the arm with highest pressure were used when one brachial pressure was higher than the opposite brachial pressure in both measurement sets, and the two brachial pressures differed by 10 or more mmHg in at least one measurement set. In these cases, subclavian stenosis was possible.²⁰ The lowest leg ABI was used in analyses.

Functional performance

Functional performance measures were obtained at baseline and annually for up to 4 years.

Six-minute walk—Following a standardized protocol,^{13,14,16} participants walked up and down a 100-foot hallway for 6 minutes after being given instructions to cover as much distance as possible.

Four-meter walking velocity—Walking velocity was measured with a 4-meter walk performed at ‘usual’ and ‘fastest’ pace according to a previously defined protocol.^{13,14,16}

Repeated chair rises—Participants sat in a straight-backed chair with arms folded across their chest and stood five times consecutively as quickly as possible. Time to complete five chair rises was measured.²¹

Standing balance—Participants were asked to hold three increasingly difficult standing positions for 10 seconds each: standing with feet together side-by-side and parallel (side-by-side stand), standing with feet parallel with the toes of one foot adjacent to and touching the

heel of the opposite foot (semi-tandem stand), and standing with one foot directly in front of the other (tandem stand).²¹

Short Physical Performance Battery (SPPB)—The SPPB combines data from the usual-paced 4-meter walking velocity, time to rise from a seated position five times, and standing balance. Individuals receive a zero score for each task they are unable to complete. Scores of 1 to 4 are assigned for remaining tasks, based upon quartiles of performance from the Established Populations for the Epidemiologic Study of the Elderly.²¹ Scores are summed to obtain the SPPB, ranging from 0 to 12.

Death

Information on deaths was obtained through 23 May 2009 from family members, proxies, primary care physicians, and the Social Security Administration Death Index. Death certificates were obtained from the state in which death occurred or the patient's medical record. Cardiovascular disease (CVD) deaths were those with International Classification of Disease-10 codes in the range I01.0 through I99.9, including deaths from coronary heart disease, stroke, PAD, and other CVD.

Calf muscle cross-sectional area

Computed tomography (CT) scans (LightSpeed; General Electric Medical Systems, Waukesha, WI, USA) of calf skeletal muscle were performed at baseline, 2-year follow-up, and 4-year follow-up with 2.5 mm cross-sectional images of the calves at 66.7% of the distance from the distal to the proximal tibia.¹³ Images were analyzed using BonAlyse (BonAlyse Oy, Jyväskylä, Finland) software to quantify muscle tissue, fat, and bone.¹³

Peripheral nerve function

Electrodiagnostic testing of peripheral nerve function was performed at baseline and 2-year follow-up in both legs and in a randomly selected ulnar motor nerve by the electrodiagnostic supervisor at the Northwestern Memorial Hospital.¹⁸

Vitamin D levels

Levels of 25-hydroxyvitamin D were measured using the direct, competitive, chemiluminescence immunoassay with the DiaSorin LIAISON® 25-OH Vitamin D Total assay (Heartland Assays, Ames, IA).^{22,23} The coefficient of variation percent (CV) for measurement of vitamin D among 81 split sample specimens was 3.74. Values were adjusted for the season in which they were collected.

Comorbidities

Validated algorithms combining data from patient report, physical examination, medical record review, medications, laboratory values, and a primary care physician questionnaire were used to verify and document comorbidities at baseline.²⁴ For example, a diagnosis of diabetes mellitus required the presence of two of the following four criteria: (1) patient-reported history of physician-diagnosed diabetes mellitus; (2) an elevated hemoglobin A1C value from medical record review; (3) use of insulin or an oral hypoglycemic agent; and (4)

a report of diabetes mellitus on the primary care physician questionnaire. A participant was also classified with diabetes mellitus if none of the first three criteria were true, but the physician reported the presence of diabetes mellitus on the primary care physician questionnaire and this was confirmed when the physician was re-contacted to verify the presence of diabetes. Comorbidities assessed were diabetes mellitus, pulmonary disease, cancer, number of cardiovascular diseases (angina, myocardial infarction, stroke, heart failure) and number of arthritic diseases (spinal stenosis, disk disease, knee or hip osteoarthritis, and rheumatoid arthritis).

Other measures

Height and weight were measured. Body mass index (BMI) was calculated as weight (kg)/(height (m))². Cigarette smoking history and alcohol consumption were based on self-report. Physical activity was measured using patient-reported blocks walked in the past week.²⁵

Statistical analyses

Baseline 25-hydroxyvitamin D levels were categorized using definitions from the Institute of Medicine, which defined deficient vitamin D status as 25-hydroxyvitamin D levels < 30 nmol/L, possibly inadequate vitamin D status as 30–50 nmol/L, and sufficient levels as 50 nmol/L or greater.²⁶ The Institute of Medicine stated that levels above 75 nmol/L are not associated with additional benefit. Therefore, the following four categories of vitamin D levels were defined: vitamin D < 30 nmol/L, vitamin D 30 to < 50 nmol/L, vitamin D 50 to < 75 nmol/L, and vitamin D 75 to < 120 nmol/L. Participants with values $\geq$ 120 nmol/L were excluded. Analyses of variance and statistical tests for trend were used to compare baseline characteristics across these vitamin D categories among participants with and without PAD.

Associations of baseline vitamin D categories with average annual change in functional performance measures, calf muscle characteristics, and peripheral nerve function were analyzed using mixed-effects regression models, in which a subject-specific random effect accounted for the potential correlations among successive annual differences in each outcome measure. Dependent variables in each mixed-effect regression analysis were the successive annual changes in functional performance, muscle outcomes, and nerve function, respectively. Analyses adjusted for age, race, sex, ABI, BMI, smoking, comorbidities, physical activity, study cohort (WALCS vs WALCS II), and prior year functional performance (for functional outcomes), prior year muscle measure (for muscle outcomes), or prior year nerve function (for nerve outcomes). Analyses of change in calf muscle area additionally adjusted for tibia length.

Proportional hazards analyses were used to compare differences in all-cause and cardiovascular disease mortality across baseline vitamin D categories, adjusting for age, sex, race, number of CVD diseases at baseline, pulmonary disease, diabetes (for all-cause mortality only), smoking, BMI, physical activity, and study cohort (WALCS vs. WALCS II). The proportional hazards assumption was examined with martingale residuals and was not violated. Statistical analyses were performed using SAS statistical software (version 9.2; SAS Institute Inc., Cary, NC, USA).

Results

Of 478 participants with PAD with baseline blood samples, 349 (73%) participated in at least one follow-up visit for functional performance and 392 (82%) contributed to the mortality outcome. Of 351 participants without PAD with baseline blood samples, 240 (68%) had at least one annual follow-up visit for functional performance and 263 (75%) contributed to the mortality outcome. The mean follow-up was 39.3 ± 16.4 months for functional outcomes, 47.5 ± 16.3 months for mortality, 43.1 ± 14.9 months for calf muscle measures, and 25.0 ± 3.3 months for peripheral nerve function. Among PAD participants, there were no significant differences between those included in analyses and those missing follow-up or covariate data (data not shown). Among non-PAD participants, those included in analyses had higher vitamin D levels than those excluded due to missing follow-up or covariate data: 55.69 ± 23.75 vs 40.84 ± 16.26 , $p=0.04$.

Mean vitamin D levels were 53.9 ± 25 vs 55.7 ± 23.7 nmol/L among participants with and without PAD, respectively ($p=0.362$). Eighty (20%) of 395 PAD participants and 36 (14%) of 263 participants without PAD had a baseline vitamin D level < 30 nmol/L, consistent with vitamin D deficiency.

Among participants with or without PAD, lower vitamin D levels were associated with higher BMI, lower physical activity, and higher prevalences of African-Americans and diabetes mellitus (Table 1). Among participants with PAD, low vitamin D levels were associated with higher prevalences of women and current smoking and a lower prevalence of vitamin D supplementation (Table 1). Among participants without PAD, low vitamin D levels were associated with a higher prevalence of heart failure.

Among PAD participants, vitamin D levels were associated with a faster decline in the 6-minute walk (p trend=0.012), adjusting for age, sex, race, comorbidities, BMI, smoking, physical activity, ABI, prior year performance, and study cohort (Figure 1). PAD participants with baseline vitamin D levels < 30 nmol/L had a faster decline in the 6-minute walk compared to those with vitamin D levels of 50 to < 75 ($p=0.040$), a faster decline in the SPPB score compared to those with vitamin D levels of 30 to < 50 ($p=0.028$), and a faster decline in the SPPB score as compared to those with vitamin D levels of 50 to < 75 nmol/L ($p=0.034$) (Figure 1).

Among participants without PAD, lower baseline vitamin D levels were associated with a faster decline in the fast-paced 4-meter walking velocity, adjusting for age, sex, race, comorbidities, BMI, smoking, physical activity, ABI, study cohort, and prior year performance (p trend=0.003). Non-PAD participants with baseline vitamin D levels < 30 nmol/L had a faster decline in the fast-paced 4-meter walking velocity, compared to those with baseline vitamin D levels of 75 to < 120 nmol/L ($p=0.0164$) (Figure 2).

Among participants with and without PAD, associations of baseline vitamin D with subsequent functional decline did not substantially change when analyses were repeated with additional adjustment for missing data patterns (data not shown). Associations of baseline vitamin D with subsequent functional decline did not substantially change when

analyses were repeated separately among tertiles of physical activity, measured by blocks walked in the past week (data not shown).

Among PAD participants, 93 (24%) died during follow-up. Of these, 31 (33%) deaths were due to CVD. Among participants with PAD, there were no associations of baseline vitamin D levels with all-cause or CVD mortality, adjusting for age, sex, race, BMI, pulmonary disease, number of CVD diabetes (adjusted for in all-cause mortality analyses only), physical activity, or study cohort (Table 2).

Among participants without PAD, 31 (12%) died during follow-up. Of these, 12 (39%) deaths were due to CVD.

Among participants with PAD, there were no associations of baseline vitamin D levels with all-cause or CVD mortality, adjusting for age, sex, race, BMI, pulmonary disease, number of CVD diseases, diabetes (adjusted for in all-cause mortality analyses only), physical activity, or study cohort (Table 2).

PAD participants with baseline vitamin D levels < 30 nmol/L had a greater decline in calf muscle area compared to those with baseline vitamin D levels of 50 to < 75 nmol/L ($p=0.009$), adjusting for age, sex, race, BMI, smoking, comorbidities, prior muscle measurements, and study cohort. There were no other significant associations of lower vitamin D levels with change in calf skeletal muscle characteristics (Appendix). Lower baseline vitamin D levels were not associated with greater declines in peripheral nerve function at 2-year follow-up, adjusting for confounders (Appendix).

Results did not change after additional adjustment for glomerular filtration rate (data not shown).

Discussion

Among PAD participants, we found that lower vitamin D levels were associated with a faster decline in the 6-minute walk distance at the 3-year follow-up when compared to higher vitamin D levels. The magnitude of difference in the average annual decline in the 6-minute walk between the lowest and highest categories of baseline vitamin D was larger than a small meaningful difference but smaller than a large meaningful difference.²⁷ PAD participants with baseline vitamin D levels < 30 nmol/L had faster SPPB score declines when compared to those with baseline vitamin D levels of 30 to < 50 nmol and compared to those with baseline vitamin D levels of 50 to < 75 nmol/L. These differences in SPPB decline were consistent with a small meaningful difference in the SPPB.²⁷ To our knowledge, no prior studies have assessed the associations of vitamin D levels with prospectively assessed outcomes in people with PAD.

Our findings are important because people with PAD have more adverse skeletal muscle characteristics and significantly faster functional decline and mobility loss compared to people without PAD.¹⁴ Animal models suggest that low vitamin D may contribute to adverse changes in skeletal muscle and functional decline^{11,12} and recent data demonstrate that low vitamin D levels may be common in people with PAD.¹⁷ Based on our findings reported

here, further study is needed to determine whether vitamin D therapy improves walking endurance and other measures of functional performance in people with PAD. Our observational study design does not allow us to conclude that vitamin D therapy improves walking endurance or prevents a 6-minute walk decline in people with PAD.

People with PAD have reduced physical activity levels compared to people without PAD.^{16,25} Lower physical activity levels in people with PAD may lessen sunlight exposure, thereby lowering vitamin D levels. Furthermore, PAD patients with lower physical activity levels have faster functional decline than PAD patients with higher vitamin D levels.²⁵ To determine whether the association of low physical activity with reduced vitamin D levels explains our findings, we examined the association of vitamin D levels with decline in functional performance measures among PAD patients stratified by their physical activity levels. Our results showed that low vitamin D levels were associated with functional decline even within subgroups of PAD and non-PAD participants with low, medium, and high physical activity levels. These results suggest that differences in physical activity level across categories of vitamin D levels may not explain our results.

Previous studies among individuals without PAD suggest that vitamin D may be protective against cardiovascular events.^{5,28,30} However, among participants with PAD, our results show no association of lower baseline vitamin D levels with higher all-cause or CVD mortality. Although hazard ratios for participants without PAD suggested that low vitamin D was associated with increased all-cause and CVD mortality, results were not statistically significant. Together, these findings suggest that once significant atherosclerosis has developed, such as in patients with PAD, low vitamin D levels may not be an important determinant of mortality.

Our study has limitations. First, data were collected from participants in Chicago, IL, where colder winter climates may contribute to lower vitamin D levels as compared to PAD patients in southern latitudes. However, vitamin D levels among the PAD patients in our cohort are similar to those of PAD participants from the nationally representative sample of participants in the NHANES cohort.¹⁴ Second, vitamin D levels were measured from blood samples collected between 2002 and 2004. Typical levels of vitamin D levels in patients with and without PAD may have increased or decreased since 2004. Third, our sample size may have been too small to demonstrate a significant association of low vitamin D levels with increased mortality among individuals without PAD.

In conclusion, low vitamin D levels are associated with faster declines in the 6-minute walk and SPPB score but not with increased all-cause or cardiovascular mortality among individuals with PAD. Further study is needed to confirm these findings and determine whether vitamin D supplementation improves the 6-minute walk and other functional performance measures among people with PAD who have low vitamin D levels.

Acknowledgments

Funding

Funded by the National Heart, Lung, and Blood Institute and by the Office of Dietary Supplements, National Institutes of Health (R01-HL096849) (Bethesda, MD, USA). Supported by the National Institute on Aging (Bethesda, MD, USA).

Appendix

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Appendix

Adjusted associations of baseline vitamin D levels with annual change in calf muscle characteristics and peripheral nerve function among participants with and without peripheral artery disease.

	Vitamin D <30 nmol/L	Vitamin D 30 to <50 nmol/L	Vitamin D 50 to <75 nmol/L	Vitamin D 75 to <120 nmol/L	<i>p</i> trend
Participants with peripheral arterial disease					
Calf muscle area	-344.7 (-443.7 to -245.7)	-280.6 (-357.0 to -204.3)	-173.8 (-248.5 to -99.20) ^a	-374.6 (-459.7 to -289.4)	0.4153
Calf muscle percent fat	1.740 (0.919 to 2.560)	1.147 (0.533 to 1.761)	0.930 (0.335 to 1.525)	1.647 (0.963 to 2.332)	0.8011
Calf muscle density	-0.341 (-0.765 to 0.084)	-0.824 (-1.124 to -0.524)	-0.760 (-1.046 to -0.474)	-0.823 (-1.157 to -0.489)	0.3928
Participants without peripheral arterial disease					
Calf muscle area	-399.7 (-506.3 to -293.2)	-240.6 (-307.1 to -174.1)	-244.8 (-312.9 to -176.8)	-234.8 (-308.4 to -161.2)	0.3064
Calf muscle percent fat	3.078 (2.244 to 3.912)	0.942 (0.425 to 1.459)	0.987 (0.457 to 1.516)	0.865 (0.293 to 1.437)	0.0691
Calf muscle density	-0.780 (-1.320 to -0.241)	-0.776 (-1.113 to -0.438)	-0.367 (-0.713 to -0.021)	-0.382 (-0.754 to -0.011)	0.2557
Participants with peripheral arterial disease					
Peroneal nerve conduction velocity	-2.10 (-4.99 to 0.77)	-3.56 (-5.82 to -1.31)	-1.82 (-4.08 to 0.44)	-2.112 (-4.68 to 0.46)	0.519
Sural nerve conduction velocity	-3.58 (-9.19 to 1.94)	-0.81 (-5.18 to 3.563)	0.87 (-3.53 to 5.27)	-1.78 (-6.75 to 3.19)	0.776
Ulnar nerve conduction velocity	-2.35 (-3.82 to -0.88)	-1.54 (-2.72 to -0.36)	-0.99 (-2.17 to 0.18)	-1.14 (-2.48 to 0.20)	0.405
Participants without peripheral arterial disease					
Peroneal nerve conduction velocity	-1.30 (-3.54 to 0.94)	-1.69 (-3.02 to -0.35)	-1.05 (-2.38 to 0.28)	-1.35 (-2.82 to 0.12)	0.676
Sural nerve conduction velocity	4.46 (-2.20 to 11.12)	-0.49 (-4.44 to 3.47)	-0.63 (-4.63 to 3.37)	-4.70 (-9.03 to -0.36)	0.072
Ulnar nerve conduction velocity	-0.58 (-2.31 to 1.14)	-0.57 (-1.62 to 0.47)	-1.58 (-2.63 to -0.53)	-1.60 (-2.76 to -0.44)	0.230

p trends were based on actual vitamin D value.

^aPairwise *p*-value < 0.05 relative to participants with vitamin D levels < 30 nmol/L.

References

1. Gallagher JC. The effects of calcitriol on falls and fractures and physical performance tests. *J Steroid Biochem Mol Biol*. 2004; 90:497–501.
2. Watson KE, Abrolat ML, Malone LL, et al. Active serum vitamin D levels are inversely correlated with coronary calcification. *Circulation*. 1997; 96:1755–1760. [PubMed: 9323058]
3. Cranney, A.; Horsley, T.; O'Donnell, S., et al. Evidence Report/Technology Assessment No. 158. Agency for Healthcare Research and Quality; Rockville, MD: Aug. 2007 Effectiveness and safety of vitamin D in relation to bone health.. AHRQ Publication No. 07-E013
4. Giovannucci E, Liu Y, Hollis BW, et al. 25-hydroxyvitamin D and risk of myocardial infarction in men. *Arch Intern Med*. 2008; 168:1174–1180. [PubMed: 18541825]
5. Dobnig H, Pilz S, Scharnagl H, et al. Independent association of low serum 25-hydroxyvitamin D and 1,25 dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Arch Intern Med*. 2008; 168:1340–1349. [PubMed: 18574092]
6. De Boer IH, Levin G, Robinson-Cohen C, et al. Serum 25-hydroxyvitamin D concentration and risk for major clinical disease events in a community-based population of older adults. A cohort study. *Ann Intern Med*. 2012; 156:627–634. [PubMed: 22547472]
7. Freedman LP. Strategies for transcriptional activation by steroid/nuclear receptors. *J Cell Biochem*. 1999; (Suppl 32–33):103–109.
8. Simpson RU, Thomas GA, Arnold AJ. Identification of 1,25-dihydroxyvitamin D3 receptors and activities in muscle. *J Biol Chem*. 1985; 260:8882–8891. [PubMed: 2991224]
9. Bischoff HA, Borchers M, Gudat F, et al. In situ detection of 1,25-dihydroxyvitamin D3 receptor in human skeletal muscle tissue. *Histochem J*. 2001; 33:19–24. [PubMed: 11352397]
10. Costa E, Blau H, Feldman D. 1,25(OH)2-D3 receptors and humeral responses in cloned human skeletal muscle cells. *Endocrinology*. 1986; 119:2214–2217. [PubMed: 3021437]
11. Pleasure D, Qyszynski B, Sumner A, et al. Skeletal muscle calcium metabolism and contractile force in vitamin D-deficient chicks. *J Clin Invest*. 1979; 64:1157–1167. [PubMed: 227925]
12. Wassner SJ, Li JB, Sperduto A, Norman ME. Vitamin D deficiency, hypocalcemia, and increased skeletal muscle degradation in rats. *J Clin Invest*. 1983; 72:102–112. [PubMed: 6308041]
13. McDermott MM, Hoff F, Ferrucci L, et al. Lower extremity ischemia, calf skeletal muscle characteristics, and functional impairment in peripheral arterial disease. *J Am Geriatric Soc*. 2007; 55:400–406.
14. McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA*. 2004; 292:453–461. [PubMed: 15280343]
15. Ankle Brachial Index Collaboration. Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA*. 2008; 300:197–208. [PubMed: 18612117]
16. McDermott MM, Greenland P, Liu K, et al. The ankle brachial index as a measure of leg functioning and physical activity in peripheral arterial disease: the walking and leg circulation study. *Ann Intern Med*. 2002; 136:873–883. [PubMed: 12069561]
17. Melamed ML, Muntner P, Michos ED, et al. Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease: Results from NHANES 2001–2004. *Arterioscler Thromb Vasc Biol*. 2008; 28:1179–1185. [PubMed: 18417640]
18. McDermott MM, Sufit R, Nishida T, et al. Lower extremity nerve function in patients with lower extremity ischemia. *Arch Intern Med*. 2006; 166:1986–1992. [PubMed: 17030832]
19. McDermott MM, Criqui MH, Liu K, et al. The lower ankle brachial index calculated by averaging the dorsalis pedis and posterior tibial arterial pressures is most closely associated with leg functioning in peripheral arterial disease. *J Vasc Surg*. 2000; 32:1164–1171. [PubMed: 11107089]
20. Shadman R, Criqui MH, Bundens WP, et al. Subclavian artery stenosis: Prevalence, risk factors, and association with cardiovascular diseases. *J Am Coll Cardiol*. 2004; 44:618–623. [PubMed: 15358030]

21. Guralnik JM, Ferrucci L, Simonsick EM, et al. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med*. 1995; 332:556–561. [PubMed: 7838189]
22. Wagner D, Hanwell HE, Vieth R. An evaluation of automated methods for measurement of serum 25-hydroxyvitamin D. *Clin Biochem*. 2009; 42:1549–1556. [PubMed: 19631201]
23. Ersfeld DL, Rao DS, Body JJ, et al. Analytical and clinical validation of the 25 OH vitamin D assay for the LIAISON automated analyzer. *Clin Biochem*. 2004; 37:867–874. [PubMed: 15369717]
24. Guralnik, JM.; Fried, LP.; Simonsick, EM., et al. Appendix E. National Institute on Aging; Bethesda, MD: 1995. The Women's Health and Aging Study: health and social characteristics of older women with disability.. NIH publication No. 95–4009, www.grc.nia.nih.gov/branches/leps/whasbook/appendix/appendixE.pdf [31 December 2013]
25. Garg PK, Liu K, Tian L, et al. Physical activity during daily life and functional decline in peripheral arterial disease. *Circulation*. 2009; 119:251–260. [PubMed: 19118256]
26. Institute of Medicine of the National Academies. [31 December 2013] Report Dietary Reference Intakes for Vitamin D and Calcium. 2010. www.iom.edu/Activities/Nutrition/DRIVitDcalcium.aspx
27. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc*. 2006; 54:743–749. [PubMed: 16696738]
28. Li YC, Qiao G, Uskokovic M, et al. Vitamin D: a negative endocrine regulator of the renin-angiotensin system and blood pressure. *J Steroid Biochem Mol Biol*. 2004; 89–90:387–392.
29. Xiang W, Kong J, Chen S, et al. Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems. *Am J Physiol Endocrinol Metab*. 2005; 288:E125–E132. [PubMed: 15367398]
30. Krause R, Buhning M, Hopfenmuller W, et al. Ultraviolet B and blood pressure. *Lancet*. 1998; 352:709–710.

Figure 1.

Adjusted average annual change in functional performance across baseline vitamin D categories among participants with peripheral artery disease.

Figure 2.
Adjusted average annual change in functional performance across baseline vitamin D categories among participants without peripheral artery disease.

Table 1Baseline characteristics associated with vitamin D levels among study participants ($n=658$).

Participants with peripheral artery disease ($n=395$)					
	Group 1 (<30)	Group 2 (30 VD<50)	Group 3 (50 VD<75)	Group 4 (75 VD<120)	<i>p</i> trend
	<i>n</i>=80	<i>n</i>=110	<i>n</i>=113	<i>n</i>=92	
Age, years	73.3 (7.7)	75.5 (7.6)	76.3 (8.7)	75.1 (7.7)	0.118
Ankle-brachial index	0.62 (0.16)	0.62 (0.14)	0.64 (0.18)	0.63 (0.16)	0.674
Body mass index, kg/m ²	28.9 (5.8)	28.1 (4.9)	28.3 (4.6)	26.4 (4.3)	0.004
Male sex, %	48.8	50.9	52.2	63.0	0.044
Black race, %	28.8	21.8	8.9	6.5	<0.0001
Current smoker, %	31.3	11.8	11.5	13.0	0.002
Pulmonary disease, %	46.3	47.3	43.4	42.4	0.476
Diabetes, %	53.8	34.6	23.9	20.6	<0.0001
Cancer, %	16.3	23.6	16.8	25.0	0.319
Angina, %	35.0	40.4	27.4	41.1	0.589
Myocardial infarction, %	30.0	24.56	19.5	32.9	0.592
Heart failure, %	36.3	30.0	28.3	25.0	0.170
Stroke, %	27.5	19.1	15.9	28.3	0.805
Hip arthritis, %	7.5	2.7	2.6	2.2	0.124
Knee arthritis, %	16.3	12.7	14.2	10.9	0.525
Disk disease, %	38.8	40.9	42.5	36.9	0.830
Spinal stenosis, %	18.8	16.4	15.0	10.9	0.263
No. of blocks walked in past week	23.3 (36.2)	23.9 (36.8)	30.6 (69.6)	42.4 (89.1)	0.063
Taking vitamin D supplement, %	0.00	0.00	1.77	2.17	0.049

Participants without peripheral artery disease ($n=263$)					
	Group 1 (<30)	Group 2 (30 VD<50)	Group 3 (50 VD<75)	Group 4 (75 VD<120)	<i>p</i> trend
	<i>n</i>=36	<i>n</i>=84	<i>n</i>=84	<i>n</i>=59	
Age, years	70.4 (7.3)	73.0 (7.8)	71.3 (7.5)	72.9 (7.7)	0.532
Ankle-brachial index	1.07 (0.10)	1.09 (0.11)	1.10 (0.09)	1.08 (0.10)	0.675
Body mass index, kg/m ²	33.4 (6.9)	29.9 (7.0)	28.9 (5.9)	27.2 (4.4)	<0.0001
Male sex, %	36.1	50.0	45.2	45.8	0.886
Black race, %	44.4	26.2	10.7	10.2	<0.0001
Current smoker, %	5.6	5.9	2.4	6.8	0.978
Pulmonary disease, %	38.9	30.9	40.5	30.5	0.592
Diabetes, %	47.2	22.6	16.7	18.6	0.032
Cancer, %	22.2	22.6	23.8	18.6	0.637
Angina, %	40.0	19.1	14.5	22.4	0.109
Myocardial infarction, %	22.2	20.2	10.7	22.0	0.387
Heart failure, %	19.4	23.8	9.5	6.8	0.009
Stroke, %	13.9	4.8	7.1	10.2	0.979
Hip arthritis, %	11.1	1.2	2.4	5.1	0.447

Participants without peripheral artery disease (n=263)					
	Group 1 (<30)	Group 2 (30 VD<50)	Group 3 (50 VD<75)	Group 4 (75 VD<120)	p trend
	n=36	n=84	n=84	n=59	
Knee arthritis, %	33.3	25.0	14.3	22.0	0.138
No. of blocks walked in past week	19.4 (24.9)	31.8 (52.0)	59.0 (81.4)	47.4 (64.7)	0.003
Taking vitamin D supplement, %	0.00	0.00	2.38	1.69	0.294

Data given as means or percentages.

Table 2

Adjusted associations of baseline vitamin D levels with mortality among individuals with and without PAD.

Participants with peripheral arterial disease					
	Vitamin D<30 nmol/L	Vitamin D 30 to <50 nmol/L	Vitamin D 50 to <75 nmol/L	Vitamin D 75 to <120 nmol/L	p trend
	n=80	n=110	n=113	n=92	
Model 1: Adjusting for age and sex only					
All-cause mortality	1.02 (0.57–1.85)	0.72 (0.41–1.27)	0.78 (0.43–1.39)	1.00 (reference)	0.97
Cardiovascular disease mortality	0.88 (0.30–2.58)	0.42 (0.14–1.28)	1.15 (0.47–2.85)	1.00 (reference)	0.306
Model 2: Adjusting for age, sex, race, BMI, smoking, comorbidities, physical activity, study cohort					
All-cause mortality	0.91 (0.48–1.72)	0.71 (0.40–1.28)	0.88 (0.49–1.60)	1.00 (Reference)	0.597
Cardiovascular disease mortality	0.54 (0.17–1.75)	0.39 (0.12–1.26)	1.18 (0.46–3.00)	1.00 (Reference)	0.099
Participants without peripheral arterial disease					
	Vitamin D<30 nmol/L	Vitamin D 30 to <50 nmol/L	Vitamin D 50 to <75 nmol/L	Vitamin D 75 to <120 nmol/L	p trend
	n=36	n=84	n=84	n=59	
Model 1: Adjusting for age and sex only					
All-cause mortality	3.13 (0.88–11.15)	2.34 (0.77–7.13)	1.64 (0.48–5.65)	1.00 (reference)	0.133
Cardiovascular disease mortality	5.75 (0.59–55.73)	4.28 (0.51–35.67)	1.69 (0.159–18.76)	1.00 (reference)	0.104
Model 2: Adjusting for age, sex, race, BMI, smoking, comorbidities, physical activity, study cohort					
All-cause mortality	2.40 (0.63–9.05)	2.70 (0.87–8.45)	1.87 (0.53–6.59)	1.00 (Reference)	0.248
Cardiovascular disease mortality	3.16 (0.28–35.18)	4.98 (0.54–46.29)	1.88 (0.16–22.81)	1.00 (Reference)	0.398